Serum Uric Acid Level and Risk of Chronic Kidney Disease in Elderly from Longevity Areas in China: A Postprint Study

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Abstract

Background: Elevated serum uric acid (SUA) leading to hyperuricemia (HUA) has been confirmed as an independent risk factor for the occurrence and progression of chronic kidney disease (CKD), but there are few cohort studies in China on the association between SUA levels and CKD occurrence and progression in the elderly.

Objective: To investigate the association of baseline SUA levels and their changes with the risk of CKD incidence and changes in estimated glomerular filtration rate (eGFR) among elderly individuals in longevity areas of China.

Methods: Based on the sub-cohort of the Chinese Longitudinal Healthy Longevity Survey (CLHLS)—the Healthy Aging Biomarkers Cohort Study (HABCS), elderly individuals who underwent health examinations and had biomedical indicators collected from 2012 to 2014 were selected as study subjects. Biomedical indicators including age, sex, blood pressure, blood lipids, and blood glucose were collected at baseline and follow-up. Cox proportional hazards regression models were used to analyze the association between different SUA levels and CKD incidence risk; Spearman rank correlation and generalized linear models were used to analyze the correlation between baseline SUA levels and baseline eGFR, and the correlation between changes in SUA levels and changes in eGFR among the elderly.

Results: A total of 981 subjects were included, with a median age of 79 (70, 88) years. The prevalence of HUA was 6.8% (67/981). The cumulative follow-up was 2,029 person-years, with a median follow-up of 2.05 years. There were 179 new CKD cases, and the cumulative incidence of CKD during follow-up was 18.2% [95%CI (15.9%, 20.8%)], with an incidence density of 88.22/1,000 person-years [95%CI (76.24/1,000 person-years, 101.41/1,000 person-years)]. Cox proportional hazards regression model analysis with SUA quartile grouping as the

dependent variable showed that compared with the lowest baseline SUA quartile group (Q1), the HR value for CKD incidence risk in the highest quartile group (Q4) was 2.08 [95%CI (1.27, 3.41), P=0.004]. Cox proportional hazards regression model analysis with SUA level as the dependent variable showed that for every 10 mol/L increase in baseline SUA level, the risk of CKD incidence increased by 4% [95%CI (2%, 7%), P<0.001]. Cox proportional hazards regression model analysis with HUA presence as the dependent variable showed that compared with elderly individuals without baseline HUA, those with HUA had an increased CKD incidence risk, with an HR value of 2.00 [95%CI (1.20, 3.24), P=0.007]. The median baseline SUA level in the elderly was 270.60 (223.10, 325.90) mol/L, and the median baseline eGFR was 84.07 (73.08, 98.38) $ml \bullet min^{-1} \bullet (1.73\ m^2)^{-1}$. Spearman rank correlation analysis showed a negative correlation between the two (rs=-0.363, P<0.001). Generalized linear model analysis showed that for every 10 mol/L increase in baseline SUA level, baseline eGFR decreased by 0.897 $ml \bullet min^{-1} \bullet (1.73\ m^2)^{-1}$ (P<0.001). During follow-up, the median ΔSUA in the elderly was -3.55 (-40.60, 31.90) mol/L, and the median ΔeGFR was 3.49 (-8.13, 15.89) $ml \bullet min^{-1} \bullet (1.73\ m^2)^{-1}$. Spearman rank correlation analysis showed a negative correlation between the two (rs=-0.355, P<0.001). Generalized linear model analysis showed that for every 10 mol/L increase in SUA level during follow-up, eGFR decreased by 1.027 $ml \bullet min^{-1} \bullet (1.73\ m^2)^{-1}$ (P<0.001).

Conclusion: Elevated SUA levels in the elderly are associated with an increased risk of new-onset CKD and a decline in eGFR.

