Hyperuricemia is associated with progression of CKD: uric acid aggravates renal function

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Abstract
Background: With the change of living standard and dietary structure, the incidence of hyperuricemia is on the rise. Hyperuricemia has become one of the metabolic diseases threatening human health. There is paucity of literature on the association between serum uric acid levels and the progression of CKD. This study aimed at assessing the effect of serum baseline uric acid level on the progression of CKD. Methods: This retrospective study included 800 CKD patients in our center. The information on baseline and follow-up characteristics were collected from our Renal Treatment System (RTS) database. Cox regression analysis was used to evaluate the risk factors for CKD progression. The Kaplan–Meier analysis was used to test associations between serum uric acid levels and renal survival rates. Results: A total of 800 patients were included in the study, and the mean age at entry was 36.6±14.4 years. There was no significant difference in gender distribution. The mean eGFR, Cr, serum uric acid at baseline were 99.23±31.54 ml/min/1.73㎡, 82.08±41.40 μmol/L, 371.60±103.18 μmol/L, respectively. 306 (38.3%) patients had HUA and 494 (61.7%) had non-HUA. We established different adjusted models and found that HUA was a risk factor for CKD patients to reach the composite endpoint after adjustment in six models. All models show that HUA was a risk factor for the progression of CKD. Among them, model 4 (adjusted for Cr + Alb + age + BP + gender) was the best model with the largest HR value (HR:2.010, 95%CI:1.310-3.084, P<0.05). The cumulative survival rate of non-hyperuricemia group was higher than that of hyperuricemia group (P<0.001). Conclusions: Hyperuricemia was not only widespread in patients with CKD, but also a risk factor for the progression of CKD. Anti-hyperuricemia therapy may need to be considered in CKD patients to slow the disease progression, which needs to be tested further in clinical studies.

Key words: hyperuricemia, chronic kidney disease, renal function, progression

Background
The incidence of chronic kidney disease (CKD) is increasing. Prevention and slowing progression of CKD has been a focus of public health[1, 2]. At present, no definitive pharmacological agents to completely reverse the development of CKD. However, early intervention of risk factors for CKD progression can prolong the time to develop end-stage renal disease (ESRD) and improve the prognosis of kidney disease[3].

Uric acid is the product of purine metabolism in human body. Hyperuricemia (HUA) can not only lead
to gout clinically, but is also associated with an increased risk of development of hypertension, diabetes, coronary heart disease, stroke and other diseases[4-9]. Furthermore, HUA is a common phenomenon seen in patients with CKD[2, 10]. Previous studies have shown that hyperuricemia was a risk factor for CKD[5-7]. However, due to the complex and bidirectional interactions between HUA and renal function, the exact association between HUA and the progression of CKD remains uncertain. We have therefore conducted a retrospective cohort study assessing the effect of baseline serum uric acid levels on the progress of CKD.

Methods

Study Participants and Data Collection

Patients with CKD in our renal center (Renal Department and Nephrology Institute, Sichuan Provincial People’s Hospital) were screened from our Renal Treatment System (RTS) database and the selection period was from 2010 to 2016 January 2010 to December 2016. Those with adequate information on baseline and follow-up (more than 3 months) characteristics were included in this study. Exclusion criteria was defined as familial hyperuricemia, transient hyperuricemia, primary gout, transient tubular injury, malignant hypertension, pregnancy, renal cancer, cirrhosis, recent chemotherapy or immunosuppressive therapy, solid organ transplantation, or patients receiving dialysis therapy[11]. Patients who were unable to provide consent or enrolling in competing studies were excluded as well. Finally, 800 individuals (383 males and 417 females) were included in the present study. The baseline and follow up clinical and demographic characteristics were collected from our RTS database, including age, gender, serum uric acid level, estimated glomerular filtration rate (eGFR), serum creatinine, urea, albumin level, 24 hours urinary protein quantitation (24h-u-pro) and blood pressure measurements (BP). The eGFR was calculated by the CKD-EPI (CKD Epidemiology Collaboration) equation[12]. The study was approved by the Ethics Committee of the Sichuan Provincial People’s Hospital (Chengdu, China, No.2017-124) and all patients signed informed consents to join in this study.

