Serum Uric Acid Is Associated With Microalbuminuria in Prehypertension

Jung Eun Lee, Yoon-Goo Kim, Yoon-Ho Choi, Wooseong Huh, Dae Joong Kim, Ha Young Oh

Abstract—Serum uric acid is associated with cardiovascular disease. However, the independent role of uric acid in the development of cardiovascular disease is uncertain. This study examined the cross-sectional association of serum uric acid level with microalbuminuria among 6771 subjects without diabetes or hypertension. Blood pressure was categorized as prehypertension (systolic blood pressure, 120 to 140 mm Hg or diastolic blood pressure, 80 to 90 mm Hg) and normotension (systolic blood pressure, <120 mm Hg and diastolic blood pressure, <80 mm Hg). Microalbuminuria was found in 4.0% of normotensive subjects (n = 4819) and in 7.9% of prehypertensive subjects (n = 1952). Prehypertensive subjects with microalbuminuria had higher uric acid level than those with normalalbuminuria (men, 387 [68] mmol/L versus 371 [69] mmol/L; P = 0.017; women 286 [56] mmol/L versus 262 [54] mmol/L; P = 0.006). However, the difference in serum uric acid level according to the presence or absence of microalbuminuria was not found in the normotensive group. Multiple logistic regression models showed that, in the prehypertensive group, after adjustment for other cardiovascular risk factors, the highest uric acid quartile entailed >2 times greater risk for microalbuminuria than the lowest quartile in both men (odds ratio, 2.12; 95% CI, 1.16 to 3.87) and women (odds ratio, 3.36; 95% CI, 1.17 to 9.69). In the normotensive group, serum uric acid quartile did not show the independent association with microalbuminuria. In conclusion, serum uric acid level was strongly associated with microalbuminuria in prehypertensive subjects. (Hypertension. 2006;47:962-967.)

Key Words: uric acid • albuminuria • cardiovascular diseases • risk factors • blood pressure

Several large epidemiological studies have reported that elevated serum uric acid level is associated with cardiovascular disease.1–5 Some investigators have suggested that uric acid plays a causal role in the development of cardiovascular disease,6 whereas others have concluded that uric acid merely reflects other concomitant risk factors, such as hypertension, insulin resistance, obesity, or lipid abnormality.7 The independent association of uric acid with cardiovascular disease appears to be stronger in persons with hypertension than in the general population.3,8–10

Microalbuminuria is associated with an increased risk of cardiovascular morbidity in patients with diabetes,11,12 hypertension,13–15 and in the general population.16–18 The amount of urinary albumin excretion is considered to be a reflection of generalized endothelial dysfunction associated with a variety of risk factors.19 Therefore, microalbuminuria is a useful biological marker for the identification of people who are at high risk for cardiovascular events and who require more intensive therapy.20

The relationship between uric acid and microalbuminuria in healthy adults without other cardiovascular risk factors may help to clarify the role of uric acid in cardiovascular disease. In this study, we examined that elevated serum uric acid level was associated with microalbuminuria among nondiabetic and nonhypertensive subjects without a history of cardiovascular disease or renal dysfunction. We were particularly interested in subjects with prehypertension. The relationship between blood pressure and blood pressure–related morbidity is continuous over the whole range of blood pressure. If hyperuricemia has an independent role in target organ damage among hypertensive subjects, perhaps in combination with prehypertension, it might also be associated with microalbuminuria.21–23

Methods

Study Population
We reviewed the medical record at the Health Promotion Center of Samsung Medical Center in Seoul, Korea. The standardized medical checkup services include medical questionnaire, physical examination, and laboratory tests for a variety of adult diseases, such as hypertension, diabetes, hypercholesterolemia, liver disease, kidney disease, or malignancy. All of the examinations and tests were done in the same day.

Between April 2004 and May 2005, a total of 9607 subjects completed a standardized medical checkup including urinary albumin:creatinine ratio (ACR) measurements. Of these, we excluded the following people: 334 persons with a history of cardiovascular disease, or malignancy. All of the examinations and tests were done in the same day.

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From the Division of Nephrology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.
The first 2 authors contributed equally to this work.
Correspondence to Ha Young Oh, Division of Nephrology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-Dong, Gangnam-Gu, Seoul, Korea 135-710. E-mail hayoung.oh@samsung.com

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disease or cerebrovascular accidents, 185 persons with glomerular filtration rate (GFR) <60 mL/min/1.73 m², 617 persons with diabetes, 1678 persons with hypertension, and 22 persons with overt proteinuria. This left 6771 subjects for our primary analyses.

