High Levels of Uric Acid Correlate with Decline of Glomerular Filtration Rate in Chronic Kidney Disease

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Background: Clinical studies have suggested that high levels of uric acid may contribute to the development of hypertension and kidney disease. However, the relation between uric acid and chronic kidney disease (CKD) has been inconsistent.

Objective: To examine the association between plasma concentration of uric acid, and estimated glomerular filtration rate (GFR) in CKD subjects.

Material and Method: In a cross-sectional study, authors surveyed 5,558 subjects, but only 750 CKD subjects in whom GFR was between 15 and 60 ml/min/1.73 m² were included in the study. The GFR values were calculated by Cockcroft-Gault formula.

Results: There were 65.5% males, mean age of 50.29 ± 6.39 years and body mass index (BMI) of 21.68 ± 2.64 kg/m². The mean value of estimated GFR was 53.86 ± 6.29 ml/min/1.73 m². In subjects with serum uric acid fourth quartile displayed significantly higher BMI, higher systolic blood pressure (BP), higher diastolic BP, higher BUN, and higher serum creatinine, and lower estimated GFR as compared with the three lower quartiles. The correlation analysis showed that estimated GFR was negatively correlated with serum uric acid (r = -0.208, p < 0.01), age (r = -0.171, p < 0.01), systolic BP (r = -0.148, p < 0.01) and BMI (r = -0.147, p < 0.01). Multiple regression analysis, the presence of high serum uric acid levels were independently associated with a decline of GFR.

Conclusion: In CKD subjects, high levels of uric acid were independent associated with GFR decline. Our finding suggests that early detection and prevention on hyperuricemia in CKD subjects are critical.

Keywords: Hyperuricemia, Chronic kidney disease, Glomerular filtration rate

Chronic kidney disease (CKD) is now widely accepted as a risk factor for cardiovascular disease and mortality[1]. The most important established risk factors for CKD are diabetes and hypertension. Although prevention relies in part on modification of underlying risk, few factors have been identified in the development and progression of CKD, many CKD patients eventually progress to end-stage renal disease (ESRD). Therefore, additional risk factors are identified at an early stage may prevent or slow the progression to ESRD.

Chronic hyperuricemia is strongly associated with chronic tubulointerstitial disease, and many of these patients have decreased renal function[2,3]. Further evidence reported on an association of uric acid with hypertension and renal disease[4]. An animal model of mild hyperuricemia accelerates renal progression via a potential mechanism link to high systemic blood pressure (BP) and cyclooxygenase-2 (COX-2)-mediated, thromboxane-induced vascular disease[5], and microvascular changes leading to endothelial dysfunction[6].

Recently, high levels of uric acid have emerged as a potential risk factor for CKD[7-9]. However, many authorities do not consider an elevated uric acid level to be a true hypertensive and CKD risk factors[10,11], because patients with hyperuricemia often have other well-established risk factors for hypertension, such as renal disease, obesity, dyslipidemia, and insulin
resistance. To our knowledge, no study has addressed whether elevated uric acid is an independent associated with renal progression in Thai CKD patients whom the setting of various genetic factors differ from those in western countries. Thus, this study was performed to determine the association between serum uric acid with glomerular filtration rate (GFR) of CKD in Thai adults.

**Material and Method**

The study population included 5,558 Thai army population and their relatives in age from 15 to 60 years. The subjects were obtained from yearly medical examinations from January to December 2007 at the Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand. An estimate of the GFR was obtained by the Cockcroft-Gault formula using variables for age, gender, body weight, and serum creatinine; 

\[
\text{GFR} = \frac{[(140-\text{age}) \times \text{weight} \times 0.85 \text{ if female}]}{72 \times \text{serum creatinine}}
\]

All subjects with GFR < 60 mL/min/1.73 m² were classified as having CKD. Only CKD patients in whom estimated GFR was between 15 and 60 mL/min/1.73 m² were analysis. The institutional review board of Phramongkutklao Hospital and College of Medicine approved the study protocol.

