Serum uric acid and chronic kidney disease: the Severance cohort study

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Abstract

Background. Both serum uric acid (SUA) and chronic kidney disease (CKD) are associated with the risk of cardiovascular disease; however, it is unclear whether SUA independently increases the risk of CKD based on longitudinal data.

Methods. To investigate the relationship between SUA levels and CKD development, we initiated a 10.2-year prospective cohort study. Data from 14,939 Koreans, 20–84 years of age, who completed a questionnaire and medical examination at the Severance Health Promotion Center were evaluated. The outcome of interest, CKD, was defined as an estimated glomerular filtration rate (GFR) of <60 mL/min/1.73m² via the simplified Modification of Diet in Renal Disease equation.

Results. A multivariate Cox proportional hazard model, controlling for age, lifestyle and other cardiovascular risk factors, showed an increased risk of developing CKD for men [hazard ratio (HR) 2.1; 95% confidence interval (CI) 1.6–2.9] and women (HR = 1.3; 95% CI = 1.0–1.8) in the highest quartiles of SUA compared to their counterparts in the lowest quartiles. The relationship between SUA and CKD was linear and stepwise in men. The HRs for renal function Grade 2 (75–89.9 mL/min/1.73m²), Grade 3 (60–74.9 mL/min/1.73m²) and Grade 4 (<60 mL/min/1.73m²) increased with an increase in SUA quartiles as compared to the baseline GFR group (Grade 1, ≥90 mL/min/1.73m²).

Conclusions. Higher SUA levels increased the risk of CKD, suggesting that at least part of the reported association between SUA and cardiovascular disease may be connected to CKD.

Keywords: cohort study; epidemiology; kidney disease; serum uric acid

Introduction

Hyperuricemia may be directly pathogenic rather than simply acting as a marker for other associated risk factors [1–3]. It has recently been reported that hyperuricemia can cause hypertension and plays a role in the progression of end-stage renal disease (ESRD) [4]. Several studies have suggested a
positive association between hyperuricemia and ESRD [3, 5–8], macro-cardiovascular diseases [5, 9] and mortality [10]. However, whether serum uric acid (SUA) is independently associated with chronic kidney disease (CKD) is still undetermined in relation to cardiovascular risk factors. The components involved are strongly interrelated and adequate control of each confounding factor is challenging. Due to the complexity of this issue, it will continue to be debated until more definitive data become available from cohort studies. Therefore, we undertook a prospective cohort study to examine the relationship between hyperuricemia and CKD in a healthy Korean population.

Materials and methods

Study subjects

The cohort consisted of 20 348 Korean men and women, ranging in age from 20 to 84 years, who participated in at least one medical evaluation at the Severance Health Promotion Center between 1994 and 2004 [11, 12]. To avoid confounding the association of SUA with the incidence of CKD due to any pre-existing conditions, we excluded the following: 31 participants who were deceased before 1 January 1994 and 1192 participants due to any pre-existing conditions, we excluded the following: 31 participants who were deceased before 1 January 1994 and 1192 participants who reported having cardiovascular disease (n = 100), CKD (n = 1015) or gout (n = 14) at or prior to their initial visit. We also excluded subjects for whom information on gout medication (Zyloric) was missing (n = 63).

In addition, 4186 subjects with missing information with regard to smoking status and alcohol intake were also excluded. The final study sample included 14 939 subjects. The Institutional Review Board of Human Research of Yonsei University approved this study.

Data collection

Participants were asked to describe their smoking habit (never smoked, ex-smoker or current smoker) and alcohol consumption (non-drinker or drinker of any amount of alcohol) as well as other demographic characteristics such as age, gender and past history of diabetes or hypertension. Subjects were asked if they participate in regular exercise and were sub-sequently divided into either an exercise or non-exercise group. Body weights and heights were measured while participants were wearing light clothing. A registered nurse or blood pressure (BP) technician measured BP using a standard mercury sphygmomanometer while the subjects were in a seated position. Systolic and diastolic BP was measured after a minimum 5-min rest period.