Full Text

Association between Serum Uric Acid Level and the Risk of Chronic Kidney Disease among the Elderly in Longevity Areas of China

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Abstract

Background: Hyperuricemia (HUA) caused by elevated serum uric acid (SUA) has been shown to be an independent risk factor for the development and progression of chronic kidney disease (CKD). However, few cohort studies have examined the correlation between SUA level and CKD development and progression among the elderly in China.

Objective: To explore the association of baseline SUA level and its changes with the risk of CKD and estimated glomerular filtration rate (eGFR) among the elderly in longevity areas of China.

Methods: Based on the Healthy Aging and Biomarkers Cohort Study (HABCS), a sub-cohort of the Chinese Longitudinal Healthy Longevity Survey (CLHLS), we selected older adults who received physical examinations and had biomedical indicators collected from 2012 to 2014 as study subjects. Age, gender, blood pressure, blood lipids, blood glucose, and other biomedical indicators were collected at baseline and follow-up. Cox proportional hazards regression models were used to analyze the association between different SUA levels and CKD risk. Spearman rank correlation and generalized linear model analyses were used to examine the association between baseline SUA level and baseline eGFR, and the linear correlation between changes in SUA level and eGFR changes, respectively.

Results: A total of 981 subjects were included with a median age of 79 (70, 88) years. The prevalence of HUA was 6.8% (67/981). The cumulative follow-up was 2,029 person-years with a median follow-up of 2.05 years. There were 179 new CKD cases, with a cumulative incidence of 18.2% [95%CI (15.9%, 20.8%)] and an incidence density of 88.22/1,000 person-years [95%CI (76.24/1,000 person-years, 101.41/1,000 person-years)]. Cox proportional hazards regression analysis with SUA quartile grouping as the independent variable showed that compared with the lowest quartile group of baseline SUA (Q1), the hazard ratio (HR) for CKD risk in the highest quartile group (Q4) was 2.08 [95%CI (1.27, 3.41), P=0.004]. Analysis with SUA level as a continuous independent variable showed that for every 10 mol/L increase in baseline SUA, the risk of CKD increased by 4% [95%CI (2%, 7%), P<0.001]. Analysis with HUA as the independent variable showed that elderly with HUA had an increased CKD risk compared to those without HUA (HR=2.00 [95%CI (1.20, 3.24), P=0.007]). The median baseline SUA was 270.60 (223.10, 325.90) mol/L and median baseline eGFR was 84.07 (73.08, 98.38) $ml \bullet min^{-1} \bullet (1.73\ m^2)^{-1}$. Spearman rank correlation analysis showed a negative correlation between these two measures (r =-0.363, P<0.001). Generalized linear model analysis showed that for every 10 mol/L increase in baseline SUA, baseline eGFR decreased by 0.897 $ml \bullet min^{-1} \bullet (1.73\ m^2)^{-1}$ (P<0.001). During follow-up, the median ΔSUA was -3.55 (-40.60, 31.90) mol/L and median ΔeGFR was 3.49 (-8.13, 15.89) $ml \bullet min^{-1} \bullet (1.73\ m^2)^{-1}$. Spearman rank correlation analysis showed a negative correlation between these changes (r =-0.355, P<0.001). Generalized linear model analysis showed that

for every 10 mol/L increase in SUA during follow-up, eGFR decreased by 1.027 $ml \bullet min^{-1} \bullet (1.73\ m^2)^{-1}$ ($P<0.001$).

Conclusion: Elevated SUA level among the elderly is associated with an increased risk of CKD and declining eGFR in China.

Keywords: Chronic kidney disease; Hyperuricemia; Glomerular filtration rate; Aged; Cohort study

Introduction

Chronic kidney disease (CKD) has become a major global public health threat. In China, the prevalence of CKD among adults aged 18 and above is nearly 10.8%, affecting approximately 119 million people, yet the awareness rate is only 12.5% [1]. Individuals over 65 years represent the fastest-growing and largest population of end-stage renal disease patients [2-3]. As population aging intensifies in China, the increasing prevalence of hypertension, diabetes, and overweight/obesity has led to a rising incidence of CKD. Early identification and intervention of CKD risk factors are crucial for preventing and delaying CKD progression and reducing complications in the elderly.