Assessment of Blood Pressure and Albuminuria
Blood pressure was measured in the sitting position using a mercury sphygmomanometer. The average of 3 readings was recorded. Hypertension was defined as systolic blood pressure of ≥140 mm Hg, diastolic blood pressure of ≥90 mm Hg, or use of antihypertensive drugs, including diuretics. Subjects were classified into 1 of the 2 nonhypertensive blood pressure categories according to the criteria of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and the International Society of Hypertension: prehypertension (systolic blood pressure of 120 to 140 mm Hg or diastolic blood pressure of 80 to 90 mm Hg) and normotension (systolic blood pressure <120 mm Hg and diastolic blood pressure <80 mm Hg).24

A random urine sample was obtained for ACR measurements. Urinary albumin was measured by an immunoturbidimetric assay, and urinary creatinine was measured by Jaffe rate reaction. To define microalbuminuria in random urine specimens, we used the ACR cutoff values of 30 to 300 g/mg for both men and women. Subjects with an ACR <30 μg/mg were defined as having normoalbuminuria; those with ACR >300 μg/mg were defined as having overt proteinuria.

Assessment of Other Variables
The assessment of medical history, smoking status, and medication was based on the standardized questionnaire in the medical record. Body mass index (BMI) was computed as weight in kilograms divided by the square of height in meters. Blood samples for biochemical tests were obtained during an 8-hour fasting state. Serum glucose, HDL cholesterol, and triglycerides were obtained by enzymatic methods. LDL cholesterol was calculated using the Friedewald equation.25 The GFR was measured in mL/min/1.73 m² by the abbreviated Modification of Diet in Renal Disease Study Equation.25

The GFR was measured in mL/min/1.73 m²=186×(SCr exp[−1.154])×(age exp[−0.208])×(0.742 if female), where SCr is the serum creatinine in mg/dL, and exp is the exponential.

Statistical Analyses
All of the data were expressed as a mean±SD. Differences between normoalbuminuria and microalbuminuria were tested by Student t test. Differences between the uric acid quartile groups were tested by the likelihood ratio test for trend. To assess the independent contribution of uric acid to microalbuminuria, we used logistic regression analyses, and for ACR, we used linear regression analyses. P<0.05 was considered statistically significant. All of the statistical analyses for this study were conducted with SPSS 11.0 for Windows.

Results
The prevalence of prehypertension was 29%. Table 1 shows the baseline characteristics of our study population on the basis of blood pressure categories. The prevalence of microalbuminuria was 4.0% in the normotensive group and 7.9% in the prehypertensive group. Hyperuricemia was found in 20.0% of normotensive men and in 24.8% of prehypertensive men. The prevalence of hyperuricemia was 1.4% in normotensive women and 1.7% in prehypertensive women.

Figure 1 shows the mean serum uric acid levels according to blood pressure categories and albuminuria status. In the normotensive group, there was no difference in serum uric acid level according to the presence or absence of microalbuminuria for both men and women. However, prehypertensive subjects with microalbuminuria had higher uric acid levels than those with normoalbuminuria (men, 387 [68] mmol/L versus 371 [69] mmol/L; P=0.017; women 286 [56] mmol/L versus 262 [54] mmol/L; P=0.006). Next, we compared the prevalence of microalbuminuria according to blood pressure categories and uric acid quartiles (Figure 2). Because men had higher serum uric acid levels than women, subjects were stratified by sex-specific uric acid quartile cut points. In the prehypertensive group, the prevalence of microalbuminuria showed a significant linear trend with uric acid quartiles (men, 6.6%, 5.1%, 7.2%, and 12.0%, respectively; P=0.003 for trend; women, 4.5%, 7.6%, 8.6%, and 11.9%, respectively; P=0.032 for trend). Conversely, the prevalence of
microalbuminuria was similar among uric acid quartiles in the normotensive group.

Table 2 shows the standardized regression coefficients obtained from the multiple linear regression models for ACR. Serum uric acid level was independently associated with ACR in the prehypertensive group ($\beta=0.078; P=0.008$). However, serum uric acid level was not an independent factor for ACR in the normotensive group. Female sex, systolic blood pressure, and serum glucose were independent factors for ACR in both blood pressure groups. Additionally, C-reactive protein (CRP) and fibrinogen in the normotensive group and BMI and GFR in the prehypertensive group had an independent association with ACR. Of note is that GFR correlated positively with ACR in the prehypertensive group ($\beta=0.072; P=0.003$).