Measurement of biomarkers

For the clinical chemistry assay, serum was separated from peripheral venous blood samples obtained from each participant after 12 h of fasting and stored at –70°C. Serum creatinine was measured using the kinetic rate Jaffe method. SUA and metabolic syndrome biomarkers such as fasting blood glucose, total cholesterol, high-density lipoprotein-cholesterol and triglyceride were measured using a Hitachi-7600 analyzer (Hitachi Ltd, Tokyo, Japan). All measurements were performed by a central laboratory at Severance Hospital, Yonsei University Health System, Seoul, Korea. Data quality control was maintained in accordance with the procedures of the Korean Association of Laboratory Quality Control.

Assessment of renal function

Renal function was estimated by the simplified Modification of Diet in Renal Disease equation, in which glomerular filtration rate (GFR) (mL/min/1.73m2) = 186 × P1.134 × age−0.203 × P0.742, if female; × 1.122, if the individual is black) [13].

Kidney function was divided into Grades 1 (≥90 mL/min/1.73m2), 2 (75–89.9 mL/min/1.73m2), 3 (60–74.9 mL/min/1.73m2) and 4 (<60 mL/min/1.73m2) using the calculated GFR.

Follow-up and outcome of interest: CKD

The main outcome variable in our study was CKD, which was defined as a GFR of <60 mL/min/1.73m2. For individuals who had more than one CKD event during the follow-up period from January 2004 to June 2010, only the first event was included in our statistical analysis. During the follow-up period (up to 6.5 years), all participants had more than one medical examination; 48.5% had more than two examinations; 28.5% had more than three examinations and 17.4% had more than four examinations. Computerized searches for death certificates were performed using the identification number assigned at birth by the National Statistical Office.

Statistical analysis

We divided our study samples into quartiles based on SUA levels (<3.1, 3.1–5.7, 5.8–6.5, ≥6.6 mg/dL for men; <3.5, 3.5–5.9, 4.0–4.5, ≥4.6 mg/dL for women). Overweight and obesity were defined as a body mass index (BMI) ≥25 kg/m2 and ≥30 kg/m2, respectively. Additionally, we created a category for diabetes by combining participants with self-reported treatment for diabetes or with fasting serum glucose levels ≥126 mg/dL. Hypertension was defined as systolic BP of at least 140 mmHg, diastolic BP of at least 90 mmHg or self-reported treatment for hypertension.

To examine the association between hyperuricemia and GFR, Cox proportional hazard models were examined after adjusting for age and other potential confounding factors, including smoking status, alcohol consumption, exercise, BMI, hypertension, diabetes and dyslipidemia. Cox proportional hazard models were used to calculate the risk of having CKD (GFR of <60 mL/min/1.73m2) comparing the highest and lowest quartiles of SUA. All analyses were performed separately for men and women, using SAS statistical software, version 9.1 (SAS Institute Inc., Cary, NC). All statistical tests were two sided, and statistical significance was determined as P < 0.05.

Results

Cohort characteristics

As shown in Table 1, the majority of cohort members were middle-aged. The mean age of the study population was 44.0 (SD 9.8) years for men and 43.2 (SD 10.5) years for women. The average estimated GFR was 81.5 mL/min/1.73m2 and 85.5 mL/min/1.73m2 for men and women, respectively. The average BMI was 24.3 kg/m2 for men and 22.8 kg/m2 for women. Mean SUA was 5.8 mg/dL for men and 4.0 mg/dL for women and was greater in men than in women for all age groups. The distribution of SUA levels is shown in Figure 1. The assignments of various variables with SUA quartiles at baseline in men and women are shown in Table 2. In men, BMI, total cholesterol, obesity, current smoking and drinking showed consistent positive relationships with SUA quartiles. In women, BMI, systolic BP, total cholesterol, hypertension, obesity and current smoking were positively related to SUA levels.

