Original Paper

Gender Difference in the Association of Hyperuricemia with Chronic Kidney Disease in Southern China

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Key Words

Hyperuricemia • Chronic kidney disease • Gender • Epidemiology

Abstract

Background: The effect of hyperuricemia on chronic kidney disease (CKD) is controversial, and little is known about gender as it relates to hyperuricemia and CKD. **Methods:** This was a cross-sectional study of 7,053 adults in the general Chinese population in Southern China using a multi-stage stratified sampling method. In which associations between hyperuricemia and indicators of CKD (defined by albuminuria (urinary albumin-to -creatinine ratio $\geq 30\text{mg/g}$) or decreased modified MDRD equation estimated GFR ($<60\text{ml/min per }1.73\text{m}^2$) were tested using multivariate logistic regression. **Results:** After adjustment for potential confounders, hyperuricemia was associated with increased risk of reduced renal function and CKD but not albuminuria, with odds ratios (ORs) (95% CI) of 4.39 (3.38-5.70, $P < 0.001$), 1.54 (1.31-1.82, $P < 0.001$) and 0.96 (0.78-1.17, $P = 0.671$), respectively. The interaction between gender and hyperuricemia with CKD was significant ($P = 0.010$); and stratified analysis showed a stronger association of hyperuricemia with CKD in males (OR (95% CI): 2.04 (1.56-2.67), $P < 0.001$) than in females (1.45 (1.17-1.80), $P = 0.001$). **Conclusions:** We observed an independent association of hyperuricemia with CKD that was stronger in males, and this independent association in male might imply some gender specific mechanisms. These results should be confirmed in future prospective studies.

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Introduction

Chronic kidney disease (CKD) is increasing worldwide, and is a major public health problem [1]. The prevalence rate of CKD in China varies between 10.8% and 19% [2-5]. Identifying modifiable risk factors of CKD may elucidate preventive strategies. Hyperuricemia is associated with confirmed CKD risk factors such as hypertension and diabetes [6]. However, the relationship of hyperuricemia with CKD has been controversial, with some studies reporting that hyperuricemia is an independent risk factor of incident CKD [7-11] but others showing no statistically significant relationship between hyperuricemia and incident CKD [12]. Furthermore, little is known about gender difference as it relates to hyperuricemia and CKD.

We examined the independent association between hyperuricemia and CKD in a cross-sectional study of 7053 general adults in southern China and investigated the gender interaction in this relation.

Subjects and Methods

Study population

A cross-sectional study of CKD and associated risk factors in the general adult population in urban city of Guangzhou and rural area of Zhuhai in Guangdong province (southern China) was conducted from July 2006 to June 2007. Subjects were local residents aged 20 years or older who had lived in the region for at least 5 years. Subject sampling, recruitment and evaluation have been described previously [3]. Briefly, twelve communities in Guangzhou and 4 villages in Zhuhai were randomly selected using a multistage, stratified sampling method. Then, a simple randomized method was used to select households from the chosen communities or villages, and all subjects fulfilling the inclusion criteria were selected. Lastly, 6311 subjects in Guangzhou and 1214 subjects in Zhuhai were enrolled into this study (total of 7525 subjects). Of these participants, 7053 (93.7%) subjects completed the entire survey. Both Guangzhou and Zhuhai are two major big cities in Guangdong province in southern China, people living there have similar life styles, and there is no statistical significance in demographic and socioeconomic characteristics between these two cities (data not shown). We selected the urban citizens of Guangzhou city and the rural population of Zhuhai city as the representative sample population from southern China, and when we pooled the 7053 subjects for the statistical analyses, the city of residence was still considered as a potential confounding factor in the multivariate regression analysis. The study was approved by the Human Ethics Committees of Sun Yat-sen University (Guangzhou, China). Written informed consent was obtained from all participants.

