Associations of Serum Uric Acid With Markers of Inflammation, Metabolic Syndrome, and Subclinical Coronary Atherosclerosis

Thais de A. Coutinho, Stephen T. Turner, Patricia A. Peyser, Lawrence F. Bielak, Patrick F. Sheedy II, and Iftikhar J. Kullo

**Background:** We examined the associations of serum uric acid (UA) with indices of coronary heart disease (CHD) risk, including the 10-year probability of CHD (10y-CHDr), metabolic syndrome (MS), inflammation (C-reactive protein [CRP] and fibrinogen), and the presence and quantity of coronary artery calcium (CAC).

**Methods:** Subjects (n = 1100, mean age 58 years, 59% women) belonged to sibships with ≥2 individuals with hypertension diagnosed before age 60 years. UA was measured by a colorimetric method, CAC by electron beam computed tomography, and CAC score calculated using the method of Agatston. The correlation of UA with 10y-CHDr, MS components, log CRP, and fibrinogen was assessed after adjustment for age and gender. Multivariable regression was used to assess whether UA was associated with CAC presence and quantity after (1) adjustment for age and gender, and (2) additional adjustment for CHD risk factors.

**Results:** Most subjects (71%) had hypertension and 14% had diabetes. Mean (± SD) UA level was 5.97 ± 1.6 mg/dL, and CAC was detectable in 63% of patients. After adjustment for age and gender, UA was significantly correlated with 10y-CHDr, number of MS components, log CRP, and fibrinogen. UA was associated with CAC presence and quantity after adjustment for age and gender but not after further adjustment for systolic blood pressure (BP), diabetes, total and HDL-cholesterol, smoking, and body mass index (BMI).

**Conclusions:** Serum UA was significantly correlated with several indices of CHD risk. UA was associated with presence and quantity of CAC, but not independently of conventional risk factors. Am J Hypertens 2007;20:83–89 © 2007 American Journal of Hypertension, Ltd.

**Key Words:** Uric acid, coronary artery calcium, C-reactive protein, cardiac imaging, metabolic syndrome, atherosclerosis.

Uric acid (UA) is the main end product of metabolism of purines, which in turn are derived mostly from diet, de novo biosynthesis, and breakdown of nucleic acids. Serum UA levels, therefore, increase with higher protein intake, increased endogenous production of urate, or decreased excretion of monosodium urate by the kidneys. More than 50 years ago, Gertler and co-workers noted an association between elevated levels of serum UA and coronary heart disease (CHD). Since then, several studies have attempted to establish whether UA is related to CHD events, independent of the known CHD risk factors. An independent association of UA with CHD events was observed in the National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study and by Alderman et al. On the other hand, the Framingham Heart Study, the Atherosclerosis Risk in Communities (ARIC) study, and Wheeler et al., did not find an independent association of UA with CHD events. Thus, whether UA is independently associated with CHD remains a subject of debate.

To better understand the role of UA as a cardiovascular risk marker, we sought to investigate its association with...
several measures of CHD risk that are currently used in clinical practice, including the estimated 10-year probability of CHD (10y-CHDr), metabolic syndrome, and markers of systemic inflammation. Estimating the 10y-CHDr based on the Framingham risk score is the initial step in CHD risk assessment. The metabolic syndrome is associated with an increased risk of cardiovascular events and the need for its recognition in clinical practice has been emphasized by recent guidelines. C-reactive protein (CRP) and fibrinogen, markers of systemic inflammation, have been shown to predict CHD events independent of conventional risk factors, and an American Heart Association (AHA) scientific statement has suggested measurement of CRP to be an option in subjects with intermediate 10y-CHDr. In addition, we sought to investigate the association of UA with the presence and extent of subclinical coronary atherosclerosis, using coronary artery calcification (CAC) as a surrogate. Coronary artery calcification is an established quantitative, objective measure of coronary artery atherosclerosis, and CAC scores have been shown to be related to CHD risk factors and cardiovascular events. We tested whether UA was independently associated with presence and quantity of CAC after adjustment for conventional cardiovascular risk factors.

