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Association between serum uric acid/HDL-cholesterol ratio and chronic kidney disease: a cross-sectional study based on a health check-up population

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ABSTRACT

Objective Evidence suggests that both serum uric acid (SUA) and high-density lipoprotein cholesterol (HDL-C) are risk factors for chronic kidney disease (CKD). The SUA-to-HDL-C ratio (UHR) has recently attracted attention as a new biomarker to evaluate the role between inflammatory and anti-inflammatory substances. Thus, we explored the association between UHR and CKD in a large Chinese population.

Design A cross-sectional study.

Setting Annual health check-up population in Nanjing.

Participants 19 458 individuals who underwent an annual health check-up in 2019 were included in our study.

Main outcome measure CKD was diagnosed according to an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2.

Results Correlation analysis showed that UHR was negatively associated with eGFR after adjusting for confounding factors (r=−0.34). In addition, participants in the highest quartile of UHR had a higher risk of CKD than those in the lowest quartiles (OR=9.28, p<0.001).

Conclusion We found that high UHR values were positively associated with CKD risk in health check-up population. An increased UHR may be a useful measure by which to assess CKD risk in the preclinical stage.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first cross-sectional study based on a large sample size of over 10 000 individuals assessing the association between serum uric acid/high-density lipoprotein cholesterol ratio and chronic kidney disease risk.
⇒ The exposure distribution of all risk factors was estimated on the basis of original data.
⇒ The findings are only statistical associations and do not imply causality because of the cross-sectional study design.
⇒ Some confounding variables include important variables such as marital status, education level, household income, smoking, drinking and nutritional status.
⇒ Residual confounding cannot be fully ruled out, although the adjusted ORs and the consistency of the results across various strata minimise this possibility.

INTRODUCTION

Chronic kidney disease (CKD), the third most prevalent chronic disease worldwide, is characterised by irreversible changes in kidney structure and function.[1] In China, the estimated prevalence of CKD reached approximately 10.8%, resulting in a high social burden.[2 3] Inflammation is a prominent feature of CKD, which affects 10%–15% of the population worldwide.[4–6] Studies demonstrated that it already exists in the early stage of CKD, and deteriorates along with the decline of kidney function.[7–9]

For the early detection of CKD, diverse researchers have directed their efforts to the identification of potential biomarkers related to the incidence or progression of CKD.[10 11] Important and differential metabolites, including uric acid (UA) and indicators of dyslipidaemia, have been identified in patients with CKD in the past decades.[12–18] Several longitudinal and cross-sectional studies supported that UA, a product of purine metabolism, is involved in the incidence of CKD with an OR of 1.07,[19] while high-density lipoprotein cholesterol (HDL-C) decreased the odds of developing kidney disease by 20%.[20]

However, in patients with CKD, such associations are complex and even contradictory.[21–23] Liu *et al* identified that hyperuricaemia was not significantly associated with patients in stage 3–5 CKD.[24] A U-shaped relationship may exist between HDL-C and the mortality of CKD.[25] It was speculated that a single parameter of serum UA (SUA) or HDL-C does not predict the occurrence of CKD very well. Mechanistic studies further showed that the adverse cardiovascular effects

of hyperuricaemia and low HDL-C are mainly through the synergistic effect of endothelial oxidative damage and reduced insulin sensitivity.[26–29] In addition, recent studies showed that SUA-to-HDL-C ratio (UHR) is an inflammatory and oxidative stress marker for CKD. Thus, the combined measurement of SUA and HDL-C may have a better predictive value for CKD than the single parameter alone.

Recently, studies have reported that UHR can be used as an independent indicator of diabetic control and metabolic syndrome.[30 31] However, few studies have investigated the prognostic value of the UHR in CKD. Thus, a cross-sectional study was performed to explore the association between UHR and CKD risk in a large-scale health check-up population.

METHODS

Study population

We conducted a single-center, cross-sectional study based on a database of 28 821 Chinese individuals in the health management institution of the Jiangsu Province Geriatric Hospital (Nanjing, China) from January to December 2019. Participants with missing data on height (n=2646), systolic blood pressure (SBP) (n=18), fasting plasma glucose (FPG) (n=420), triglycerides (TGs) (n=5556), HDL-C (n=506) or SUA (n=217) were excluded from our study, and eventually 19 458 individuals were included.