Measurements

Screening protocol and evaluation criteria were described previously [3]. Staffs in this study were doctors and medical students, who received intensive training in epidemiologic screening methods. Data were collected at local health stations or community clinics. The standard questionnaire was used during the face-to-face interview to collect socio-demographic status, lifestyle habits, health history and medications for each subject. Anthropometric measurements were obtained using standard protocols and techniques. After removal of shoes and heavy clothing, each subject underwent weight, height and waist measurements, using a calibrated scale. Body mass index (BMI) was calculated as weight in kilograms divided by height squared in squared meters. A fasting venous blood sample was collected for measuring various biomarkers. A clean-catch, midstream, morning urine specimen was collected for dipstick urinalysis (Roche Diagnostics, Mannheim, Germany) and microscopic analysis at the local survey site. All blood and urine samples were refrigerated at -20°C , transferred and tested in the laboratory of the First Affiliated Hospital, Sun Yat-sen University. Urinary albumin and creatinine were measured on a morning urine sample using an automatic analyzer (COBAS INTEGRA 400 plus, Roche, Basel, Switzerland). Urinary creatinine was measured by Jaffe's kinetic method, and albuminuria was measured by immunoturbidimetric methods. Urinary albumin-to-creatinine ratio (ACR, milligram per gram) was calculated. Microalbuminuria and macroalbuminuria were defined according to the guideline of American Diabetes Association as an increase in ACR between 30 and 299 mg/g and 300 mg/g or over, respectively.

Serum uric acid was measured by the auto-analyzer (COBAS INTEGRA 400 plus, Roche, Basel, Switzerland). Serum creatinine (Scr) was measured using the same method as that for urinary creatinine. Before the study, the laboratory in our center calibrated serum creatinine measurements with samples at the laboratory of the Peking University First Hospital, where the modified equation was developed [3, 13]. Estimated glomerular filtration rate (eGFR) was calculated using a modification of the Modification of Diet in Renal Disease (MDRD) equation based on the data from Chinese subjects with CKD [13], defined as $eGFR (mL/min/1.73 m^2) = 175 \times Scr (mg/dL)^{-1.234} \times age(year)^{-0.179}$ [female $\times 0.79$].

Serum fasting blood glucose, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride were measured by auto-analyzer (COBAS INTEGRA 400 plus, Roche, Basel, Switzerland). Diabetes was defined as the use of insulin or oral hypoglycaemic agents or a fasting plasma glucose ≥ 7 mmol/L, and/or 2-h postprandial plasma glucose ≥ 11.1 mmol/L. Hyperlipidemia was defined as the presence of either hypercholesterolemia (serum total cholesterol ≥ 5.72 mmol/L) or hypertriglyceridemia (serum triglyceride ≥ 1.70 mmol/L). Arterial blood pressure was measured with a mercury sphygmomanometer after sitting for at least 15 minutes. Blood pressure measurements were taken according to the Joint National Committee VII criteria (JNC VII) [14]. Three readings were taken at 5-min intervals. The mean of the three measurements was recorded. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg, or self-reported diagnosis of high blood pressure and use of antihypertensive medication [14].

Definitions of Hyperuricemia and Chronic Kidney Disease

Hyperuricemia was defined as the serum uric acid level >7.0 mg/dL in males and >6.0 mg/dL in females [15]. CKD was defined as the presence of either decreased estimated GFR or albuminuria [1]. Albuminuria was defined as the presence of either microalbuminuria (urinary albumin-to-creatinine ratio (ACR) between 30 and 299 mg/g) or macroalbuminuria (ACR greater than 300 mg/g). Reduced renal function was defined as an eGFR <60 mL/min/1.73 m².

Statistical Analysis

Data entry and management were performed using Epidata software, version 3.0 (Epidata Association, Odense, Denmark). Data were presented as the mean $\pm$ standard error for continuous variables and as proportions for categorical variables. Differences between subjects were analyzed using one way ANOVA for continuous variables and chi-square test for categorical variables. Multivariate logistic regression was used to calculate adjusted odds ratios (ORs) and 95% confidence intervals (CI) of reduced renal function, albuminuria and CKD in different models with adjustment for the potential confounders. In model 1, city of residence, age, gender and educational level were adjusted for; in model 2, smoking and drinking habits were further adjusted for; finally, in model 3, BMI, hypertension, hyperlipidemia, diabetes and medications used were further adjusted for. To investigate whether there was significant gender difference in association between hyperuricemia and CKD, the interaction term between hyperuricemia and gender was tested. $P < 0.05$ was considered significant. All statistical analyses were performed using SPSS version 17.0 (SPSS, Inc., Chicago, IL, USA).