SUA and CKD

During the follow-up interval of 151 996 person-years (PYS), there were 438 cases of CKD in men and 328 in women which translated to a higher incidence rate of CKD in women than men (5.2 versus 7.8 per 1000 PYS). In multivariate Cox proportional hazard models, those in the highest SUA quartiles showed significant associations with risk of CKD compared to those in the lowest quartiles for both men and women (Table 3). The highest quartile hazard ratios (HRs) were 2.1 [95% confidence interval (CI) 1.6–2.9] in men and 1.3 (95% CI 1.0–1.8) in women. In men, high SUA was associated with an elevated risk of CKD, an effect that was stepwise with regard to the classifications (P for
Discussion

Our cohort study supports the findings of previous studies using mostly cross-sectional designs, by demonstrating that hyperuricemia was strongly associated with an increased risk of CKD when we compare the highest and lowest quartiles of SUA. This association was significantly independent of age, hypertension, diabetes, serum cholesterol, smoking, alcohol drinking and exercise.

Uric acid is the final product of purine metabolism in human beings. For years, hyperuricemia has been identified with or thought to be the same as gout [14]. To investigate the effects of asymptomatic hyperuricemia, we excluded participants with a history of gout and medication (Zyloric). In this prospective study, SUA values for men and women were divided into quartiles, and associations between SUA and CKD were determined comparing the lowest quartile (Q1) as a reference group to the second (Q2), third (Q3) and fourth quartile (Q4), respectively. For men, the HR for renal function Grade 2 (75–89.9 mL/min/1.73m²), Grade 3 (60–74.9 mL/min/1.73m²) and Grade 4 (<60 mL/min/1.73m²) increased with an increase in SUA quartiles as compared to the baseline GFR group (Grade 1, ≥90 mL/min/1.73m²).

Table 1. Demographic and clinical characteristics of study participants at baseline screenings performed between January 1994 and December 2004

<table>
<thead>
<tr>
<th></th>
<th>Men, N = 8685</th>
<th>Women, N = 6254</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>44.0 ± 9.8</td>
<td>43.2 ± 10.5</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.3 ± 2.8</td>
<td>22.8 ± 3.0</td>
</tr>
<tr>
<td>Uric acid, mg/dL</td>
<td>5.8 ± 1.2</td>
<td>4.0 ± 0.8</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>195.5 ± 33.4</td>
<td>189.6 ± 35.6</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>121.7 ± 16.0</td>
<td>115.6 ± 18.1</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>73.4 ± 11.7</td>
<td>71.2 ± 11.6</td>
</tr>
<tr>
<td>Fasting serum glucose, mg/dL</td>
<td>96.3 ± 20.8</td>
<td>90.6 ± 17.0</td>
</tr>
<tr>
<td>GFR, mL/min/1.73m²</td>
<td>81.5 ± 13.2</td>
<td>85.5 ± 17.0</td>
</tr>
</tbody>
</table>

Table 2. Association of variables with uric acid level quartiles at baseline performed between January 1994 and December 2004

<table>
<thead>
<tr>
<th>Quartile of uric acid</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>2312</td>
<td>2143</td>
<td>2252</td>
<td>1978</td>
</tr>
<tr>
<td>Age, year</td>
<td>42.4</td>
<td>42.4</td>
<td>43.0</td>
<td>44.9</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.1</td>
<td>22.4</td>
<td>22.8</td>
<td>23.9</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>113.8</td>
<td>114.2</td>
<td>115.5</td>
<td>119.3</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>70.2</td>
<td>70.3</td>
<td>71.7</td>
<td>72.7</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>182.8</td>
<td>186.0</td>
<td>190.4</td>
<td>200.1</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>90.7</td>
<td>89.6</td>
<td>90.4</td>
<td>91.7</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>11.5</td>
<td>13.3</td>
<td>17.0</td>
<td>22.6</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>2.9</td>
<td>2.0</td>
<td>2.3</td>
<td>3.0</td>
</tr>
<tr>
<td>Obesity, %</td>
<td>1.0</td>
<td>1.1</td>
<td>1.5</td>
<td>4.2</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>3.2</td>
<td>3.6</td>
<td>5.4</td>
<td>5.0</td>
</tr>
<tr>
<td>Drinking, %</td>
<td>30.9</td>
<td>31.6</td>
<td>33.2</td>
<td>34.3</td>
</tr>
<tr>
<td>Exercise, %</td>
<td>37.1</td>
<td>37.0</td>
<td>38.6</td>
<td>40.1</td>
</tr>
</tbody>
</table>

*Sex-specific quartiles for uric acid (<5.1, 5.1–5.7, 5.8–6.5, >6.6 mg/dL for men; <3.5, 3.5–3.9, 4.0–4.5, >4.6 mg/dL for women). Data expressed as mean or percentage.