Socioeconomic and demographic data were obtained through direct interviews using standardized questionnaires. The survey questionnaire included questions on previous and current diseases, dietary intake, alcohol consumption, and smoking habits. BP was measured with a mercury sphygmomanometer after a 10-minute rest in the sitting position. The average of the two readings was used for each BP variable. Height, weight, waist circumference and hip circumference were measured at each examination, and body mass index (BMI) was calculated as the weight in kilogram divided by the square of the height in meter. Blood samples were collected from the antecubital vein to determine serum concentrations of uric acid, urea (BUN), creatinine, triglycerides, cholesterol, high-density lipoprotein (HDL)-cholesterol, low density lipoprotein (LDL)-cholesterol and glucose after 10 to 12 hours of starvation. Laboratory services provided laboratory testing to the entire Thai Army in Bangkok using a single regional laboratory and standardized methods.

**Statistical analyses**

All statistical analyses were performed using the statistical software for Windows (SPSS version 12.0, Chicago, IL). Comparisons between serum uric acid quartiles were made by the ANOVA tests, as appropriate, for continuous variables and by Chi-square test for categorical variables. Correlation coefficients were calculated by simple regression analysis. Multiple regression analysis was performed to explore the relationship of estimated GFR and serum uric acid levels. All analyses were 2-tailed, and a p-value < 0.05 was considered statistically significant.

**Results**

A total of 5,558 participants were screened in the study. Of these, 750 participants who had estimated GFR between 15 and 60 mL/min/1.73 m² were included. The mean age of CKD participants was 50.29 ± 6.39 years, and 65.5% were men. Mean BMI was 21.68 ± 2.64 kg/m², and mean estimated GFR was 53.86 ± 6.29 mL/min/1.73 m². The overall prevalence of hypertension in CKD participants was 67.6%, and mean systolic and diastolic BP were 128.52 ± 18.68 and 80.10 ± 12.24 mmHg, respectively (Table 1).

The subject data according to the serum uric acid levels quartiles are presented in Table 2. In a one-way ANOVA test comparing the mean levels of estimated GFR in the four groups, there was an overall difference among groups; p = 0.01. Subjects with se-
Table 2. Characteristics of the patients according to the serum uric acid quartiles

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Quartiles (mg/dL)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First</td>
<td>Second</td>
</tr>
<tr>
<td></td>
<td>&lt; 5.22 (n = 188)</td>
<td>5.23-6.35 (n = 187)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>51.62 ± 6.04</td>
<td>51.72 ± 6.81</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>20.66 ± 2.12</td>
<td>21.06 ± 2.65</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>124.05 ± 18.24</td>
<td>127.65 ± 18.02</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>76.42 ± 11.38</td>
<td>78.90 ± 11.95</td>
</tr>
<tr>
<td>Estimated GFR (mL/min per 1.73 m²)</td>
<td>55.17 ± 4.18</td>
<td>54.10 ± 4.70</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>12.57 ± 3.35</td>
<td>13.97 ± 3.91</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.99 ± 0.17</td>
<td>1.16 ± 0.20</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>222.63 ± 42.07</td>
<td>225.25 ± 42.26</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>93.37 ± 11.74</td>
<td>106.84 ± 70.80</td>
</tr>
</tbody>
</table>

Data are mean ± SD Abbreviations: BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; FPG, fasting plasma glucose; GFR, glomerular filtration rate

The mean serum uric acid levels in CKD subjects were 6.69 ± 1.90 mg/dL. The correlation analysis showed that estimated GFR was negatively correlated with serum uric acid (r = -0.208, p < 0.001, Fig. 1), age (r = -0.171, p < 0.01), systolic BP (r = -0.148, p < 0.01) and BMI (r = -0.147, p < 0.01), but not significantly correlated with body weight, waist circumference, diastolic BP, cholesterol, triglyceride, LDL-cholesterol, HDL-cholesterol and fasting plasma glucose (Table 3). After multiple regression model analysis using potentially relevant independent variables, the presence of high serum uric acid level was independently associated with a decline of estimated GFR.