Results

Subject characteristics by gender

Demographic, lifestyle characteristics of subjects by gender are shown in Table 1. Of the 7,053 participants, 4,726 (67.0%) were female. The mean age ($\pm$ SD) of women and men were 50.5 (± 12.4) years and 53.0 (± 13.4) years, respectively. The crude prevalence of CKD was 13.7% in men and 10.4% in women. Male subjects had higher levels of educational attainment, and were more likely to smoke and drink than female subjects. Men were more likely to be suffered from hypertension, obesity, hyperlipidemia and diabetes when compared with women. Males had significantly higher level of serum uric acid (mean $\pm$ SD: 397.1 $\pm$ 91.6 vs. 319.6 $\pm$ 84.8, $P < 0.001$) than females. The prevalence rate of hyperuricemia was also significantly higher in men than in women (38.7% vs. 28.6%, $P < 0.001$).

Table 1. Demographic, lifestyle and clinical characteristics of subjects by gender

Variables	Female	Male	Total	P value
Demographics				
N (%)	4726 (67.0%)	2327 (33.0%)	7053 (100.0%)	
Age (years)	50.5±12.4	53.0±13.4	51.3±12.8	<0.001
Education categories, %				<0.001
Illiteracy/Elementary school	28.8%	16.0%	24.6%	
Middle school	29.2%	27.9%	28.8%	
High school	29.7%	32.6%	30.6%	
College or above	12.3%	23.5%	16.0%	
Life style				
Ever smoking, %	2.3%	57.0%	20.4%	<0.001
Ever drinking, %	3.0%	27.3%	11.0%	<0.001
Clinical characteristics				
Systolic blood pressure(mmHg)	123.8±20.9	126.2±18.7	124.6±20.2	<0.001
Diastolic blood pressure(mmHg)	78.5±10.6	81.5±10.7	79.5±10.7	<0.001
Hypertension, %	30.1%	35.2%	31.8%	<0.001
BMI (kg/m ²)	23.3±3.5	23.7±3.2	23.4±3.4	<0.001
Waist circumference (cm)	77.3±15.6	82.4±9.2	79.0±14.0	<0.001
Serum creatinine (μmol/L)	58.7±12.2	79.8±15.3	65.6±16.6	<0.001
Cholesterol (mmol/L)	5.8±1.2	5.5±1.1	5.6±1.2	<0.001
Triglyceride (mmol/L)	1.4±1.0	1.7±1.2	1.5±1.1	<0.001
HDL	1.6±0.4	1.4±0.4	1.6±0.5	<0.001
LDL	3.6±1.0	3.6±1.0	3.6±1.0	0.260
Hypercholesterolemia, %	44.9%	40.4%	43.4%	<0.001
Hyperlipidemia, %	53.6%	56.1%	54.4%	0.045
Fasting blood glucose (mmol/L)	5.5±1.4	5.6±1.6	5.6±1.5	0.073
Diabetes Mellitus, %	9.2%	10.6%	9.6%	0.060
Blood uric acid (μmol/L)	319.6±84.8	397.1±91.6	345.2±94.4	<0.001
Hyperuricemia, %	28.6%	38.7%	31.9%	<0.001
Reduced renal function (eGFR<60mL/min/1.73m ²), %	3.1%	8.4%	4.9%	<0.001
Albuminuria (ACR>30mg/g), %	8.1%	6.9%	7.8%	0.073
CKD, %	10.4%	13.7%	11.5%	<0.001

Subjects with missing data were excluded. All percentages are column percentage; except for percentages, all values are mean±s.d. Abbreviations: CKD, chronic kidney disease; BMI, body mass index; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol.

Demographic and clinical characteristics according to presence of reduced eGFR, albuminuria or CKD

Differences in demographic and clinical characteristics of subjects stratified by presence of reduced eGFR, albuminuria and CKD are presented in Table 2. Increasing age and lower educational attainment were associated with significantly higher prevalence of reduced eGFR, albuminuria and CKD. A history of smoking was also associated with a higher

Table 2. Demographic, lifestyle and clinical characteristics of subjects by reduced renal function, albuminuria and CKD.

