The association between plasma uric acid and renal function decline in a Chinese population-based cohort

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Abstract

Background. Uric acid may be associated with kidney damage through multiple pathways. Previous cohort studies revealed inconsistent results, and research among the non-hypertensive and non-diabetic population are extremely limited.

Methods. This prospective cohort study included 1410 residents aged 59.1 ± 9.4 years from an urban district of Beijing, China. All participants had an estimated glomerular filtration rate >60 mL/min/1.73m². Plasma uric acid was assessed at baseline; and its relation with renal function decline after 4 years’ follow-up was analyzed.

Results. During 4 years (5630 person-years) of follow-up, 168 patients (11.9%) developed renal function decline. After adjusting for potential confounders including baseline renal function, plasma uric acid levels were independently associated with an increased risk of renal function decline, with a fully adjusted odds ratio (OR) of 1.19 [per 1 mg/dL increase; 95% confidence interval (CI) 1.04–1.38]. Analysis among 615 hypertension-free and diabetes-free participants yielded similar results, with an adjusted OR of 1.50 (per 1 mg/dL increase; 95% CI 1.13–1.98).

Conclusion. Our prospective cohort study revealed that plasma uric acid level is independently associated with an increasing likelihood of renal function decline.

Keywords: chronic kidney disease; progression; uric acid

Introduction

Although the association of hyperuricemia with hypertension, diabetes and kidney disease has been observed since the 19th century, it is not until recently that studies investigating the association between uric acid levels and these conditions have resurged [1]. Elevated levels of serum uric acid are associated with increased risk of incident hypertension [2–4] and diabetes [5, 6]. Both hypertension and diabetes are well-established risk factors for kidney disease. Furthermore, the uric acid-mediated endothelial dysfunction and high rennin–angiotensin–aldosterone system activity [7, 8] may constitute a direct biological link between hyperuricemia and kidney damage.

Previous cohort studies have shown inconsistent results regarding the association of uric acid with development of end-stage renal disease (ESRD) [9–11] and with incident kidney disease [12, 13]. Furthermore, previous study was limited either by the generalizability [12] or by inability to precisely exclude patients with hypertension or and diabetes [14].

In this study, we prospectively examined the association between plasma uric acid and renal function decline among a population-based cohort with baseline estimated glomerular filtration rate (eGFR) >60 mL/min/1.73m². Furthermore, since both hypertension and diabetes are potential confounders in the uric acid–chronic kidney disease (CKD) link, we carefully excluded participants with either of those conditions and repeated the analysis.

Materials and methods

Study population

The study population has been described in detail elsewhere [11]. In brief, 1563 community-based participants aged >40 years were followed for 4 years. During the follow-up, 59 participants died. For the remaining 1504 survivors, 84 participants with baseline eGFR <60 mL/min/1.73m² were excluded from present analysis due to concern of renal function-related hyperuricemia in those participants. The ethics committee in Peking University First Hospital approved the study. All participants gave written informed consent prior to data collection.

Evaluation of renal function and uric acid at baseline

Details have been described elsewhere [15]. In brief, blood was collected after an overnight fast of at least 10 h. Plasma creatinine was measured by Jaffé kinetic method on a Hitachi 7170 autoanalyzer (Hitachi, Tokyo, Japan). eGFR was calculated using the equation developed from data based on Chinese patients with CKD [16]. Plasma uric acid was measured by the uricase method using the same autoanalyzer.

Evaluation of covariates at baseline

Information of sociodemographic status, personal health history and lifestyle behavior was obtained through a questionnaire. The body mass index (BMI) was calculated as weight (in kilograms) divided by height squared (in square meters).
Blood pressures (BPs) were measured according to the guidelines presented in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood pressure [17]. Hypertension was defined as systolic BP $\geq$140 mmHg or diastolic BP $\geq$90 mmHg or by the use of anti-hypertensive medications in the previous 2 weeks irrespective of the BP or by self-reported history of hypertension. Diabetes was diagnosed by means of a standard 75 g oral glucose tolerance test except in those with a known history of diabetes. Diabetes was defined as fasting plasma glucose $\geq$7.0 mmol/L or 2-h plasma glucose $\geq$11.1 mmol/L or by the use of hypoglycemic agents or by self-reported history of diabetes.

