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Serum uric acid, vascular aging, and endocrine comorbidities

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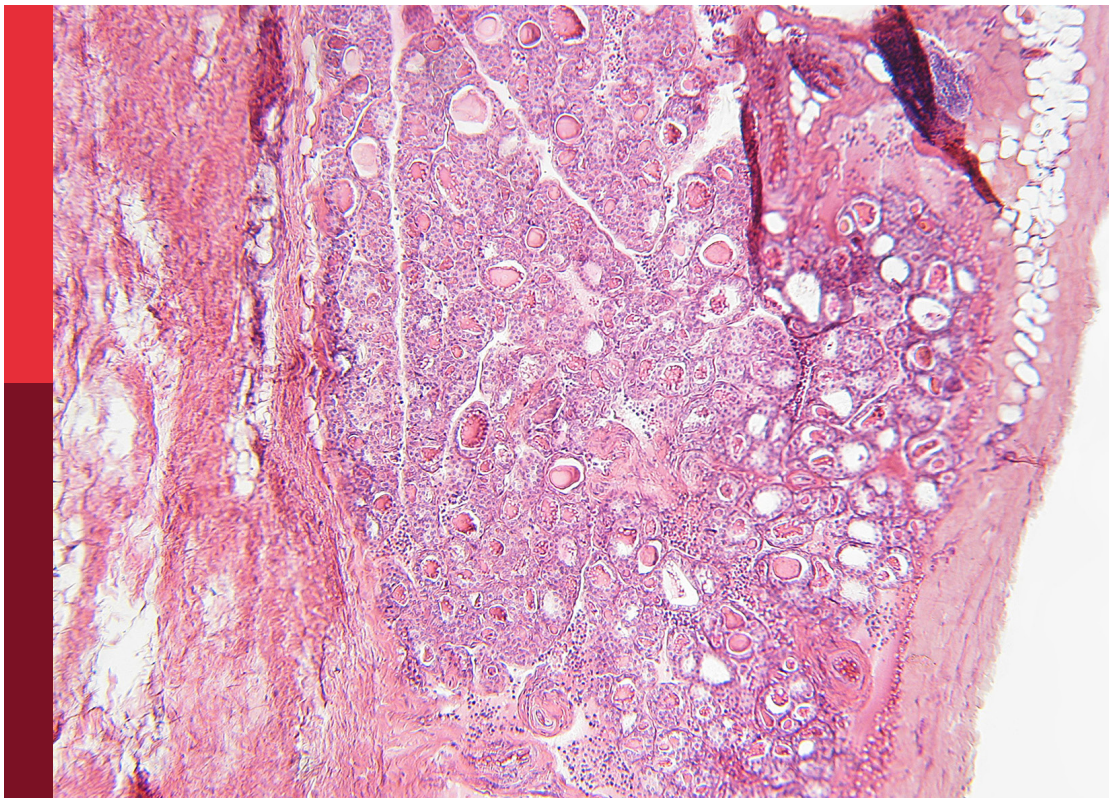
Published in
Frontiers in Endocrinology



ISSN 1664-8714
ISBN 978-2-8325-3679-7
DOI 10.3389/978-2-8325-3679-7

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Serum uric acid, vascular aging, and endocrine comorbidities

Topic editors

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Citation

Cicero, A. F. G., Hu, Y., eds. (2023). *Serum uric acid, vascular aging, and endocrine comorbidities*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-3679-7

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frontiers | Frontiers in Endocrinology

TYPE Editorial
PUBLISHED 26 September 2023
DOI 10.3389/fendo.2023.1292015

OPEN ACCESS

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RECEIVED 10 September 2023
ACCEPTED 12 September 2023
PUBLISHED 26 September 2023

CITATION
Hu Y and Cicero AFG (2023) Editorial: Serum uric acid, vascular aging, and endocrine comorbidities.
Front. Endocrinol. 14:1292015.
doi: 10.3389/fendo.2023.1292015

Editorial: Serum uric acid, vascular aging, and endocrine comorbidities

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KEYWORDS

uric acid, aging, vascular health, comorbidities, pathophysiology

Editorial on the Research Topic
Serum uric acid, vascular aging, and endocrine comorbidities

It is largely known that uric acid is the final product of purine metabolism, and that its increased serum levels have been directly involved in the pathogenesis and natural history of a number of endocrino-metabolic and cardiovascular diseases (1).