Variables	Reduced renal function			Albuminuria			CKD		
	Yes	No	P value	Yes	No	P value	Yes	No	P value
Demographics									
N (%)	343 (4.9%)	6710 (95.1%)		549 (7.8%)	6504 (92.2%)		814 (11.5%)	6239 (88.5%)	
Male gender, %	56.9	31.7	<0.001	29.5	33.2	0.073	39.2	32.2	<0.001
Age (years)	62.8±9.8	50.8±12.7	<0.001	56.9±12.4	50.9±12.7	<0.001	58.7±12.0	50.4±12.6	<0.001
Education categories, %			0.007						<0.001
Illiteracy/Elementary school	30.4	24.3		40.0	23.3		35.8	23.1	
Middle school	25.4	29.0		25.9	29.0		26.2	29.1	
High school	25.1	30.9		23.5	31.2		23.5	31.5	
College or above	19.2	15.9		10.7	10.7		14.5	16.3	
Life style									
Ever smoking, %	35.7	19.6	<0.001	20.1	20.4		25.8	19.7	<0.001
Ever drinking, %	13.6	10.9	0.077	10.3	11.1		11.7	10.9	0.279
Clinical characteristics									
Systolic blood pressure (mmHg)	136.2±22.6	124.0±19.9	<0.001	138.1±25.2	123.5±19.3	<0.001	136.2±23.9	123.1±19.2	<0.001
Diastolic blood pressure (mmHg)	82.7±11.9	79.4±10.6	<0.001	84.7±12.8	79.1±10.4	<0.001	83.6±12.4	79.0±10.4	<0.001
Hypertension, %	58.5	30.4	<0.001	53.0	30.0	<0.001	53.0	29.0	<0.001
BMI (kg/m ²)	24.6±3.4	23.4±3.4	<0.001	24.2±3.7	23.4±3.4	<0.001	24.3±3.5	23.3±3.4	<0.001
Waist circumference (cm)	83.7±9.7	78.8±14.1	<0.001	81.6±10.2	78.8±14.3	<0.001	82.1±10.0	78.6±14.4	<0.001
Serum creatinine (μmol/L)	106.7±22.9	63.6±13.1	<0.001	71.7±27.3	65.1±15.2	<0.001	81.8±28.1	63.6±13.1	<0.001
Cholesterol (mmol/L)	5.9±1.1	5.6±1.2	<0.001	5.9±1.2	5.6±1.1	<0.001	5.9±1.2	5.6±1.1	<0.001
Triglyceride (mmol/L)	1.8±1.2	1.5±1.1	<0.001	1.7±1.3	1.5±1.0	<0.001	1.7±1.2	1.5±1.0	<0.001
HDL	1.4±0.5	1.6±0.4	<0.001	1.5±0.4	1.6±0.4	0.107	1.5±0.4	1.6±0.4	<0.001
LDL	3.9±1.0	3.6±1.0	<0.001	3.8±1.1	3.6±1.0	<0.001	3.8±1.1	3.5±1.0	<0.001
Hypercholesterolemia, %	53.1	42.9	<0.001	51.4	42.7	<0.001	51.9	42.3	<0.001
Hyperlipidemia, %	65.0	53.9	<0.001	61.4	53.8	<0.001	62.7	53.4	<0.001
Fasting blood glucose (mmol/L)	5.8±1.4	5.5±1.5	0.006	6.3±2.7	5.5±1.3	<0.001	6.1±2.3	5.5±1.3	<0.001
Diabetes Mellitus, %	19.2	9.1	<0.001	21.7	8.6	<0.001	19.9	8.3	<0.001
Blood uric acid (μmol/L)	462.0±108.7	339.2±89.6	<0.001	354.8±102.6	344.3±93.6	0.012	389.7±115.2	339.4±89.7	<0.001
Hyperuricemia, %	72.3	29.8	<0.001	35.8	31.6	0.023	47.1	29.9	<0.001

Subjects with missing data were excluded. All percentages are column percentages; except for percentages, all values are means±s.d. Abbreviations: CKD, chronic kidney disease; BMI, body mass index; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol.

prevalence of reduced eGFR and CKD. Generally, subjects with reduced eGFR, albuminuria or CKD had significantly higher levels of BP, BMI, cholesterol, triglyceride, fasting blood glucose and blood uric acid, as well as higher prevalence of hypertension, obesity, hyperlipidemia, diabetes mellitus and hyperuricemia, as compared with subjects without these conditions.