Methods

Study Population

The study population consisted of 1107 non-Hispanic white participants from the Genetic Epidemiology Network of Arteriopathy (GENOA) study in which sibships with at least two members diagnosed with hypertension before the age of 60 years were included. Between January 2001 and December 2004, 1241 participants completed the study protocol. Ninety-nine subjects with known CHD, 30 subjects with a history of stroke, and 5 participants with incomplete risk factor information were excluded. The study protocol project was approved by the Mayo Institutional Review Board and participants gave informed consent. Diabetes was considered present if a subject was being treated with insulin or oral agents, or had a fasting glucose level ≥126 mg/dL. “Ever” smoking was defined as having smoked more than 100 cigarettes in the past. The diagnosis of hypertension was established based on blood pressure (BP) levels measured at the study visit (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg) or report of a prior diagnosis of hypertension and current treatment with medications for hypertension. Weight was measured by an electronic scale, height by a stadiometer, and body mass index (BMI) was calculated in units of kg/m². Information about the use of medications, including statins, was obtained at the time of the study visit.

Blood was drawn by venipuncture after an overnight fast. Total cholesterol, HDL-cholesterol, and fasting glucose were measured by standard enzymatic methods. Serum creatinine was measured by a colorimetric method, and UA was measured by a colorimetric method on a Hitachi 912 chemistry analyzer (Roche Diagnostics Co., Indianapolis, IN). The coefficient of variation of the UA assay was 6.6% to 7.5%. Fibrinogen was measured by the von Clauss (clotting time-based) method and CRP by a highly sensitive immunoturbidimetric assay.

The 10y-CHDr was estimated based on the Framingham risk score, and participants were classified as low risk (<10%), intermediate risk (10% to 20%), and high risk (>20%). Metabolic syndrome was defined as the presence of three or more of the following components: (1) waist circumference >35 inches in women or ≥40 inches in men, (2) BP ≥130/85 mm Hg or treatment for hypertension, (3) fasting triglycerides ≥150 mg/dL, (4) HDL cholesterol <40 mg/dL in men or <50 mg/dL in women, and (5) fasting blood glucose ≥110 mg/dL or treatment for diabetes.

Electron Beam Computed Tomography of the Heart

The quantity of CAC was measured with an Imatron C-150 electron beam computed tomography (EBCT) scanner (Imatron Inc., San Francisco, CA) as previously described. A score for each focus of CAC was determined, and the total calcium score was obtained by summing individual foci scores from each of the four anatomic sites (left main, left anterior descending, circumflex, and right coronary arteries).

Statistical Methods

Serum creatinine and CRP levels were log transformed to reduce skewness. Not all patients had detectable CAC, and the distribution of CAC scores among those who had detectable CAC was positively skewed. Therefore, CAC scores were log-transformed after adding 1.

We performed multivariable linear regression to identify variables that influence interindividual variation in UA levels. Variables included in the analyses were: age, male gender, total and HDL-cholesterol, diabetes, systolic BP, smoking, hypertension, BMI, log serum creatinine, use of statins and diuretics, alcohol ingestion, and markers of inflammation (CRP and fibrinogen). Backward elimination was then performed with a criteria of P < .10 to enter and P < .05 to stay in the model.

We calculated Pearson correlation coefficients of UA with 10y-CHDr, log CRP, fibrinogen, and log (CAC + 1) before and after adjustment for age and gender. Comparison of mean UA levels among the various groups defined on basis of 10y-CHDr and number of metabolic syndrome components was performed using analysis of variance, and Student t test was used to assess the difference of UA levels in paired groups. The association of UA with presence and quantity of CAC was also assessed after adjustment for age, gender, and the CHD risk factors, one at a time.