Discussion

The present study describes the relationship of estimated GFR with serum uric acid levels in Thai CKD population. The results indicate that in Thai CKD population, a high of serum uric acid levels are correlated with a decline of estimated GFR. After multiple regression model analysis using potentially relevant independent variables do not change the estimate significantly. These results support the idea that uric acid may be involved in the pathogenesis of CKD.

Recent epidemiologic studies have demonstrated that uric acid is a major and independent risk factor for the development of hypertension and renal disease(7-9). Thus, both experimental and epidemiologic studies including ours clearly show that
Table 3. Correlation coefficients of estimated GFR and other variable factors

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Estimated GFR (mL/min per 1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>-0.171*</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>-0.148*</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>-0.065</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>-0.078</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>-0.147*</td>
</tr>
<tr>
<td>Waist circumference (inch)</td>
<td>-0.092</td>
</tr>
<tr>
<td>Serum uric acid (mg/dL)</td>
<td>-0.208*</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>-0.066</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>-0.094</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dL)</td>
<td>-0.001</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dL)</td>
<td>-0.048</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>-0.054</td>
</tr>
</tbody>
</table>

*Correlation is significant at the 0.01 level. Abbreviations: BMI, body mass index; BP, blood pressure; FPG, fasting plasma glucose; GFR, glomerular filtration rate; HDL, high density lipoprotein; LDL, low density lipoprotein

subjects with hyperuricemia are at marked associated factor for hypertension and renal disease. In the present study, although we showed that serum uric acid levels are correlated with the severity of estimated GFR, the correlation coefficient was -0.208*, significant correlation. The reason may be the multiple factors in the pathogenesis of CKD. High levels of uric acid are thought to be only one of many pathogenesis factors that develop hypertension and CKD.

There is also increasing evidence to show that hyperuricemia may have a pathogenetic role in the progression of kidney diseases, rather than merely reflecting decreased kidney uric acid excretion. The precise mechanism is not known. However, findings from experimental animal support that hyperuricemia can induce systemic hypertension, and glomerular hypertrophy/hypertension by the activation of the renin-angiotensin, various inflammatory mediators, and cox-2 systems in progressive renal disease(12-14). Furthermore, several evidences suggest that uric acid is responsible for renal interstitial fibrosis, with collagen deposition and macrophage infiltration(15) as well as arteriolopathy of the pre-glomerular vessels(16). For animal models of established kidney diseases, correction of the hyperuricemic state can also significantly improve BP control, decrease proteinuria, and decrease the amount of glomerulosclerosis, tubulointerstitial fibrosis, and vasculopathy(17). These findings are supported by small clinical pilot trials in which allopurinol treatment significantly decreases serum uric acid levels in hyperuricemic patients with CKD and helps preserve kidney function during 12 months of therapy compared with controls(19). Whereas a number of previous studies have suggested that chronic hyperuricemia by itself does not contribute to renal damage, most of these studies were not based on prospective or randomized, and some did not achieve a reduction in uric acid levels(19,20).

Our study linking a decline of GFR with an increase of BP and BMI are of great interest. High of BP and BMI are the component of metabolic syndrome that is a significant predictor for developing microalbuminuria and CKD(21). Moreover, risk of CKD increased progressively with a higher number of components of the numbers of metabolic syndrome(22). Each component of metabolic syndrome, per se, causes renal damage. High BP is well-established risk factors for CKD(23) and high BMI and/or obesity is a significant risk factor for the development of proteinuria and CKD independently of both hypertension and diabetes(24), which are consistent with our findings.

This study has several potential limitations, despite being conducted on a large representative sample of the CKD subjects and initial impressions of a close association of uric acid with GFR in the CKD subjects. First, the cross-sectional design makes it difficult to infer a causal relationship between uric acid and estimated GFR. Therefore, we could not exclude the possibility that the presence of CKD may confound the diagnosis of hyperuricemia. A prospective study is required to investigate the relationship between uric acid and estimated GFR. Second, we used estimated GFR rather than direct measurements of GFR to define CKD, as data on our study population were obtained from the yearly health exam of Thai Army population. Third, primary analyses were based on only one visit, and a single measurement of creatinine, it is not possible to confirm the chronicity of renal impairment in our subjects.