Table 3. Adjusted odds ratios (ORs) with associated 95% confidence interval (CI) for reduced renal function, albuminuria and CKD

Variables	Reduced renal function			Albuminuria			CKD		
	OR	95%CI	P value	OR	95%CI	P value	OR	95%CI	P value
Model 1									
Gender (male vs. female)	2.49***	1.94-3.19	<0.001	0.79*	0.64-0.97	0.027	1.23*	1.04-1.45	0.014
Hyperuricemia (yes vs. no)	4.57***	3.54-5.90	<0.001	1.03	0.85-1.26	0.749	1.63***	1.40-1.94	<0.001
Gender*Hyperuricemia			0.388			0.651			0.019
Model 2									
Gender (male vs. female)	2.23***	1.64-3.04	<0.001	0.74*	0.56-0.98	0.035	1.12	0.90-1.39	0.296
Hyperuricemia (yes vs. no)	4.62***	3.58-5.97	<0.001	1.03	0.85-1.26	0.737	1.64***	1.40-1.92	<0.001
Gender*Hyperuricemia			0.455			0.628			0.014
Model 3									
Gender (male vs. female)	2.28***	1.67-3.11	<0.001	0.76	0.57-1.01	0.055	1.15	0.92-1.43	0.216
Hyperuricemia (yes vs. no)	4.39***	3.38-5.70	<0.001	0.96	0.78-1.17	0.671	1.54***	1.31-1.82	<0.001
Gender*Hyperuricemia			0.474			0.549			0.010

Model 1 was adjusted for city of residence, age, and educational level. Model 2 was adjusted for city of residence, age, educational level, ever smoking and ever drinking. Model 3 was adjusted for city of residence, age, educational level, ever smoking, ever drinking, BMI, hypertension, hyperlipidemia, diabetes and medications. *p<0.05, **p<0.01, ***p<0.001

Table 4. Adjusted odds ratios (ORs) with associated 95% confidence interval (CI) of hyperuricemia for CKD stratified by gender

Variables	Female			Male		
	OR	95%CI	P value	OR	95%CI	P value
Model 1	1.63***	1.33-2.00	<0.001	2.04***	1.59-2.61	<0.001
Model 2	1.64***	1.34-2.01	<0.001	2.05***	1.60-2.64	<0.001
Model 3	1.45**	1.17-1.80	0.001	2.04***	1.56-2.67	<0.001

Model 1 was adjusted for city of residence, age and educational level. Model 2 was adjusted for city of residence, age, educational level, ever smoking and ever drinking. Model 3 was adjusted for city of residence, age, educational level, ever smoking, ever drinking, blood pressure category, BMI, hypertension, hyperlipidemia, diabetes and medications. **p<0.01, ***p<0.001

Association between hyperuricemia and CKD

Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) of gender and hyperuricemia for reduced renal function, albuminuria and CKD are shown in Table 3. In model 1 (adjustment for city of residence, age, and educational level), males were more likely to suffer from reduced renal function (OR (95% CI): 2.49 (1.94-3.19), P<0.001) and CKD (1.23 (1.04-1.45), P=0.014), but were less likely to have albuminuria (0.79 (0.64-0.97), P=0.027) compared to females. Hyperuricemia was associated with increased OR for reduced renal function (4.57 (3.54-5.90), P<0.001) and CKD (1.63 (1.40-1.94), P<0.001) but not albuminuria (1.03 (0.85-1.26), P=0.749).

In model 2 (which included additional adjustments for histories of smoking and alcohol drinking) and model 3 (with additional adjustments for BMI, hypertension, hyperlipidemia, diabetes and medications), the results were similar to those in model 1. Hyperuricemia was significantly associated with increased risk for reduced renal function and CKD; however, male gender was associated with increased risk of reduced renal function only but not albuminuria or CKD.