Fig. 1. Distribution of SUA levels at baseline in men and women. Screenings were performed between January 1994 and December 2004.

Fig. 2. Comparison of GFR among uric acid quartiles. 

- <0.0001 in a multiple adjusted Model 3. In Figure 2, SUA values for men and women were divided into quartiles and associations between SUA and CKD were determined comparing the lowest quartile (Q1) as a reference group to the second (Q2), third (Q3) and fourth quartile (Q4), respectively. For men, the HR for renal function Grade 2 (75–89.9 mL/min/1.73m²), Grade 3 (60–74.9 mL/min/1.73m²) and Grade 4 (<60 mL/min/1.73m²) increased with an increase in SUA quartiles as compared to the baseline GFR group (Grade 1, ≥90 mL/min/1.73m²).
that hyperuricemia may be directly pathogenic rather than simply acting as a marker for other associated risk factors [1–3, 15]. It has recently been reported that hyperuricemia has a potential causal role with regards to hypertension and ESRD [3, 5–8]. In another study, the SUA level is an independent determinant of coronary artery disease severity in patients with mild to moderate CKD [16]. There is a distinct difference in mean SUA levels between men and women (Figure 1). The difference in mean levels became smaller as the population aged, suggesting the involvement of sex hormones. In women, SUA levels increase in those ≥50 years of age, indicating the role of estrogen [5]. However, since the mean age of our study participants was ~44, and more than half were of pre-menopausal status, the average level of SUA among women in our study was low (4.0 mg/dL). Even though our female participants were young with low SUA levels, the association between SUA and kidney dysfunction was as strong as that seen in the men. Although we observed a gender difference in SUA levels, we did not observe a gender difference in the relationship between hyperuricemia and GFR in this Korean population (Table 3). In previous studies, the risk for ESRD conferred by SUA levels was greater among women than men. Such gender differences related to SUA were also recognized in regard to cardiovascular events in the Framingham study [9, 17] and a positive correlation between SUA levels and extra coronary atherosclerosis has only been reported for women [18]. The inconsistencies related to gender may be due to the fact that females in the present study population were relatively healthy with limited cases of CKD or renal insufficiency compared to the foreign study of Western populations. The possible causes of the gender-related differences with regard to GFR necessitate further research.

In this study, because our subjects were healthy people, we categorized GFR into four groups, which were different from the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines for CKD patients. We used ‘mild renal dysfunction’ to reflect Stage 1 according to K/DOQI guidelines and GFR 60–89 mL/min/1.73m² as Grades 2 and 3 to avoid confusion [12, 19]. The HR for GFR Grades 2, 3 and 4 increased with an increase in SUA quartiles compared to the baseline GFR group (Grade 1, ≥90 mL/min/1.73m²) for both men and women.

Although there is controversy about the association between SUA level and CKD, there are several possible mechanisms that suggests higher SUA level could induce CKD. High SUA level may induce endothelial dysfunction,
SUA and CKD

glomerular hypertrophy, vascular smooth muscle cell proliferation, which caused by activation of cyclooxygenase-2 and monocyte chemoattractant protein-1, and activation of rennin–angiotensin system [20–23]. Therefore, SUA may play a role in development of CKD.

This study has the following limitations: (i) the representativeness of the background population is limited because study subjects were recruited from individuals who went to the health promotion center to check their health status and (ii) a single assessment of creatinine levels may be susceptible to short-term variations, which could bias the results toward null. Despite these limitations, there are two factors that indicate a significant association between SUA and kidney dysfunction: (i) intra-individual creatinine levels of a single assessment are reasonably stable over time and (ii) a strong association between actual SUA and kidney dysfunction was shown.

In this study, it was confirmed that higher SUA level independently increased the risk of CKD and renal function grade increased with an increase in SUA level. In conclusion, higher SUA levels increased the risk of CKD, suggesting that at least part of the reported association between SUA and cardiovascular disease may be connected to CKD. This result establishes the importance of monitoring SUA and GFR and supports timely screening to access changes.

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References


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