The independent relationship between serum uric acid level and microalbuminuria was confirmed by the results of multiple logistic regression analyses (Table 3). In the prehypertensive group, after adjustment for other cardiovascular risk factors (age, BMI, smoking status, serum glucose, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, CRP, fibrinogen, and GFR), upper uric acid quartiles were associated with a higher risk of microalbuminuria for both men ($P=0.004$ for trend) and women ($P=0.025$ for trend). Compared with the lowest quartile, the highest uric acid quartile entailed >2 times greater risk for microalbuminuria in both men (odds ratio, 2.12; 95% CI, 1.16 to 3.87) and women (odds ratio, 3.36; 95% CI, 1.17 to 9.69). In the normotensive group, serum uric acid quartile was not an independent factor for microalbuminuria.

Next, we evaluated whether the presence of hyperuricemia was associated with a higher risk of microalbuminuria. In the prehypertensive men, odds ratio for microalbuminuria for the presence of hyperuricemia was 1.86 (95% CI, 1.21 to 2.86; $P=0.004$). In the normotensive men, hyperuricemia was not a significant factor (odds ratio, 1.37; 95% CI, 0.87 to 2.16). The independent association between hyperuricemia and microalbuminuria could not be tested in women, because the prevalence of hyperuricemia was low.

**Figure 2.** The prevalence of microalbuminuria on the basis of serum uric acid quartiles and blood pressure categories. Division points for quartiles: 318, 366, and 408 μmol/L for men; 222, 258, and 294 μmol/L for women. *$P=0.003$ and **$P=0.032$ for interquartile trend.

<table>
<thead>
<tr>
<th>TABLE 2. Multiple Linear Regression Analyses for ACR</th>
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<tr>
<td>Variables</td>
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<tr>
<td>Sex (women)</td>
</tr>
<tr>
<td>Age</td>
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<tr>
<td>Smoking status</td>
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<tr>
<td>SBP, mm Hg</td>
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<tr>
<td>BMI, kg/m$^2$</td>
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<tr>
<td>Serum glucose, mmol/L</td>
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<tr>
<td>LDL-C, mmol/L</td>
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<td>HDL-C, mmol/L</td>
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<tr>
<td>Uric acid, μmol/L</td>
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<td>CRP, mg/L</td>
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<tr>
<td>Fibrinogen, μmol/L</td>
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<td>GFR, ml/min per 1.73 m$^2$</td>
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</tbody>
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SBP indicates systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; NS, not significant.
possible causal relationship. It has been shown previously that increased uric acid level in the prehypertensive group may have a pathological role in target organ damage. After adjustment for other cardiovascular risk factors in the prehypertensive group. These findings suggest that increased uric acid level in the prehypertensive group may have a pathological role in target organ damage.

Several mechanisms have been proposed to explain a possible causal relationship. It has been shown previously that hyperuricemia induced endothelial dysfunction, glomerular hypertension, and renal hypertrophy, even in conditions of mild hypertension in experimental rat models. Our human data consistently showed that the serum uric acid level in prehypertensive subjects was associated with microalbuminuria and that GFR correlated positively with ACR in this setting. Prehypertensive subjects with microalbuminuria had higher GFR levels than those with normoalbuminuria (86 [13] versus 83 [11] mL/min/1.73 m²; P=0.002). Therefore, we presumed that increased serum uric acid level combined with prehypertension might cause an endothelial dysfunction and result in glomerular hypertension, which would induce microalbuminuria and hyperfiltration. It is still unclear whether microalbuminuria in this setting can act as an early marker for renal progression.

Several studies have demonstrated that subjects with prehypertension are at increased cardiovascular risk and may already have evidence of end organ damage, such as impaired ventricular relaxation or microalbuminuria. However, there is no data to prove that pharmacological therapy in prehypertension improves outcomes. Drug therapy in high-risk patients. The Joint National Committee-7 report recommends antihypertensive drugs in patients with diabetes or chronic kidney disease as high-risk patients. Our observational data imply that prehypertensive subjects with hyperuricemia may also be a high-risk group that could benefit from lowering blood pressure. In fact, the prevalence of microalbuminuria in the prehypertensive subjects with the highest uric acid quartile (12%) was similar to that indicated among the hypertensive subjects of 1678 patients (13%), who were not included in our original study.