Multivariable logistic and linear regression models were used to investigate the association of UA with the
Table 1. Participant characteristics (n = 1107)

<table>
<thead>
<tr>
<th><strong>Mean ± SD</strong></th>
<th><strong>Median (range)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>58.1 ± 10.1</td>
</tr>
<tr>
<td>Male gender (n (%))</td>
<td>450 (40.7%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.8 ± 6.4</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>100 ± 16</td>
</tr>
<tr>
<td>Hypertension (n (%))</td>
<td>781 (70.6%)</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>130 ± 16</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>200 ± 34</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>52 ± 15</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>156 ± 95</td>
</tr>
<tr>
<td>Statin use (n (%))</td>
<td>262 (23.7%)</td>
</tr>
<tr>
<td>Diabetes (n (%))</td>
<td>159 (14.4%)</td>
</tr>
<tr>
<td>Diuretic use (n (%))</td>
<td>415 (37.5%)</td>
</tr>
<tr>
<td>Hypertension medication use (n (%))</td>
<td>740 (66.9%)</td>
</tr>
<tr>
<td>Metabolic syndrome (n (%))</td>
<td>521 (47%)</td>
</tr>
<tr>
<td>Metabolic “score”</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>10-year CHD risk (%)</td>
<td>9.3 ± 6.9</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.9 ± 0.3</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>0.4 ± 0.7</td>
</tr>
<tr>
<td>Fibrinogen (mg/dL)</td>
<td>317 ± 77</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>6.0 ± 1.6</td>
</tr>
<tr>
<td>Detectable CAC (n (%))</td>
<td>697 (63%)</td>
</tr>
<tr>
<td>CAC score</td>
<td>202 ± 490</td>
</tr>
<tr>
<td>Log (CAC + 1)</td>
<td>2.8 ± 2.6</td>
</tr>
</tbody>
</table>

BMI = body mass index; CAC = coronary artery calcium; CHD = coronary heart disease; CRP = C-reactive protein; SBP = systolic blood pressure.

presence and quantity of CAC, respectively, after adjustment for age, gender, and CHD risk factors (total cholesterol, HDL-cholesterol, diabetes, smoking, systolic BP, BMI), serum creatinine, statin use, and hypertension medication use.

As our cohort consisted of sibships, we used population-averaged generalized estimating equations (GEE) to account for the possible impact of familial correlations on the analyses. A P value < .05 was considered to be statistically significant. Statistical analyses were performed with SAS v 8.2 (SAS Institute, Cary, NC).

Results

The mean age of participants was 58 years, 60% were women, 14% were diabetic, and 70.5% were hypertensive (Table 1). Mean (± SD) UA level was 6.0 ± 1.6 mg/dL. Coronary artery calcification was present in 63% of the patients, and the mean CAC score was 202. The remaining participant characteristics are presented in Table 1.

The majority of subjects (n = 709, 64%) were classified as low 10y-CHDr (<10%), 297 (27%) as intermediate risk (10% to 20%), and 101 (9%) as high risk (>20%). Nearly half (n = 521, 47%) of the subjects had metabolic syndrome based on the National Cholesterol Education Program (NCEP) criteria,17 and the prevalence was similar among men and women. Independent predictors of higher UA levels were greater age (P < .0001), male gender (P < .0001), higher total cholesterol (P < .0001), lower HDL-cholesterol (P = .0001), higher BMI (P < .0001), higher number of alcoholic drinks per week (P = .0015), diuretic use (P < .0001), log serum creatinine (P < .0001), and log CRP (P = .005). The association between UA and fibrinogen was of borderline significance (P = .08).

UA was significantly correlated with 10y-CHDr, metabolic “score,” and markers of inflammation (log CRP, and fibrinogen), before and after adjustment for age and gender (Table 2). Mean UA levels increased significantly with increasing 10y-CHDr (P < .001; Fig. 1) and with increasing metabolic score (P < .0001; Fig. 2). Accordingly, UA levels were higher in subjects with metabolic syndrome versus those without the metabolic syndrome (6.5 mg/dL v 5.5 mg/dL, respectively, P < .0001).

In simple logistic regression analyses, UA was significantly associated with the presence of CAC (β ± SE = 0.38 ± 0.05; P < .0001); the association was weakened but remained statistically significant after adjustment for age and gender (β ± SE = 0.19 ± 0.05; P = .0005). In simple linear regression analyses, UA was significantly associated with the quantity of CAC (β ± SE = 0.46 ± 0.05; R² = 0.08; P < .0001); the association was weakened but remained statistically significant after adjustment for age and gender (β ± SE = 0.12 ± 0.05; model R² = 0.37; P = .001). After further adjustment for CHD risk factors (total and HDL-cholesterol, history of smoking, diabetes, systolic BP, and BMI), statin use, hypertension medication use, and log serum creatinine, UA was no
longer independently associated with the presence (Table 3) or quantity of CAC ($\beta \pm \text{SE} = -0.004 \pm 0.047; P = 0.93$). Factors independently associated with presence of CAC were age, male gender, higher total cholesterol, lower HDL-cholesterol, history of smoking, diabetes, BMI, and hypertension medication use (Table 3). These factors, as well as statin use ($P = 0.006$), were also independently associated with CAC quantity.