Gender difference in the association of hyperuricemia with CKD

An interaction between gender and hyperuricemia was identified for all three models for CKD (P=0.019 in model 1, P=0.014 in model 2, and P=0.010 in model 3) but not for reduced renal function or albuminuria, documenting that the association between hyperuricemia and CKD was different for male and females (Table 3).

Stratified analyses of the association between hyperuricemia and CKD by gender are shown in Table 4. All three models showed that the association of hyperuricemia with CKD

in males was significantly stronger than that in females, with adjusted ORs for CKD of 2.04 (1.56-2.67, $P < 0.001$) and 1.45 (1.17-1.80, $P = 0.001$), respectively (model 3).

Discussion

We found that hyperuricemia was independently associated with increased risk of reduced renal function and CKD but not albuminuria. Furthermore, there was a statistically significant interaction between gender and hyperuricemia on CKD; and the stratified analysis showed the association of hyperuricemia with CKD in males was significantly stronger than in females.

Although hyperuricemia is associated with the confirmed CKD risk factors such as hypertension and diabetes [6], the independent effect of hyperuricemia on CKD is controversial. Most epidemiologic studies have found that hyperuricemia is an independent risk factor for the onset of CKD, while the associations of hyperuricemia with declined eGFR or increased ESRD is supported by several cohort studies [7-10, 12, 16-19], but not all [20, 21]. Hsu et al. found that increased serum uric acid is an independent risk factor for ESRD over a 25 year follow-up period evaluated in a cohort of 177,570 participants [18]. However, the data of 840 participants in the MDRD Study did not confirm that uric acid levels to be an independent risk factor for progression to ESRD despite a 10 year follow-up [20]. In the present cross-sectional study we found that hyperuricemia was associated with reduced eGFR but not with albuminuria. A similar observation was noted in subjects with type 1 diabetes [22]. These findings may be result from the effect of eGFR decline on hyperuricemia. Unfortunately, the observational studies are unable to address this concern, more prospective interventional studies need to be performed to address this question.

A different effect of gender on progression of CKD has been reported [23-25]. However, little is known about gender difference in the effect of hyperuricemia on CKD. The present results suggest that uric acid may have independent effects on CKD prevalence more prominent in men. We found the association of hyperuricemia with CKD in males was significantly stronger than that in females, with the adjusted ORs of hyperuricemia for CKD were 2.04 (1.56-2.67) and 1.45 (1.17-1.80) for males and female, respectively. Male gender was associated with increased risk of reduced eGFR and the association of hyperuricemia with CKD was significantly stronger in males. Several observational cohort studies have also examined the gender difference in hyperuricemia predicted an increased risk of CKD progression. Interestingly, in a report from a pooled study of two separate cohort studies (the Atherosclerosis Risks in Communities and the Cardiovascular Health Study) with 13,338 participants, Weiner et al. found that baseline serum uric acid was associated with a significantly increased risk of CKD in women (OR (95% CI): 1.10 (1.01-1.18)) but not in men (1.05 (0.96-1.1)), however, the interaction term of serum uric acid and gender was not statistically significant ($P = 0.8$). Iseki K et al. reported that hyperuricemia was an independent risk factor for ESRD in women (adjusted HR 5.78, 95% CI 2.3-14.4; $P < 0.001$) but not in men (HR 2.0, 95% CI 0.90-4.45; $P = \text{not significant}$) [16]. A potential explanation for these conflicted results of relationships of hyperuricemia with the prevalence or prognosis of CKD, may lie in the fact that estrogen is a uricosuric agent, and the possible mechanism for the gender difference in the hyperuricemia with the progression of CKD in cohort study might be, at least in part, linked to menopause.

Notably, animal study suggested that there is gender-divergent expression of Urat1 transporter (which is important uric acid transport and has been shown to transport uric acid into vascular smooth muscle cells)[26, 27]. The male-predominant of Urat1 transporters in mouse kidneys is primarily due to stimulatory effects of androgens[27]. That imply the potential mechanism of gender hormonal influences on the handling of uric acid by kidney. However, the underlying mechanisms of gender difference of uric acid on the CKD could not be determined in the present study, and remain a matter for further investigation.