Definitions

ESRD was defined as eGFR <15 mL/min/1.73 m², initiation of dialysis for more than 3 months or receiving transplantation[13]. The primary endpoint was defined as a composite of a decline in eGFR by > 30% from baseline, doubling creatinine and development of ESRD. Hyperuricemia was defined as a fasting serum uric acid more than 420μmol/L (7mg/dl) for male and more than 357μmol/L (6mg/dl) for female [14].

Statistical analysis

Proportions was used to describe categorical variables. Mean ± standard deviation (SD) (normally distributed) or median (range) with interquartile ranges (IQR) (non-normally distributed) were used to displayed continuous variables. When comparing the differences between groups, continuous data
were compared using the student t-test and comparisons of categorical variables were performed by the Chi-square test. Cox regression model analysis was used to evaluate the risk factors for CKD progression. The Kaplan–Meier analysis was used to test associations between serum uric acid levels and renal survival rates.

Results

**Baseline and follow-up clinical characteristics**

Among all the 800 individuals, the median follow up was 10.3 months, and the mean baseline serum uric acid level was 371.60 μmol/L (21.73mg/dl). Hyperuricemia was seen in 306 (157 males and 149 females) of 800 (38.3%) (383 males and 417 females) patients. Patients with hyperuricemia had worse renal function, as compared to those without hyperuricemia (Table 1). With a median follow-up period of 10.3 months, a total of 107 (13.4%) patients reached the primary endpoint. The number of patients who had reductions in eGFR by > 30%, doubling Cr and development of ESRD were 105, 19, 8 (13.1%, 2.4%, 1.0%), respectively. The average annual declining rate of eGFR in all patients, HUA group and non-HUA group were 1.5%, 1.1%, 1.6%, respectively (Table 2).

**Uric acid levels contributed to the complex endpoint**

The univariate Cox regression analysis showed that age, gender, serum uric acid levels, Cr, eGFR were associated with the primary outcome (Table 3). The previous literature showed that urinary protein and serum albumin level were also closely related to the progression of renal function in CKD patients. Therefore, we added these two variables to perform the multivariate Cox regression analysis. Six different models (Model 1: Cr + age + BP + gender; Model 2: eGFR + age + BP + gender; Model 3: Cr + 24h-u-pro + age + BP + gender; Model 4: Cr + Alb + age + BP + gender; Model 5: eGFR + 24h-u-pro + age + BP + gender; Model 6: eGFR + Alb + age + BP + gender) were constructed. All the models suggested that HUA was a risk factor for the progression of CKD. Furthermore, model 4 (adjusted for Cr + Alb + age + BP + gender) showed the highest risk with the largest HR value (HR:2.010, 95%CI:1.310-3.084, P<0.05) (Table 4).

Endpoints and survivals from combined renal endpoint in patients with different baseline uric acid levels

The cumulative survival rate of non-hyperuricemia group was higher than that of hyperuricemia group (P<0.001) (Figure 1).

Discussion

In this retrospective cohort study, we included 800 CKD patients and found that baseline hyperuricemia was associated with worse renal function. Patients with baseline hyperuricemia were
more likely develop the composite renal outcomes. Our study also identified that age, gender, baseline renal function were predictors for CKD progression. A number of models used in our study confirmed that HUA was a risk factor for CKD progression. Furthermore, HUA in the model with adjustment for serum creatinine, albumin, age, gender and blood pressure demonstrated the highest risk of CKD progression by 2.1 folds.