Clinical assessment

We derived demographic, clinical and laboratory datasets from the records of the Jiangsu Province Geriatric Hospital. Height, body weight and blood pressure were measured by trained nurses as previously reported.[32] Body mass index (BMI) was calculated as weight in kilograms divided by height in metres squared. FPG, the lipid profile (HDL-C, low-density lipoprotein cholesterol (LDL-C), TG and total cholesterol (TC)), SUA and serum creatinine (Scr) were measured after an overnight fast of more than 11 hours. The estimated glomerular filtration rate (eGFR) was measured by Scr, age and gender based on the equations of Modification of Diet in Renal Disease.[33]

Outcomes and definitions

We defined hypertension as SBP ≥140 mm Hg, diastolic blood pressure (DBP) ≥90 mm Hg or a self-reported history of hypertension. Type 2 diabetes mellitus was defined as FPG ≥7.0 mmol/L or a self-reported history of diabetes and the exclusion of type 1 diabetes. In this study, the CKD progression was defined as exacerbation in the eGFR category based on the Kidney Disease: Improving Global Outcome guidelines.[34] eGFR categories were defined as G3: eGFR 30–60, G4: 15–30, and G5: <15 mL/min/1.73 m^2. Patients meeting the criteria with an eGFR <60 mL/min/1.73 m^2 were classified as CKD group; the rest were non-CKD group. Among the patients, they were further categorised into the moderate and severe CKD groups, with which moderate referred to patients with G3, severe referred to those with G4 and G5.

Statistical analysis

UHR was calculated by dividing SUA (mg/dL) by HDL-C (mg/dL). To achieve similar distributions of UHR between women and men, we further divided UHR levels by sex-specific tertiles as follows: quartile 1: ≤10.96% (men) and ≤6.47% (women); quartile 2: 10.96%–13.74% (men) and 6.47%–8.17% (women); quartile 3: 13.74%–17.06% (men) and 8.17%–10.39% (women); and quartile 4: ≥17.06% (men) and ≥10.39% (women). We first used the 'nortest' package to test normality of the continuous data. Then, characteristics of the general population are reported as the mean±SD (normal distribution) or median with IQR (non-normal distribution) for continuous variables or as a percentage for categorical variables, as appropriate. To examine differences between tertiles, we used one-way analysis of variance (normal distribution) or the Kruskal-Wallis test (non-normal distribution) for continuous variables, and used the chi-squared test for categorical variables. Univariate and multiple logistic regression analyses were applied to test the association between the UHR index and CKD. The correlations between the three parameters (SUA, HDL-C and UHR) and eGFR levels were determined through Pearson's analysis. To assess the shape of the relationship between UHR and CKD risk, we plotted a restricted cubic spline curve in the logistic regression model. We also employed ordinal logistic regression to determine associations between UHR and moderate and severe CKD groups. The cut-off values of UHR for predicting CKD were determined based on receiver operating characteristic (ROC) curves.

In our study, we used R software (V.3.0.2) to analyse the data and set the significance level at $p<0.05$.

Patient and public involvement

No patients were involved in the design, recruitment or conduct of the study. The results of our study are not intended to be disseminated directly to participants, as our data source is deidentified health check-up data. However, we will make this report available to all participants.

RESULTS

A total of 19 458 participants were enrolled in our research, among whom 57.70% were men, the median age was 50 years old and the CKD prevalence was 3.81%, as shown in table 1. Subjects in the highest quartile of UHR had higher levels of BMI, SBP, DBP, FPG, LDL-C, TGs and SUA, and a higher prevalence of CKD but had lower levels of HDL-C and eGFR ($p<0.001$). As shown in figure 1, correlative analysis showed that both SUA and UHR were all negatively correlated with decreased eGFR, while HDL-C was positively correlated (SUA: r=−0.41, UHR%: r=−0.34 and HDL-C: r=0.16, respectively). We further describe the prevalence of CKD for each quartile