The present study has several limitations. Firstly, the cross-sectional study is naturally incapable of concluding whether hyperuricemia is a cause or a consequence of reduced renal function and CKD. Therefore, the results should be confirmed in future prospective cohort and interventional studies. Second, only one urine sample examination was obtained for each subject, which made it impossible to confirm whether the albuminuria was persistent. Results from NHANES III [28] demonstrated that using two urine tests to confirm kidney damage revealed a lower prevalence rate of stage 1 and stage 2 CKD, compared with using one urine sample. Third, use of the same cut-off value of microalbuminuria for men and women leads to higher values of prevalence for women than men. Furthermore, our study is limited by oversampled female subjects and using the modified MDRD study equation which may underestimate GFR at higher values. However, the principle aim of the present study was not to estimate the prevalence of CKD but to test the interrelationship between hyperuricemia and CKD. And to the best of our knowledge, the interaction between hyperuricemia and gender has not been studied in Chinese population-based CKD study.

In summary, hyperuricemia is independently associated with reduced renal function but not albuminuria in present studied population, and the interaction between gender and hyperuricemia with CKD was significant with a stronger association of hyperuricemia with CKD in males than in females. Our studies suggest a gender-specific linking mechanism, which emphasizing the need for further prospective studies.

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References

- 1 Levey AS, Atkins R, Coresh J, Cohen EP, Collins AJ, Eckardt KU, Nahas ME, Jaber BL, Jadoul M, Levin A, Powe NR, Rossert J, Wheeler DC, Lameire N, Eknoyan G: Chronic kidney disease as a global public health problem: approaches and initiatives—a position statement from Kidney Disease Improving Global Outcomes. *Kidney Int* 2007;72:247-259.
- 2 Zhang L, Wang F, Wang L, Wang W, Liu B, Liu J, Chen M, He Q, Liao Y, Yu X, Chen N, Zhang JE, Hu Z, Liu F, Hong D, Ma L, Liu H, Zhou X, Chen J, Pan L, Chen W, Wang W, Li X, Wang H: Prevalence of chronic kidney disease in China: a cross-sectional survey. *Lancet* 2012;379:815-822.
- 3 Chen W, Chen W, Wang H, Dong X, Liu Q, Mao H, Tan J, Lin J, Zhou F, Luo N, He H, Johnson RJ, Zhou SF, Yu X: Prevalence and risk factors associated with chronic kidney disease in an adult population from southern China. *Nephrol Dial Transplant* 2009;24:1205-1212.
- 4 Zhang L, Zhang P, Wang F, Zuo L, Zhou Y, Shi Y, Li G, Jiao S, Liu Z, Liang W, Wang H: Prevalence and factors associated with CKD: a population study in Beijing. *Am J Kidney Dis* 2008;51:373-384.
- 5 Chen W, Liu Q, Wang H, Chen W, Johnson RJ, Dong X, Li H, Ba S, Tan J, Luo N, Liu T, He H, Yu X: Prevalence and risk factors of chronic kidney disease: a population study in Tibetan population. *Nephrol Dial Transplant*. 2011;26:1592-1599.
- 6 Johnson RJ, Segal MS, Srinivas T, Ejaz A, Mu W, Roncal C, Sánchez-Lozada LG, Gersch M, Rodriguez-Iturbe B, Kang DH, Acosta JH: Essential hypertension, progressive renal disease, and uric acid: a pathogenetic link? *J Am Soc Nephrol* 2005;16:1909-1919.