With the change of life style and dietary structure, the incidence of hyperuricemia is on the rise due to the excessive production of uric acid or the decrease of uric acid excretion[15]. As the kidney is the main organ to excrete uric acid, renal impairment can cause hyperuricemia[16-19]. Hyperuricemia, in turn may also be associated with worsening renal function and has some effects on the development of CKD and the progression of CKD to ESRD[20, 21]. Most scholars believe that uric acid itself may harm patients with CKD by contributing to increased inflammation and CKD progression[7, 21, 22]. However, some studies did not show an effect of hyperuricemia on worsening renal function. For example, a study involving 5808 patients with 5 years of follow-up showed no significant association between increased serum uric acid levels and CKD progression[4]. Our finding was in line with most studies, and showed that hyperuricemia was a strong risk factor for CKD progression. In addition, our previous study showed that serum uric acid not only correlated with renal function, but also with renal pathology. Hyperuricemia was an independent risk factor for segmental glomerulosclerosis and tubular atrophy/interstitial fibrosis[11]. Uric acid may be considered as a marker for tubulointerstitial lesions in early stage of IgAN[23]. In this study, further subgroup analysis in patients with IgA nephropathy also showed that hyperuricemia was associated with worse renal function and lower survivals (Table 5).

Our study has the following strength. Firstly, in this retrospective study, we included 800 CKD patients and found that the baseline and follow-up data were recorded. Baseline uric acid levels were found to be associated with end-point renal events. Secondly, uric acid predicts adverse outcomes in renal function. What is more, the association of HUA and the progression of CKD, suggests that early treatment of hyperuricemia is necessary in order to slow CKD progression.

Our study has several limitations. Firstly, short duration of follow up of the study did not allow us to assess the long-term prognosis of patients. Secondly, we were unable to justify if patients received uric acid-lowering drugs or not due to lack of information on pharmaceutical therapies in this dataset. Thirdly, as a retrospective study, potential confounders may not be collected and included in our analyses, which may have an impact on the results.

Conclusion
Hyperuricemia was not only widespread in patients with CKD, but also a risk factor for the progression of CKD. Anti-hyperuricemia therapy may need to be considered in CKD patients to slow the disease progression, which needs to be tested further in clinical studies.
Abbreviations
CKD: chronic kidney disease
HUA: hyperuricemia
RTS: Renal Treatment System
UA: uric acid
eGFR: glomerular filtration rate
Cr: creatinine
Alb: albumin
24h-u-pro: 24 hours protein quantitation
BP: blood pressure

Declarations
Ethics approval and consent to participate
The study was approved by the Ethics Committee of the Sichuan Provincial People’s Hospital (Chengdu, China, No.2017-124). The de-identified data was obtained from RTS database. All patients gave fully informed written consent.

Consent for publication
Not applicable.

Availability of data and materials
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interest
All authors declare that they have no competing interests.

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Authors’ contribution
FSL collected and processed the data, helped with the study design and drafted the manuscript. ZY collected the data and helped to draft the manuscript. XMJ processed the data and performed the statistical analysis. HDQ, WAY, and LGS conceived the study, participated in its design and coordination: All authors read and approved the final manuscript.
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Tables

Table 1 Baseline and follow-up clinical characteristics of HUA and non-HUA groups

|                      | Total  | HUA    | non-HUA |
|----------------------|--------|--------|---------|
|                      | n=800  | n=306  | n=494   |
| Age at entry(years)  | 36.6±14.4 | 27.1±14.1 | 36.3±14.6 |
| Male (n, %)          | 383(47.8) | 157(51.3) | 226(45.7) |
| Cr (μmol/L)          | 82.08±41.40 | 98.55±51.28 | 71.87±29.63 |
| eGFR (ml/min/1.73)   | 99.23±31.54 | 87.11±34.90 | 106.73±26.68 |
| Urea (mmol/L)        | 6.41±3.28 | 7.60±4.11 | 5.67±2.36 |
| Alb (g/L)            | 33.24±9.29 | 33.72±9.16 | 32.94±9.37 |
| UA (μmol/L)          | 371.60±103.18 | 472.0±76.41 | 309.39±59.20 |
| 24h-u-pro (g/d)      | 1.64(0.52,3.99) | 1.71(0.76,3.86) | 1.54(0.31,4.05) |
| IgAN (n, %)          | 331(41.4) | 143(46.7) | 188(38.1) |