In particular, serum uric acid (SUA) has been associated with the risk of developing hypertension and subclinical vascular damage (2), as well as an increased risk of myocardial infarction, stroke, heart failure, and different arrhythmias (in particular atrial fibrillation) by affecting thickness, function, and other features of the vascular tissue. As regards metabolic diseases, SUA is not only associated with a risk of gout, but also metabolic syndrome, non-alcoholic fatty liver disease, obesity, and type 2 diabetes. The risk of type 2 diabetes macrovascular and microvascular complications are also associated with increased SUA levels.

Meanwhile, suboptimal SUA levels have been associated with an increased risk for cardiovascular disease mortality, in particular in type 2 diabetes patients. This suggests a use for SUA levels as markers of vascular injury and vascular related diseases, which in turn can be associated with endocrine comorbidities.

But serum uric acid is not only related to insulin-resistance and type 2 diabetes. Since the 70s it was known the relationship between thyroid and parathyroid disorders and hyperuricemia (3). However, the association between uric acid levels, thyroid/parathyroid function and vascular damage has not yet deeply investigated.

In this context, Frontiers in Endocrinology hosted a Research Topic on serum uric acid, vascular aging and endocrine comorbidities. Li et al. observed in a large cohort of Chinese patients, that SUA levels are strongly related with metabolic syndrome and its component, but not with early sign of carotid aging in patients affected by type 2 diabetes. This data is partly in contrast with what known in general population, but patients with type 2 diabetes could have an increased vascular aging independently from other factors. On the other side, always in this Research Topic, Gao et al. showed in a different patients cohort with different degree of glucose-metabolism impairment, that carotid aging is more relevant in hyperuricemic subjects than in the normouricemic ones, more relevant in subjects

affected by impaired fasting glucose and (even more) in diabetic ones. These evidences suggest a strong, but complex relationship between serum uric acid, glucose impairment and carotid aging. Less investigated is the nexus between serum uric acid and microvascular damage. In this Research Topic, Yang et al. interestingly suggested that serum uric acid is associated with a lower retinal capillary plexus measured by optical coherence tomography angiography in a large cohort of Chinese subjects. A similar trend has been recently observed as regards the relationship between serum uric acid and hypertensive white matter hyperintensity in dementia and stroke free patients (4). On the other side, serum uric acid association with microvascular damage could be tissue-specific, since it has not been observed in skin (5).

Among others, the large URRAH study identified SUA cut-off largely lower than the ones usually considered a risk factor for the development of gout (6, 7).

Beyond the rapidly increasing evidence relating SUA levels with all these risk factors, diseases, and mortality, more data are yet needed to clearly define the SUA cut-off associated with different outcomes in different populations and patients' groups, where SUA is pathogenetic or an epiphenomenon, and the role of SUA-lowering therapies to prevent SUA related damages.

In this Research Topic, Hu et al. discovered a nonlinear relationship between SUA and phase angle (PhA) among type 2 diabetes mellitus patients. The PhA was increased with elevated SUA within a certain range, and the effect was insignificant beyond a specific threshold. These results suggest that SUA may function as a dual indicator of health and disease. Below a certain threshold, SUA can serve as a nutritional marker and antioxidant. However, above that threshold, SUA is harmful as an oxidant that accelerates tissue damage. In a cohort of Chinese patients with chronic heart failure (CHF), Wang et al. found that hyperuricemia and chronic kidney disease (CKD) significantly increased the risk of in-hospital mortality and long-term mortality. The evidence presented in this study showed the impact of both hyperuricemia and CKD on heart failure outcomes, emphasizing the importance of managing SUA in CHF patients. Additionally, a large cohort study conducted in the Korean population by Kang et al. found that patients with gout had a slightly higher incidence of stroke, ischemic heart disease, or heart failure compared to control subjects. This study demonstrated that gout was an independent risk factor for cardiovascular disease. On the other hand, a cross-sectional analysis conducted by Shen et al. indicated that low levels of urinary iodine concentration were significantly associated with a decreased prevalence of metabolic disorders and associated diseases in American participants. This association could potentially introduce novel dietary interventions to treat patients with metabolic disorders.