Table 1 General characteristics of the subjects by quantiles of UHR

Variables*	All subjects (n=19 458)	Q1 (n=4860)	Q2 (n=4877)	Q3 (n=4854)	Q4 (n=4867)	P value†
Age range (years)	50 (37–63)	50.00 (38.00–63.00)	49.00 (36.00–62.00)	49.00 (37.00–62.00)	51.00 (37.00–64.00)	<0.001
Gender male, n (%)	11 228 (57.70)	2805 (57.72)	2811 (57.64)	2800 (57.68)	2812 (57.78)	0.999
BMI (kg/m^2)	23.95 (21.80–26.20)	22.30 (20.40–24.40)	23.50 (21.50–25.60)	24.30 (22.40–26.40)	25.60 (23.55–27.65)	<0.001
SBP (mm Hg)	128 (117–139)	126.00 (115.00–138.00)	127.00 (116.00–138.00)	128.00 (117.00–139.00)	132.00 (121.00–143.00)	<0.001
DBP (mm Hg)	76 (69–83)	74.00 (68.00–81.00)	75.00 (69.00–82.00)	77.00 (70.00–83.00)	78.00 (71.00–85.00)	<0.001
FPG (mmol/L)	5.27 (4.96–5.69)	5.20 (4.91–5.59)	5.23 (4.93–5.63)	5.28 (4.97–5.69)	5.38 (5.05–5.85)	<0.001
HDL-C (mg/dL)	48.72 (41.38–57.62)	60.71 (52.98–69.22)	51.43 (45.63–58.39)	45.63 (40.99–51.82)	39.06 (34.80–44.47)	<0.001
LDL-C (mg/dL)	114.08 (93.19–135.73)	109.44 (90.10–130.70)	115.24 (95.13–136.51)	117.17 (96.29–138.44)	114.46 (92.03–136.51)	<0.001
TG (mg/dL)	106.25 (75.26–155.84)	78.81 (61.98–104.48)	96.51 (70.84–132.82)	115.11 (84.12–162.04)	157.61 (111.57–224.02)	<0.001
TC (mg/dL)	189.29 (165.89–214.23)	191.80 (169.76–215.39)	189.10 (166.28–213.07)	188.71 (164.35–213.85)	187.55 (163.19–214.23)	<0.001
SUA (mg/dL)	5.45 (4.49–6.47)	4.39 (3.68–5.23)	5.18 (4.37–5.97)	5.77 (4.88–6.59)	6.72 (5.76–7.65)	<0.001
UHR (%)	11.21 (8.18–14.90)	7.26 (5.66–9.55)	11.34 (7.45–12.55)	14.11 (9.35–15.43)	17.89 (13.00–20.35)	<0.001
eGFR (mL/min/1.73 m^2)	89.32 (77.94–102.07)	92.58 (81.70–105.38)	90.16 (79.11–103.28)	89.01 (77.71–102.00)	85.05 (73.57–97.67)	<0.001
CKD, n (%)	742 (3.81)	107 (2.20)	120 (2.46)	161 (3.32)	354 (7.27)	<0.001
Moderate	723 (3.72)	105 (2.16)	119 (2.44)	159 (3.28)	340 (6.99)	<0.001
Severe	19 (0.09)	2 (0.04)	1 (0.02)	2 (0.04)	14 (0.28)	

*Chi-squared test was used to examine the differences for categorical variables.
†Comparisons between groups analysed by ANOVA or Kruskal-Wallis test for continuous variables.
ANOVA, analysis of variance; BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SUA, serum uric acid; TC, total cholesterol; TG, triglyceride; UHR, SUA/HDL-C ratio.

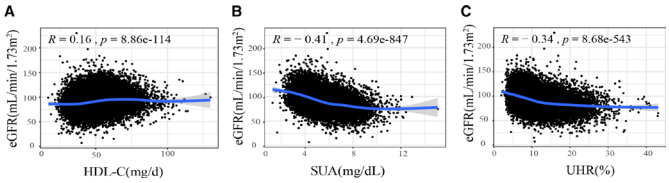

Figure 1 Scatter plots of (A) high-density lipoprotein cholesterol (HDL-C), (B) serum uric acid (SUA) and (C) SUA/HDL-C ratio (UHR) versus eGFR in the whole population. Linear correlation analysis (Pearson) is also represented. eGFR, estimated glomerular filtration rate.

of UHR. As the UHR level increased, the percentage of CKD increased from 2.20% in the first quartile to 7.27% in the fourth quartile (p<0.001, figure 2A), and men had a much higher prevalence than women in all quartiles of UHR. Besides, we identified that the percentage of severe CKD increased gradually with UHR level (figure 2B).

We explored the association between the quartiles based on the UHR distributions and CKD through logistic regression analyses, and a significant association was observed with an OR of 1.58 in the univariate model (table 2). After adjusting for age, sex, BMI, FPG, SBP, DBP, TC, TGs and LDL-C, UHR remained significantly associated with increased odds of CKD (OR: 2.12; 95% CI: 1.92 to 2.34). The highest quartiles of UHR were more associated with CKD than the lowest quartiles of UHR (OR: 9.28; 95% CI: 6.82 to 12.72). We also investigated the relationship between both markers of SUA and/or HDL and CKD risk, and the results showed that a unit elevation in SUA increases the risk of CKD by 2.13 times (p<0.001, 95% CI: 1.95 to 2.32), while HDL decreases by 0.78 times (p<0.001, 95% CI: 0.71 to 0.87). In addition, we used a restricted cubic spline regression model to assess potential non-linearity (online supplemental figure 1). Excitingly, we identified that the OR (95% CI) for CKD increased slowly until approximately 11.21% of the predicted UHR and then started to increase rapidly afterward (p for non-linearity <0.001).