Table 2 Follow-up clinical characteristics of HUA and non-HUA groups
| Index           | Total n=800 | HUA n=306 | non-HUA n=494 |
|----------------|-------------|-----------|---------------|
| Cr (μmol/L)    | 90.58±80.45 | 103.17±63.90 | 82.79±88.34   |
| eGFR (ml/min/1.73) | 96.58±33.44 | 85.80±36.51 | 103.26±29.52 |
| Urea (mmol/L)  | 6.45±3.40   | 7.44±4.12  | 5.85±2.71     |
| Alb (g/L)      | 40.01±7.66  | 39.58±8.00 | 40.27±7.44    |
| UA (μmol/L)    | 386.70±109.46 | 442.86±101.14 | 352.01±99.64 |
| 24h-u-pro (g/d) | 0.39(0.09,1.61) | 0.49(0.15,1.72) | 0.35(0.07,1.58) |
| Follow-up time (month) | 10.3(4.4,22.5) | 11.4(4.3,23.6) | 10.0(4.6,21.6) |
| Change rate of eGFR | -1.5%(-14.9%,5.9%) | -1.1%(-19.5%,9.7%) | -1.6%(-13.6%,5.0%) |
| Endpoint (n, %) | 107(13.4)   | 58(19.0)   | 49(9.9)       |
| eGFR drops by 30% | 105(13.1)   | 57(18.6)   | 48(9.7)       |
| Cr doubling    | 19(2.4)     | 4(1.3)     | 15(3.0)       |
| ESRD           | 8(1.0)      | 3(1.0)     | 5(1.0)        |

Change rate of eGFR: Average annual change rate of eGFR. When the rate is greater than 0 indicates an increase in eGFR and renal function improves. When the rate is less than 0 indicates a decline in eGFR and renal function deteriorates.

**Table 3 Univariate Cox regression analysis for outcome in the whole cohort**

| Index | HR   | 95%CI          | P     |
|-------|------|----------------|-------|
| age   | 1.021| 1.008-1.034    | 0.002 |
| gender| 0.666| 0.450-0.985    | 0.042 |
| BP    | 1.152| 0.735-1.803    | 0.538 |
| UA    | 1.002| 1.001-1.004    | 0.006 |
| HUA   | 2.032| 1.389-2.972    | <0.001|
| Cr    | 1.003| 1.000-1.007    | 0.078 |
| eGFR  | 0.988| 0.983-0.994    | <0.001|
| Urea  | 1.072| 1.025-1.121    | 0.002 |
| 24h-u-pro | 1.021 | 0.989-1.053 | 0.201 |
| Alb   | 0.984| 0.964-1.004    | 0.116 |
| IgAN  | 1.282| 0.877-1.873    | 0.200 |

**Table 4 Multivariate Cox regression analysis for composite endpoint in the whole cohort**
Table 5 Multivariate Cox regression analysis for composite endpoint in IgAN

|    | HR¹ (95%CI) | HR² (95%CI) | HR³ (95%CI) | HR⁴ (95%CI) | HR⁵ (95%CI) |
|----|-------------|-------------|-------------|-------------|-------------|
| HUA| 1.909 △    | 1.699 △    | 1.872 △    | 2.010 △    | 1.658 △    |
|    | (1.250-2.916) | (1.101-2.623) | (1.198-2.923) | (1.310-3.084) | (1.050-2.620) |

△: P0.05
HR1: adjusted for Cr + age + BP + gender
HR2: adjusted for eGFR + age + BP + gender
HR3: adjusted for Cr + 24h-u-pro + age + BP + gender
HR4: adjusted for Cr + Alb + age + BP + gender
HR5: adjusted for eGFR + 24h-u-pro + age + BP + gender
HR6: adjusted for eGFR + Alb + age + BP + gender
HUA: hyperuricemia
Figure 1

The cumulative survival rate of non-hyperuricemia group (blue) was higher than that of hyperuricemia group (green). P-value was less than 0.001 according to Log-rank test.