In summary, serum uric acid levels are associated with significantly higher risk for GFR decline. These findings suggest that hyperuricemia might modulate uric-related CKD. Early detection and appropriate management of CKD would be helpful in individuals with hyperuricemia. Further studies are required to establish the benefits of uric acid reduction for ameliorating the risk of CKD and the changes of serum uric acid levels possibly contribute to the structural and functional progression of CKD.
Acknowledgments
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References
ระดับยูริกในเลือดสัมพันธ์กับการลดลงของการทำงานไตในผู้ป่วยโรคไตเรื้อรัง

บัญชา ศติระวัฒน์, อดุลภัทร์ ศุภสินธุ์, เนาวินิตย์ นาท, ดวงพร พูลสุขสมบัติ, ครุณี อุทนานม, อินทรีย์ กาญจนกูล, พรรณบุปผา ชูวิเชียร, ภูวนุสรณ์ ดวงอุไร

บทนำ: ระดับยูริกในเลือดสูงเป็นปัจจัยกระตุ้นต่อการเกิดภาวะความดันโลหิตสูงและโรคไต อย่างไรก็ตาม บทบาทของระดับยูริกในเลือดสูงกับโรคไตเรื้อรังยังไม่ทราบชัดเจน

วัตถุประสงค์: แสดงความสัมพันธ์ของระดับยูริกในเลือดสัมพันธ์กับระดับการทำงานของไตในผู้ป่วยโรคไตเรื้อรัง

วิสัยผลและวิธีการ: การศึกษาแบบเชิงพรรณนาในประชากรกองทัพไทยจำนวน 5,558 ราย คัดกรองเฉพาะผู้ป่วยโรคไตเรื้อรัง ที่มีการทำงานของไตระหว่าง 15 ถึง 60 มล./นาที/1.73 ม² จำนวน 750 ราย เข้ามาร่วมในการศึกษา

ผลการศึกษา: จากข้อมูลพื้นฐานของผู้ป่วยพบเพศชายร้อยละ 65.5 อายุเฉลี่ย 50.29 ± 6.39 ปี ค่ามันน์มวลต่อกิโลกรัม 21.68 ± 2.64 กก./ม² ระดับการทำงานของไตเฉลี่ย 53.86 ± 6.29 มล./นาที/1.73 ม² จากการแบ่งผู้ป่วยเป็น 4 กลุ่มตามระดับระดับยูริกในเลือดพบว่า กลุ่มยูริกสูงสุดมีระดับยูริกในเลือดสูงสุดมีการเพิ่มขึ้นของดัชนีมวลกาย ความดันโลหิต sistolic ความดันโลหิต diastolic ระดับยูเรีย ระดับครีอะตินิน และลดลงของระดับการทำงานของไตเมื่อเทียบกับยูริกในระดับต่ำที่สุด ผลการวิเคราะห์ผล显着กว่าจากการวิเคราะห์ความสัมพันธ์ระหว่างการลดลงของการทำงานของไตสัมพันธ์กับระดับยูริกในเลือด (r = -0.208, p < 0.01), อายุ (r = -0.171, p < 0.01), ความดันโลหิต sistolic (r = -0.148, p < 0.01) และดัชนีมวลกาย (r = -0.147, p < 0.01) หลังจากการวิเคราะห์สมมติการตอบสนองหลายตัวแปรพบว่า ระดับยูริกในเลือดสูงยังเป็นปัจจัยสำคัญต่อการลดลงของการทำงานของไตผู้ป่วยโรคไตเรื้อรัง

สรุป: ผู้ป่วยโรคไตเรื้อรังที่มีระดับยูริกในเลือดสูงสัมพันธ์กับการลดลงของการทำงานของไต จากผลการศึกษานี้คาดว่าการตรวจวินิจฉัยระยะเริ่มแรกและการป้องกันภาวะยูริกในเลือดสูงในผู้ป่วยโรคไตเรื้อรังมีความสำคัญ