- 7 Weiner DE, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS: Uric acid and incident kidney disease in the community. *J Am Soc Nephrol* 2008;19:1204-1211.
- 8 Chang HY, Tung CW, Lee PH, Lei CC, Hsu YC, Chang HH, Yang HF, Lu LC, Jong MC, Chen CY, Fang KY, Chao YS, Shih YH, Lin CL: Hyperuricemia as an independent risk factor of chronic kidney disease in middle-aged and elderly population. *Am J Med Sci*. 2010;339:509-515.
- 9 Obermayr RP, Temml C, Gutjahr G, Knechtelsdorfer M, Oberbauer R, Klauser-Braun R: Elevated uric acid increases the risk for kidney disease. *J Am Soc Nephrol* 2008;19:2407-2413.
- 10 Mok Y, Lee SJ, Kim MS, Cui W, Moon YM, Jee SH: Serum uric acid and chronic kidney disease: the Severance cohort study. *Nephrol Dial Transplant* 2011;27:1831-1835.
- 11 Sonoda H, Takase H, Dohi Y, Kimura G: Uric acid levels predict future development of chronic kidney disease. *Am J Nephrol* 2011;33:352-357.
- 12 Chonchol M, Shlipak MG, Katz R, Sarnak MJ, Newman AB, Siscovick DS, Kestenbaum B, Carney JK, Fried LF: Relationship of uric acid with progression of kidney disease. *Am J Kidney Dis* 2007;50:239-247.
- 13 Ma YC, Zuo L, Chen JH, Luo Q, Yu XQ, Li Y, Xu JS, Huang SM, Wang LN, Huang W, Wang M, Xu GB, Wang HY: Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. *J Am Soc Nephrol* 2006;17:2937-2944.
- 14 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee: The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560-2572.
- 15 Chuang SY, Chen JH, Yeh WT, Wu CC, Pan WH: Hyperuricemia and increased risk of ischemic heart disease in a large Chinese cohort. *Int J Cardiol* 2012;154:316-321.
- 16 Iseki K, Ikemiya Y, Inoue T, Iseki C, Kinjo K, Takishita S: Significance of hyperuricemia as a risk factor for developing ESRD in a screened cohort. *Am J Kidney Dis* 2004;44:642-650.
- 17 Ben-Dov IZ, Kark JD: Serum uric acid is a GFR-independent long-term predictor of acute and chronic renal insufficiency: the Jerusalem Lipid Research Clinic cohort study. *Nephrol Dial Transplant*. 2011;26:2558-2566.
- 18 Hsu CY, Iribarren C, McCulloch CE, Darbinian J, Go AS: Risk factors for end-stage renal disease: 25-year follow-up. *Arch Intern Med* 2009;169:342-350.
- 19 See LC, Kuo CF, Chuang FH, Shen YM, Ko YS, Chen YM, Yu KH: Hyperuricemia and metabolic syndrome: associations with chronic kidney disease. *Clin Rheumatol* 2011;30:323-330.
- 20 Madero M, Sarnak MJ, Wang X, Greene T, Beck GJ, Kusek JW, Collins AJ, Levey AS, Menon V: Uric acid and long-term outcomes in CKD. *Am J Kidney Dis* 2009;53:796-803.
- 21 Sturm G, Kollerits B, Neyer U, Ritz E, Kronenberg F: Uric acid as a risk factor for progression of non-diabetic chronic kidney disease? The Mild to Moderate Kidney Disease (MMKD) Study. *Exp Gerontol* 2008;43:347-352.
- 22 Rosolowsky ET, Ficociello LH, Maselli NJ, Niewczas MA, Binns AL, Roshan B, Warram JH, Krolewski AS: High-normal serum uric acid is associated with impaired glomerular filtration rate in nonproteinuric patients with type 1 diabetes. *Clin J Am Soc Nephrol* 2008;3:706-713.
- 23 Neugarten J, Acharya A, Silbiger SR: Effect of gender on the progression of nondiabetic renal disease: a meta-analysis. *J Am Soc Nephrol* 2000;11:319-329.
- 24 Silbiger S, Neugarten J: The impact of gender on the progression of chronic renal disease. *Am J Kidney Dis* 1995;25:515-533.
- 25 Eriksen BO, Ingebrechtsen OC: The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. *Kidney Int* 2006;69:375-382.
- 26 Cheng X, Maher J, Chen C, Klaassen CD: Tissue distribution and ontogeny of mouse organic anion transporting polypeptides (Oatps). *Drug Metab Dispos* 2005;33:1062-1073.
- 27 Cheng X, Klaassen CD: Tissue Distribution, Ontogeny, and Hormonal Regulation of Xenobiotic Transporters in Mouse Kidneys. *Drug Metab Dispos* 2009;37:2178-2185.
- 28 Mazzali M, Hughes J, Kim YG, Jefferson JA, Kang DH, Gordon KL, Lan HY, Kivlighn S, Johnson RJ: Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. *Hypertension* 2001;38:1101-1106.