Albumin and creatinine were measured on a spot urine sample. Albuminuria was measured by immunoturbidimetric methods (Audit Diagnostics, Cork, Ireland). Urinary creatinine was measured by the same means of serum creatinine. A urinary albumin-to-creatinine ratio (ACR, mg/g) was then calculated. Albuminuria was defined by ACR $\geq$30 mg/g in females and ACR $\geq$20 mg/g in males.

**Outcomes**

The eGFRs were re-evaluated using the same strategy after 4-year follow-up. Intra-assay coefficients of variation for creatinine assay were 3.7%. The eGFRs were re-evaluated using the same strategy after 4-year follow-up and eGFR $<60$ mL/min/1.73 m$^2$ as the outcome. The same multivariable regression models as in the primary analysis were built. Ten participants were excluded from analysis due to insufficient blood samples.

**Statistical analyses**

Baseline characteristics were reported as mean $\pm$ SD for continuous variables and as percentage for binary variables. Comparisons between those with and without renal function decline were made using t-test for continuous variables and Fisher exact test for binary variables.

The association between plasma uric acid and renal function decline were analyzed using logistic regression models. In our primary analysis, plasma uric acid was analyzed as continuous variable. Other covariates in the models included age (continuous), sex (female versus male), BMI (continuous), current smoking (yes/no), hypertension (yes/no), diabetes (yes/no), albuminuria (yes/no) and baseline eGFR (continuous). Since the interaction term between sex and plasma uric acid level was not statistically significant (P = 0.96), we did not perform stratified analysis by sex. Then, three secondary analyses were performed. Firstly, participants with hypertension and/or diabetes were excluded, and the analysis was repeated. Secondly, plasma uric acid levels were analyzed in sex-specific quartiles. The 25, 50 and 75 percentile for males was 4.6, 5.3 and 6.3 mg/dL, respectively. The 25, 50 and 75 percentile for females was 3.7, 4.4 and 5.1 mg/dL, respectively. Finally, we performed a sensitivity analysis using new-onset eGFR $<60$ mL/min/1.73 m$^2$ as the outcome. The same multivariable logistic regression models as in the primary analysis were built. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported.

The association between plasma uric acid and albuminuria was explored using the same strategy among 1328 participants without albuminuria at baseline.

All P-values are two tailed. Statistical tests were performed using SPSS statistical package, version 10.0 (SPSS, Inc., Chicago, IL).

**Results**

At baseline, the mean age of 1410 participants was 59.1 $\pm$ 9.4, and 48.5% were males. The mean eGFR was 86.8 $\pm$ 15.8 mL/min/1.73 m$^2$, and 5.8% of participants had albuminuria.

During 4 years (5630 person-years) of follow-up, the median change of eGFR was $-9.0$ mL/min/1.73 m$^2$ [interquartile range (IQR) 2.7 to $-20.6$ mL/min/1.73 m$^2$]. Altogether 168 patients (11.9%) developed renal function decline, with median change of eGFR of $-26.0$ mL/min/1.73 m$^2$ (IQR $-22.6$ to $-33.7$ mL/min/1.73 m$^2$). Comparisons of baseline characteristics between those with and without renal function decline are shown in Table 1. Participants who developed renal function decline were older and had a higher percentage of hypertension, diabetes and albuminuria. The plasma uric acid levels were significantly higher among participants with renal function decline compared with those without (5.4 versus 4.9 mg/dL; P < 0.001). The median eGFR change (IQR) for uric acid Quartiles 1–4 was $-4.2$ ($-13.1$ to 4.2), $-5.1$ ($-13.7$ to 4.0), $-5.2$ ($-14.1$ to 2.8) and $-6.7$ (17.5 to 1.6), respectively.