The lack of an independent association between UA and quantity of CAC was confirmed in linear regression analyses stratified by gender ($P = 0.55$ in men, $P = 0.94$ in women), hypertension status ($P = 0.42$ in normotensives, $P = 0.89$ in hypertensives), 10y-CHD risk category ($P = 0.73$ in low-risk, $P = 0.44$ for intermediate-risk, and $P = 0.84$ in high-risk patients), presence of the metabolic syndrome ($P = 0.18$ with metabolic syndrome, $P = 0.16$ without metabolic syndrome), and diuretic use ($P = 0.24$ in diuretic users, $P = 0.60$ in nonusers).

**Discussion**

The main finding of this study is that UA is a marker of CHD risk, given its significant associations with several indices of CHD risk including estimated 10y-CHD risk (based on the Framingham risk equation), number of components of the metabolic syndrome, and markers of systemic inflammation. Furthermore, UA was associated with the presence and extent of subclinical coronary atherosclerotic burden after adjustment for age and gender, but the association was not independent of the conventional risk factors for CHD.

UA was significantly related to the 10y-CHD risk based on the Framingham risk equation. This is likely because of the significant associations of UA with several conventional risk factors including age, male gender, total cholesterol, HDL-cholesterol, and BMI, that we noted. Previous studies have also shown UA levels to be associated with several CHD risk factors.\(^5\)\(^6\) Participants with the metabolic syndrome had significantly higher UA levels than those without the metabolic syndrome, and an increasing metabolic score was associated with increasing

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**Table 2.** Pearson correlation coefficients between uric acid and markers of CHD risk, before and after adjustment for age and gender

<table>
<thead>
<tr>
<th></th>
<th>Uric acid</th>
<th>10-y CHD risk</th>
<th>Log CRP</th>
<th>Fibrinogen</th>
<th>Log (CAC + 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uric acid</td>
<td>—</td>
<td>0.40</td>
<td>0.18</td>
<td>0.22</td>
<td>0.29</td>
</tr>
<tr>
<td>10-y CHD risk</td>
<td>0.18</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Log CRP</td>
<td>0.27</td>
<td>0.15</td>
<td>0.63</td>
<td>0.37</td>
<td>0.07</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>0.20</td>
<td>0.12</td>
<td>0.38</td>
<td>—</td>
<td>0.19</td>
</tr>
<tr>
<td>Log (CAC + 1)</td>
<td>0.09</td>
<td>0.20</td>
<td>0.07</td>
<td>0.12</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>0.003</td>
<td>&lt;0.0001</td>
<td>0.02</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

CAC = coronary artery calcium; CHD = coronary heart disease; CRP = C-reactive protein; Metabolic “score” = number of metabolic syndrome components.

Upper correlations are not adjusted. Correlations below the diagonal (in bold) are adjusted for age and gender.

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**FIG. 1.** Box plots showing serum uric acid levels in study participants at low (<10%), intermediate (10% to 20%), and high (>20%) 10-year CHD risk.

**FIG. 2.** Box plots of serum uric acid levels in study participants with increasing number of components of the metabolic syndrome.
UA levels, consistent with previous reports.\textsuperscript{18,19} A possible mechanism for increased UA levels in the metabolic syndrome, a hyperinsulinemic state, may be that insulin stimulates sodium and urate reabsorption in the proximal tubule.\textsuperscript{17}

We found UA to be significantly related to CRP even after adjustment for other potential confounders (age, gender, BMI, history of smoking, HDL-cholesterol, diabetes, statin use, and hypertension medication use). Several in vitro studies suggest that UA has proinflammatory effects. UA has been shown to stimulate production of monocyte chemotaxant protein-1 (MCP-1) by vascular smooth muscle cells,\textsuperscript{20} interleukin-1$\beta$, interleukin-6, and tumor necrosis factor-$\alpha$ (TNF-$\alpha$) by human mononuclear cells, and CRP by cultured human vascular cells.\textsuperscript{21} Infusion of UA into mice leads to a marked increase in circulating TNF-$\alpha$ levels.\textsuperscript{22} On the other hand, because serum urate has free radical scavenging and antioxidant properties,\textsuperscript{23} it has been suggested that elevation of UA levels occurs in response to systemic inflammation.