In addition, this cross-sectional study analyzed the association of a variety of variables with ACR in a nondiabetic

<p>| TABLE 3. Risk of Microalbuminuria for Serum Uric Acid Quartiles According to Blood Pressure Categories: Multiple Logistic Regression Analyses |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                  | Normotension (4819) | Prehypertension (1952) |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Prevalence (%)</th>
<th>Odds Ratio (95% CI)</th>
<th>Prevalence (%)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 1 (&lt;318 μmol/L)</td>
<td>3.7</td>
<td>1</td>
<td>6.6</td>
<td>1</td>
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<tr>
<td>Quartile 2 (318 to 366 μmol/L)</td>
<td>2.5</td>
<td>0.62 (0.34 to 1.14)</td>
<td>5.1</td>
<td>0.94 (0.47 to 1.88)</td>
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<tr>
<td>Quartile 3 (366 to 408 μmol/L)</td>
<td>3.5</td>
<td>0.85 (0.49 to 1.46)</td>
<td>7.2</td>
<td>1.24 (0.66 to 2.35)</td>
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<tr>
<td>Quartile 4 (&gt;408 μmol/L)</td>
<td>4.7</td>
<td>1.09 (0.63 to 1.87)</td>
<td>12.0</td>
<td>2.12 (1.16 to 3.87)</td>
</tr>
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<td>P for trend</td>
<td>NS</td>
<td>NS</td>
<td>0.003</td>
<td>0.004</td>
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<tr>
<td>Women</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Quartile 1 (&lt;222 μmol/L)</td>
<td>5.2</td>
<td>1</td>
<td>4.5</td>
<td>1</td>
</tr>
<tr>
<td>Quartile 2 (222 to 258 μmol/L)</td>
<td>3.8</td>
<td>0.76 (0.39 to 1.49)</td>
<td>7.6</td>
<td>1.73 (0.58 to 5.16)</td>
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<tr>
<td>Quartile 3 (258 to 294 μmol/L)</td>
<td>4.7</td>
<td>0.86 (0.46 to 1.63)</td>
<td>8.6</td>
<td>1.85 (0.63 to 5.40)</td>
</tr>
<tr>
<td>Quartile 4 (294 μmol/L)</td>
<td>4.9</td>
<td>0.94 (0.49 to 1.79)</td>
<td>11.9</td>
<td>3.36 (1.17 to 9.69)</td>
</tr>
<tr>
<td>P for trend</td>
<td>NS</td>
<td>NS</td>
<td>0.032</td>
<td>0.025</td>
</tr>
</tbody>
</table>

This model was adjusted for sex, age, smoking status, systolic blood pressure, diastolic blood pressure, BMI, serum glucose, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, CRP, fibrinogen, and GFR. NS indicates not significant.
nonhypertensive population. Like previous studies, blood pressure and serum glucose were strongly correlated with microalbuminuria. For the normotensive group, CRP and fibrinogen were also independent factors for ACR; this confirms findings reported in previous studies. This study has limitations that deserve mention. This was a cross-sectional study; therefore, we were unable to examine the impact of hyperuricemia over time. Also, only 1 morning urine sample was obtained for the measurements of ACR. This is commonly done in epidemiological studies, but in the clinical setting, it is recommended that several samples be obtained because of microalbuminuria variability and false-positive results. Another limitation of our study is that it occurred in a single center from a large urban teaching hospital. However, the prevalence of microalbuminuria and hypertension in our subjects was similar to those reported in previous studies of the general population. This work was supported by IN-SUNG Foundation for Medical Research and Samsung Medical Center.

Perspectives

Serum uric acid level has long been linked to adverse cardiovascular events. Controversy exists as to whether uric acid has an independent role in the development of cardiovascular disease. This study demonstrated that serum uric acid level was associated with microalbuminuria in a prehypertensive group. This finding suggests the following: (1) increased uric acid level in a prehypertensive group should be considered as a risk factor for cardiovascular disease; (2) the urinary albumin excretion rate can be used as an immediate end point to evaluate the outcome of lowering the uric acid level in future investigations, and this will help draw a conclusion regarding its relation with cardiovascular disease.

Acknowledgments

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