We further explored the relationship between UHR% values and CKD stages through multinomial logistic regressions as shown in online supplemental table 1. We found that individuals in highest UHR% quartile were more likely to be in the moderate CKD stage (OR=9.11; 95% CI 6.65 to 12.49) or in severe CKD stage (OR=32.16; 95% CI 12.23 to 84.60) compared with individuals in the lowest quartile of UHR%.

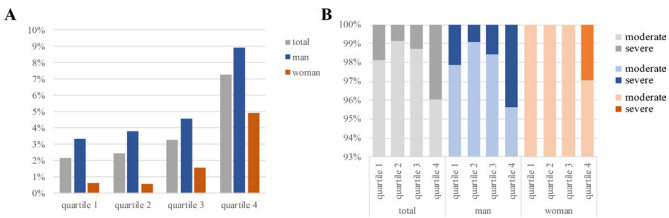

Figure 2 (A) Sex-specific prevalence of chronic kidney disease (CKD); (B) sex-specific percentages of CKD stages change.

To evaluate the effects of subgroups in modifying the association between UHR and CKD, subgroup analyses were used by age (<60 or 60 years old), sex (men or women), BMI (<24 kg/m^2 or ≥24 kg/m^2), and history of diabetes and hypertension (figure 3). We found that the p values for interactions of the subgroups were greater than 0.05, suggesting that the increased risk of renal outcome associated with UHR was prominent regardless of the above factors. Finally, in ROC analysis, a UHR level greater than 11.7% had 55.2% sensitivity and 74.2% specificity for predicting CKD (area under the curve: 0.702, 95% CI: 0.552 to 0.742, online supplemental figure 2).

DISCUSSION

In our study, evidence that UHR was positively associated with a decrease in eGFR as well as the risk of CKD was provided in a large sample of health check-up population. We also observed that this relationship was maintained, regardless of sex, BMI, and history of diabetes and hypertension, indicating that UHR is a sensitive and specific marker of kidney function.

To date, this is the first study to explore the association between UHR and decreased eGFR or the risk of CKD in the general population. In our study, we identified that the mean levels of UHR in all subsets and controls were significantly lower than that in patients with CKD, indicating that patients with CKD generally have higher SUA level and lower HDL-C level.[35] Two population cohort studies, the Cardiovascular Health Study and the Atherosclerosis Risk in Communities Study, indicated that higher UA levels are associated with the incidence or progression of CKD.[19 36] SUA, the end product of purine metabolism that is mainly eliminated in the urine, has recently been considered a risk factor for CKD.[37–42] Potential mechanisms behind this idea include inflammation, production of reactive oxygen species, activation of oxidative stress and so on.[43 44]

Monocytes play a vital role during the inflammation process,[45] by inducing the expression of pro-inflammatory cytokines and adhesion molecules.[46] HDL-C molecules could prevent monocyte migration and further remove oxidised cholesterol from endothelial cells. It could be speculated that HDL-C has both anti-inflammatory and anti-oxidant effects.[47] Recently, a study showed that HDL-C-mediated reverse cholesterol uptake is significantly impaired under conditions of chronic inflammatory and oxidative stress, such as CKD.[48] Therefore, combining the above effects of SUA and HDL-C, UHR could increase the burden of inflammation,[49 50] and further predict CKD by reflecting insulin sensitivity. In our study, we found that BMI, fasting glucose, LDL-C and TG gradually increased with the increase of UHR quartiles, which may be due to the accumulation of metabolic or inflammatory changes.