To the best of our knowledge, the present study is the first to report on the association of UA with subclinical coronary atherosclerosis as measured by CAC.\textsuperscript{24} The UA was associated with CAC presence and quantity after adjustment for age and gender, but not after additional adjustment for CHD risk factors. In particular, adiposity appeared to be a major confounding factor in the association of UA with presence and quantity of CAC. A previous study found UA to be associated with the extent of coronary artery disease on angiography in women (not men), but not independent of metabolic syndrome components.\textsuperscript{24} A study of Japanese patients (87\% men) referred for elective coronary angiography found that UA was not associated with the angiographic severity of coronary artery disease.\textsuperscript{25}

UA has been found to be associated with mortality in a high-risk population.\textsuperscript{26} However, in the present study, UA was not independently associated with presence or quantity of CAC in high-, intermediate-, or low-risk participants, defined on the basis of 10y-CHDr. UA has been reported to be an independent predictor of ischemic stroke in patients not on diuretics.\textsuperscript{27} In our study, diuretic use was an independent predictor of CAC in either diuretic users or in nonusers.

Several proatherogenic properties have been attributed to UA including activation of endothelial cells,\textsuperscript{28} platelet activation, and increased platelet adhesiveness.\textsuperscript{29} UA has also been implicated in the pathogenesis of hypertension.\textsuperscript{29} However, it has been hypothesized that increased UA levels may be a protective response given its antioxidant properties.\textsuperscript{23} Therefore, it is unclear whether UA is a marker of atherosclerosis, a mediator of the effects of conventional risk factors in the development of atherosclerotic disease, or actually part of a protective mechanism. A randomized trial of UA lowering using allopurinol may help to clarify the role of UA as a cardiovascular risk marker versus risk factor.

The cross-sectional nature of the present study does not allow us to disentangle the temporal association between UA, CHD risk factors, low grade systemic inflammation, and the formation of coronary atherosclerotic plaque. Prospective studies, ideally those that incorporate coronary artery imaging modalities and carefully ascertain CHD events, will be needed to further evaluate UA as a biomarker of CHD risk. We have previously found that CRP, although an independent risk factor for CHD events, is not associated with CAC in hypertensive siblings.\textsuperscript{30} We cannot exclude the possibility that UA is more closely related to plaque composition and CHD events, rather than the extent of coronary plaque. We also cannot rule out the possibility that UA may be independently associated with coronary atherosclerosis in younger subjects or with progression of CAC. Our findings may not be generalizable to other ethnic groups.

Serum UA can be measured simply and inexpensively and appears to be a “global” marker of cardiovascular risk given its associations with multiple indices of CHD risk. UA is commonly measured in the clinical setting, and if
increased levels are detected, institution of lifestyle modifications such as lower consumption of high-purine animal protein, initiation of exercise, and weight reduction measures, may be warranted. These lifestyle changes may need to be coupled with pharmacotherapy of CHD risk factors, including hypertension and dyslipidemia.

In conclusion, UA is associated with estimated 10-year CHD risk, number of metabolic syndrome components, markers of systemic inflammation (CRP and fibrinogen), and the presence and quantity of CAC. However, the association with CAC is weakened after adjustment for age and gender and is not statistically significant after adjustment for other conventional risk factors. Thus, UA appears to be a marker of CHD risk and subclinical atherosclerosis but is not independently associated with the latter. It is possible that UA may function in the causal pathway between various risk markers including conventional risk factors and markers of inflammation and mediate some of their effects. In that case, pharmacologic lowering of UA may have beneficial effects. Such a hypothesis is amenable to testing in a prospective study.

References