Serum uric acid (SUA) is a product of purine nucleotide metabolism, with approximately two-thirds excreted through the kidneys [4]. Hyperuricemia (HUA) caused by elevated SUA has been confirmed as an independent risk factor for CKD development and progression [5-7]. Studies show that each 1 mg/dl increase in SUA level increases CKD risk by 19% [8], and urate-lowering therapy has demonstrated clinical benefits in delaying CKD progression [9]. However, some studies report inconsistent associations between elevated SUA and CKD risk [10-11]. Previous analyses have primarily focused on adult populations, with few cohort studies examining the relationship between SUA levels and CKD development among Chinese elderly. Therefore, this study, based on the Healthy Aging and Biomarkers Cohort Study (HABCS), a sub-cohort of the Chinese Longitudinal Healthy Longevity Survey (CLHLS), investigates the association between baseline SUA levels and their changes with CKD incidence risk and estimated glomerular filtration rate (eGFR) changes among elderly individuals in Chinese longevity areas, aiming to provide scientific evidence for CKD prevention and management in this population.

Methods

Study Population Between December 2021 and May 2022, we selected elderly individuals from the HABCS sub-cohort of CLHLS who underwent health examinations and biomedical indicator collection. This cohort conducted health examinations on individuals aged $ $65 years in eight longevity areas (including Laizhou City, Yantai, Shandong; Xiayi County, Shangqiu, Henan; Zhongxiang

City, Jingmen, Hubei; Mayang County, Huaihua, Hunan; Sanshui District, Foshan, Guangdong; Yongfu County, Guilin, Guangxi; Chengmai County, Hainan; and Rudong City, Jiangsu) in 2009, 2012, and 2014, collecting blood routine, urine routine, and plasma biochemical indicators. Since the 2009 survey did not collect urinary microalbumin (Ualb) and urinary creatinine (Ucr) to calculate the urinary albumin-to-creatinine ratio (ACR), we designated the 2012 survey as baseline.

Inclusion criteria were: (1) complete baseline SUA values; (2) complete baseline serum creatinine (Scr) values; (3) complete baseline Ualb and Ucr values. Exclusion criteria were: (1) baseline eGFR <60 ml • min^{-1} • (1.73 m^2)$^{-1}$; (2) baseline ACR $ $30 mg/g; (3) history of chronic nephritis; (4) lost to follow-up. Ultimately, 981 elderly individuals were included in the cohort study. This study was approved by the Ethics Committee of Tianjin Medical University General Hospital (Approval No.: IRB2022-WZ-118).

Data Collection We collected data through the HABCS database, including: (1) general information: demographic characteristics (age, gender), health status, and disease history (hypertension, diabetes, kidney disease, and HUA); (2) physical examination data: BMI, waist circumference, calf circumference, systolic blood pressure (SBP), and diastolic blood pressure (DBP); (3) biomedical indicators: fasting blood glucose (FBG), glycated serum protein (GSP), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), high-sensitivity C-reactive protein (hs-CRP), superoxide dismutase (SOD), vitamin D3 (VD3), white blood cell count (WBC), red blood cell count (RBC), platelet count (PLT), blood urea nitrogen (BUN), Scr, UAlb, Ucr, ACR, SUA, and urinary protein.

Definitions and Diagnostic Criteria SUA level classification: (1) Baseline SUA levels were divided into quartiles: Q1 <223 mol/L, Q2 223-270 mol/L, Q3 271-325 mol/L, Q4 $ $326 mol/L. (2) HUA was defined as baseline SUA >420 mol/L in males or >360 mol/L in females, or a history of HUA [12].

CKD diagnosis followed the 2017 "Guidelines for Screening, Diagnosis, and Prevention of Chronic Kidney Disease" and the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) criteria [13-14]: eGFR <60 ml • min^{-1} • (1.73 m^2)$^{-1}$ or ACR $ $30 mg/g or newly diagnosed CKD based on medical records. eGFR was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation suitable for Chinese populations [15]. The study endpoint was incident CKD.