Table 2 Association between quartiles of UHR and CKD

Variable	Unadjusted		Adjusted*	
	OR (95% CI)	P value	OR (95% CI)	P value
UHR%	1.58 (1.47 to 1.70)	<0.001	2.12 (1.92 to 2.34)	<0.001
UHR% (quartile)				
Quartile 1	Ref		Ref	
Quartile 2	1.12 (0.86 to 1.46)	0.400	1.94 (1.45 to 2.61)	<0.001
Quartile 3	1.51 (1.18 to 1.94)	0.001	3.24 (2.41 to 4.37)	<0.001
Quartile 4	3.45 (2.78 to 4.32)	<0.001	9.28 (6.82 to 12.72)	<0.001
UA	1.96 (1.82 to 2.12)	<0.001	2.13 (1.95 to 2.32)	<0.001
UA (quartile)				
Quartile 1	Ref		Ref	
Quartile 2	1.63 (1.20 to 2.22)	0.002	1.88 (1.37 to 2.60)	<0.001
Quartile 3	2.30 (1.73 to 3.08)	<0.001	2.94 (2.17 to 4.01)	<0.001
Quartile 4	6.56 (5.09 to 8.57)	<0.001	8.85 (6.68 to 11.89)	<0.001
HDL-C	0.88 (0.83 to 0.94)	<0.001	0.78 (0.71 to 0.87)	<0.001
HDL-C (quartile)				
Quartile 1	Ref		Ref	
Quartile 2	0.70 (0.57 to 0.85)	<0.001	0.67 (0.53 to 0.84)	<0.001
Quartile 3	0.63 (0.51 to 0.77)	<0.001	0.57 (0.44 to 0.74)	<0.001
Quartile 4	0.70 (0.57 to 0.85)	<0.001	0.48 (0.35 to 0.66)	<0.001

*Adjusted for age, sex, BMI, fasting plasma glucose, systolic blood pressure, diastolic blood pressure, HDL-C, LDL-C, triglyceride and total cholesterol.
BMI, body mass index; CKD, chronic kidney disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; UA, uric acid; UHR, serum UA/HDL-C ratio.

The strength of the present study lies in that the study was based on a large sample size of over 10 000 individuals and used standardised protocols and rigid quality control procedures. Second, the exposure distribution for various factors was estimated based on the original data, allowing us to take into account potential confounding factors, such as age, sex, BMI, SBP, DBP, FPG, HDL-C, LDL-C, TGs and TC. However, several limitations should also be acknowledged. First, as this was an observational study, the findings are only statistical associations and do not imply causality. Second, we examine the relationship between UHR and CKD, controlling for demographic and clinical variables, but there are still many important variables such as marital status, education level, family income, smoking and alcohol consumption that failed to be included in our study. Besides, residual confounding cannot be fully ruled out, although the adjusted ORs and the consistency of the results across various strata minimise this possibility.

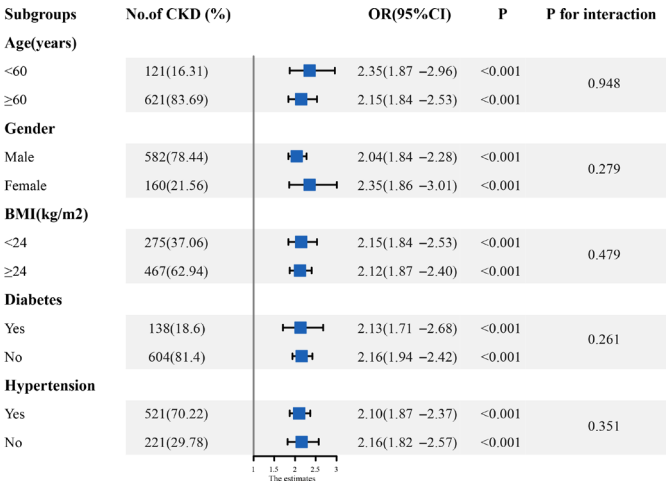

Figure 3 Subgroup analyses. A comparison of the adjusted OR of chronic kidney disease (CKD) for the subgroups is presented by forest plot. Adjusted for age, sex, body mass index (BMI), fasting plasma glucose, blood pressure, total cholesterol, triglycerides and low-density lipoprotein cholesterol for each subgroup (excluding for its own group).

CONCLUSIONS

Our study showed that UHR is positively associated with the risk of CKD, reflecting chronic inflammation. Accordingly, increased UHR may serve as a novel and reliable indicator for CKD in the preclinical stage.

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Contributors DY acted as guarantor of our study. DY, LG and HW initiated, conceived and supervised the study. HZheng, HY and YW participated in the data

collection. HZhang assisted with the study and analyses. YC completed the analyses and led the writing. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement No patients were involved in the design, recruitment or conduct of the study. Refer to the Methods section for further details.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by the Institutional Review Board of the Geriatric Hospital of Nanjing Medical University ((2020) Hospital Ethics Review Character No. 020). Written informed consent was obtained from each subject at recruitment.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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