In our primary analysis, plasma uric acid levels were associated with an increased risk of renal function decline (Table 2), with a fully adjusted OR of 1.19 (per 1 mg/dL increase; 95% CI 1.04–1.38). Analysis among 615 hypertension-free and diabetes-free participants yielded similar results, with an adjusted OR of 1.50 (95% CI 1.13–1.98). If plasma uric acid was analyzed in quartiles, a significant increased risk was observed for the uric acid level considered ‘normal’ ($>5.3$ mg/dL for men and $>4.4$ mg/dL for women). A dose–response pattern was observed across quartiles, and the adjusted OR for the top quartile was 2.14 (95% CI 1.22–3.75). In the sensitivity analysis using new-onset eGFR $<60$ mL/min/1.73 m$^2$ as outcome, the 95% CI of ORs were largely overlapped with those in the primary

### Table 1. Baseline characteristics of study participants stratified by status of renal function decline

<table>
<thead>
<tr>
<th>Variables</th>
<th>Participants without renal function decline</th>
<th>Participants with renal function decline</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants</td>
<td>1242</td>
<td>168</td>
<td>0.37</td>
</tr>
<tr>
<td>Male (%)</td>
<td>47.9</td>
<td>51.8</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>58.4 $\pm$ 9.4</td>
<td>64.1 $\pm$ 7.7</td>
<td>$&lt;$0.001</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>25.2 $\pm$ 3.4</td>
<td>25.7 $\pm$ 3.5</td>
<td>0.08</td>
</tr>
<tr>
<td>History of cardiovascular disease (%)</td>
<td>15.6</td>
<td>20.2</td>
<td>0.15</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>24.1</td>
<td>19.0</td>
<td>0.17</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>43.2</td>
<td>58.9</td>
<td>$&lt;$0.001</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>124.0 $\pm$ 17.8</td>
<td>131.2 $\pm$ 19.2</td>
<td>$&lt;$0.001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>76.8 $\pm$ 10.2</td>
<td>77.2 $\pm$ 10.8</td>
<td>0.71</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>25.6</td>
<td>32.1</td>
<td>0.05</td>
</tr>
<tr>
<td>Albuminuria (%)</td>
<td>5.4</td>
<td>8.9</td>
<td>0.08</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m$^2$)</td>
<td>87.9 $\pm$ 16.4</td>
<td>79.0 $\pm$ 7.1</td>
<td>$&lt;$0.001</td>
</tr>
<tr>
<td>Plasma uric acid (µmol/L)</td>
<td>4.9 $\pm$ 1.3</td>
<td>5.4 $\pm$ 1.3</td>
<td>$&lt;$0.001</td>
</tr>
</tbody>
</table>
analysis. For example, the OR of uric acid levels (per 1 mg/dL increase) was 1.24 (95% CI 1.08–1.43).

Among 1328 participants without albuminuria at baseline, 107 (8.1%) of them developed albuminuria during follow-up. If we restricted our analysis to those 1328 participants, uric acid was associated with new-onset albuminuria after adjusting for age and gender, with an OR of 1.17 (95% CI 1.00–1.36). The association was no longer statistically significant in the fully adjusted model, with an OR of 1.13 (95% CI 0.95–1.34).

### Discussion

In this prospective study among a community-based Chinese population with eGFR ≥60 mL/min/1.73m², plasma uric acid level is independently associated with an increasing likelihood of renal function decline.

Previous studies have shown mixed results regarding the association of uric acid with CKD. Ishani et al. [9] found that higher uric acid levels were associated with the development of ESRD in men, while the independent association was only observed for women in a study from Japan [10], and the association was not observed in an analysis using data of the Modification of Diet in Renal Disease (MDRD) study [11]. Chonchol et al. [12] analyzed data from the Cardiovascular Health Study (CHS) found that higher uric acid levels has a significant association with progression of kidney disease, while no significant association was observed between uric acid levels and incident CKD. However, participants of CHS were aged ≥65 years and with multiple chronic conditions, which limited the generalizability of the study. In a later study by Weiner et al. [13], data from the Atherosclerosis Risks in Communities (ARIC) and CHS were pooled together. They found that elevated serum uric acid level is a modest independent risk factor for incident kidney disease [13]. The authors hypothesized that the limitations of serum creatinine-based glomerular filtration rate estimates may contribute to the negative findings regarding incident CKD in Chonchol’s analysis. Because there are complex relationships among uric acid, hypertension, diabetes and CKD, previous studies were challenged due to those potential confounders. In a recent study by Bellomo et al. [14], 900 normotensive participants were examined prospectively. Uric acid was found to be independently associated with a high risk of reduced eGFR, with hazards ratio of 1.13 (95% CI 1.04–1.39) [14]. However, the study population has a male predominance (83%), and exclusion of hypertensive and diabetic participants was based on self-reported histories. In our study, we observed a positive association between uric acid levels and risk of renal function decline, even among hypertension-free and diabetes-free participants, which provide new evidence for the uric acid–CKD link.