Statistical Analysis We used Stata 13.0 software for statistical analysis. Non-normally distributed continuous variables were expressed as median (upper quartile, lower quartile) [M(P_{25}, P_{75})], with between-group comparisons using Kruskal-Wallis H tests. Categorical variables were expressed as frequency and percentage, with between-group comparisons using ^{2} tests. Cox propor-

tional hazards regression models were used to analyze the association between baseline SUA levels and CKD risk, with SUA quartile grouping, SUA level (continuous variable), and HUA status as independent variables. Trend tests were performed using median values of SUA quartile groups. Spearman rank correlation was used to analyze associations between baseline SUA and baseline eGFR, and between SUA changes (ΔSUA = baseline SUA - follow-up SUA) and eGFR changes (ΔeGFR = baseline eGFR - follow-up eGFR). Generalized linear models were used to analyze the association between baseline SUA and baseline eGFR, and between SUA changes and eGFR changes. All tests were two-sided, with P<0.05 considered statistically significant.

Results

Baseline Characteristics A total of 981 subjects were included, comprising 548 males (55.9%) with a median age of 79 (70, 88) years. The prevalence of HUA was 6.8% (67/981), with 7.8% (43/548) in males and 5.5% (24/433) in females (^{2}=2.018, P=0.155). The cumulative follow-up was 2,029 person-years with a median follow-up of 2.05 years (range 1.0-4.0 years). There were 179 new CKD cases, with a cumulative incidence of 18.2% [95%CI (15.9%, 20.8%)] and incidence density of 88.22/1,000 person-years [95%CI (76.24/1,000 person-years, 101.41/1,000 person-years)].

Baseline characteristics differed significantly across SUA quartile groups in terms of gender, BMI, waist circumference, calf circumference, SBP, GSP, TG, hs-CRP, VD3, WBC, PLT, Scr, Ucr, ΔSUA, ΔeGFR, and incident CKD proportion (P<0.05) .

SUA Levels and CKD Risk Cox proportional hazards regression analysis showed that compared with the lowest SUA quartile (Q1), the highest quartile (Q4) had a CKD risk HR of 2.08 [95%CI (1.27, 3.41), P=0.004], with a significant trend (P-trend=0.003). For each 10 mol/L increase in baseline SUA, CKD risk increased by 4% [95%CI (2%, 7%), P<0.001]. Elderly with HUA had increased CKD risk compared to those without HUA (HR=2.00 [95%CI (1.20, 3.24), P=0.007]) .

Baseline SUA and eGFR Association Median baseline SUA was 270.60 (223.10, 325.90) mol/L and median baseline eGFR was 84.07 (73.08, 98.38) $ml \bullet min^{-1} \bullet (1.73\ m^2)^{-1}$. Spearman rank correlation analysis showed a negative correlation (r =-0.363, P<0.001). Generalized linear model analysis showed that for each 10 mol/L increase in baseline SUA, baseline eGFR decreased by 0.897 $ml \bullet min^{-1} \bullet (1.73\ m^2)^{-1}$ (P<0.001) .

SUA Changes and eGFR Changes During follow-up, median ΔSUA was -3.55 (-40.60, 31.90) mol/L and median ΔeGFR was 3.49 (-8.13, 15.89)

$ml \bullet min^{-1} \bullet (1.73\ m^2)^{-1}$. Spearman rank correlation analysis showed a negative correlation between these changes (r =-0.355, P<0.001). Generalized linear model analysis showed that for each 10 mol/L increase in SUA during follow-up, eGFR decreased by 1.027 $ml \bullet min^{-1} \bullet (1.73\ m^2)^{-1}$ (P<0.001) .