There are two mechanisms may relate increased uric acid level with kidney damage. Firstly, uric acid may induce kidney damage via its effect on hypertension and diabetes. Although it has been suggested that the elevation of uric acid levels in patients with hypertension or diabetes is simply a result of those conditions, recent studies suggested that uric acid could also be a risk factor for both hypertension and diabetes. Several studies have reported that hyperuricemia precedes the development of hypertension, which indicates that it is not simply a result of hypertension per se [2–4, 18]. The uric acid-mediated endothelial dysfunction, activation of the rennin–angiotensin system and microvascular disease might be the biological explanations [1]. Similarly, hyperuricemia has been observed to precede the development of diabetes [5, 6], perhaps due to the endothelial dysfunction, as well inflammatory and oxidative changes in adipocytes induced by uric acid [1]. Therefore, hypertension and diabetes could also be mediators in the link between uric acid and CKD. However, in our analysis and in another study as well [14], adjustment of hypertension and diabetes slightly attenuated the strength of the association between uric acid and renal function decline, while the association remains statistically significant. Furthermore, after carefully excluded participants with hypertension and/or diabetes at baseline, the association remains robust, which suggests mechanisms other than hypertension and diabetes may exist. Recent experimental studies indicated that uric acid may lead to kidney damage directly, which is mediated by
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endothelial dysfunction and high rennin-angiotensin-aldosterone system activity [7, 8]. Several studies suggested that treatment of hyperuricemia resulted in delayed progression of CKD [19, 20], which provides strong evidence for the direct toxicity of uric acid to kidneys. Therefore, treatment of elevated uric acid level may constitute an important part of integrated therapy of CKD. It should be noticed that in our study, even uric acid levels still in the ‘normal’ range were associated with increased risk of renal function, which should be considered in the clinical practice.

In our study, ‘baseline eGFR <90 mL/min/1.73m²’ was included in the definition of renal function decline for the following reasons. Firstly, more than one-fourth of the participants were diabetic, and part of them might have glomerular hyperfiltration at baseline. It may not be proper to define them as having ‘renal function decline’ solely based on decrease of eGFR. Secondly, although the modified MDRD equation based on Chinese patients performed better among those with eGFR ≥60 mL/min/1.73m² compared to MDRD equation [16], the disagreement between eGFR and reference GFR was still highest among those with eGFR >90 mL/min/1.73m². Finally, regression to the mean is likely to happen among those with high eGFR results at baseline.

Our study has limitations that deserve mention. Firstly, we only have two measurements of eGFR. Although there may be variations in laboratory measurements, this type of misclassification would tend to bias our study toward not finding an association; therefore, it is possible that we underestimated the true association. Secondly, plasma uric acid was measured only once at baseline, and we do not have information of uric acid-lowering drugs. Finally, since our study was observational, the possibility of residual confounding by some unmeasured covariates exists.

In conclusion, our prospective analysis suggests that plasma uric acid level is a strong independent predictor for renal function decline among a Chinese population with normal or mildly impaired renal function. The association is independent of hypertension and diabetes. Therefore, plasma uric acid might be used for identifying patients at higher risk of CKD progression. Several recent prospective randomized trials indicated that treatment of hyperuricemia with allopurinol improves renal function among asymptomatic hyperuricemic patients and/or patients with CKD [20–22]. However, those studies were limited by relatively small sample size or lack of a placebo control. Future fully powered interventional studies are warranted to evaluate the effect of lowering uric acid level on the occurrence and progression of CKD.

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