Discussion

This study, based on the HABCS sub-cohort of CLHLS, investigated the association between baseline SUA levels and their changes with CKD incidence risk and eGFR changes among elderly individuals in Chinese longevity areas. We found that elevated baseline SUA levels and HUA were associated with increased CKD risk, and eGFR declined as SUA levels increased.

Our results showed that elderly individuals in the highest SUA quartile ($ 326$\mu mol/L$)had2.08$timeshigher$CKDriskthanthoseinthelowestquartile$[95 $6.5 mg/dl) had 6.79 times higher CKD risk [95%CI (3.45, 13.75)]. Wu et al. [17] followed 4,546 volunteers for 4 years and found that the highest SUA quartile (>5.1 mg/dl) had 2.73 times higher CKD risk [95%CI (1.65, 4.50)]. Storhaug et al. [18] assessed the association between SUA and GFR changes in the general population, finding that each 1 mg/dl increase in baseline SUA increased renal insufficiency risk by 16% [95%CI (4%, 29%)] after 13 years of follow-up.

We also found that baseline SUA levels were negatively correlated with baseline eGFR, and that during follow-up, eGFR declined as SUA levels increased. Each 10 mol/L increase in baseline SUA was associated with a 0.897 $ml \bullet min^{-1} \bullet (1.73\ m^2)^{-1}$ decrease in baseline eGFR. During follow-up, each 10 mol/L increase in SUA was associated with a 1.027 $ml \bullet min^{-1} \bullet (1.73\ m^2)^{-1}$ decline in eGFR. These findings align with previous studies. Lai et al. [16] found that each 1 mg/dl increase in baseline SUA was associated with a 1.25 $ml \bullet min^{-1} \bullet (1.73\ m^2)^{-1}$ decrease in eGFR [95%CI (-1.83 $ml \bullet min^{-1} \bullet (1.73\ m^2)^{-1}$, -0.67 $ml \bullet min^{-1} \bullet (1.73\ m^2)^{-1}$)] over 3 years of follow-up. Tsai et al. [19] reported that higher SUA levels were associated with significantly faster eGFR decline and higher renal failure risk, with each 1 mg/dl increase in baseline SUA increasing progression to renal failure risk by 7%. Ye et al. [20] also found that elevated SUA was independently associated with eGFR decline and increased new-onset CKD risk.

Potential pathological mechanisms linking elevated SUA to increased CKD risk include: (1) The kidneys are the primary excretory organ for SUA, and uric acid crystals can deposit in the kidneys causing direct nephrotoxicity and reduced renal function [21]; (2) SUA absorbed by endothelial cells inhibits nitric oxide (NO) production and accelerates its degradation, while xanthine oxidase in cytoplasm and plasma produces superoxide that reduces NO levels, leading to elevated SUA inducing renal oxidative stress and mitochondrial dysfunction, damaging endothelial cells, smooth muscle cells, and tubular cells, and activating the renin-angiotensin system [22-23]; (3) HUA can induce pre-glomerular arteriolar lesions, impairing afferent arteriole autoregulatory responses, while

increased platelet adhesion, vascular wall thickening, and hemodynamic disturbances can cause luminal occlusion and ischemia. Reduced renal perfusion is a potent vasoactive and inflammatory stimulus that can lead to tubulointerstitial inflammation and fibrosis [21,24], ultimately causing renal function decline.

This study has several limitations. First, the relatively small sample size of elderly participants may weaken the causal relationship between SUA levels and CKD risk. Second, using only single measurements of Scr and proteinuria may introduce bias in assessing true CKD incidence. Third, the median follow-up of 2.05 years is relatively short, preventing observation of end-stage renal disease events, and longer follow-up is needed to validate our findings. Future research should expand endpoint events and extend follow-up duration to continue monitoring CKD incidence in elderly populations.

In conclusion, elevated baseline SUA levels and HUA increase CKD risk among elderly individuals in Chinese longevity areas, and eGFR declines as SUA levels increase. Regular monitoring of SUA levels and early intervention to control SUA are necessary to slow future eGFR decline and reduce CKD risk in the elderly.

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