Many other interesting evidences are included in this Research Topic, suggesting the interesting interrelationship between endocrinopathies, serum uric acid, and vascular health.

Author contributions

AC: Conceptualization, Writing – original draft, Writing – review & editing. YH: Writing – original draft, Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

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ORIGINAL RESEARCH
published: 12 April 2022
doi: 10.3389/fendo.2022.855430

Association of Serum Uric Acid With Retinal Capillary Plexus

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Background: To determine the association between serum uric acid (SUA) and the retinal capillary plexus (RCP) using optical coherence tomography angiography (OCTA).

Methods: This cross-sectional study evaluated data from August 2019 to January 2020 from participants recruited from the Jidong community (Tangshan, Hebei, China). All participants completed detailed anthropometrical measurements, laboratory tests and comprehensive ophthalmic examinations. We assessed the vessel density in RCP using OCTA. We used multivariable analysis to evaluate the sex-specific association between SUA and RCP after adjusting for confounders.

Results: A total of 2730 participants were included in this study. The mean age of the participants was 44.0 ± 11.6 years, and 1463 (53.6%) were women. The multivariable βs and 95% confidence intervals (CIs) of superficial RCP vessel density in the second through fourth SUA quartiles compared with the lowest SUA quartiles were -0.27 (-0.56 – 0.03), -0.30 (-0.60 – 0.01), and -0.46 (-0.78 – -0.14) (P for trend = 0.007) in men.

Conclusions: Higher SUA levels were significantly associated with lower RCP vessel density in men. Our findings provide evidence for the detrimental effect of high SUA levels on the retinal microvasculature and imply the importance of modulating SUA to prevent the microvascular alternation especially for men.

Keywords: serum uric acid, optical coherence tomography angiography, retinal capillary plexus, epidemiology, sex

OPEN ACCESS

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Specialty section:
This article was submitted to Cardiovascular Endocrinology, a section of the journal Frontiers in Endocrinology

Received: *15 January 2022*
Accepted: *15 March 2022*
Published: *12 April 2022*

Citation:
Yang K, Li C, Shi K, Zhu X, Xiao Y, Su B, Ju Y, Lu F, Qu J, Cui L and Li M (2022) Association of Serum Uric Acid With Retinal Capillary Plexus. Front. Endocrinol. 13:855430. doi: 10.3389/fendo.2022.855430

INTRODUCTION

Serum uric acid (SUA), a product of purine metabolism and its derivatives, has long been associated with various metabolic and cardiovascular diseases (1–4). People with high SUA have an approximately 30% higher rate of cardiovascular disease and all-cause mortality (5). Several studies suggested that higher uric acid level may cause microvascular alterations (6–8), though direct noninvasive *in vivo* observations of microcirculatory alterations are still lacking thus far. The retina is an ideal window for direct noninvasive *in vivo* observation of the microcirculation (9),

Abbreviations: SUA, Serum uric acid; OCT, optical coherence tomography; OCTA, optical coherence tomography angiography; RCP, retinal capillary plexus; JECS, Jidong Eye Cohort Study; BCVA, low best corrected visual acuity; FBG, fasting blood glucose; LDL-C, low-density lipoprotein; HDL-C, high density lipoprotein; TC, total cholesterol; TG, triglyceride; eGFR, estimated glomerular filtration rate; AL, axial length; BMI, body mass index; CIs, confidence intervals.

through which systemic microvascular alterations in persons with high SUA can be indirectly observed. Additionally, sex differences were observed in many conditions about uric acid (10). Thus, it is important to exploring the sex-specific effect of SUA on the retinal microvasculature.

Previously, studies focused on the effect of SUA on retinal arterioles and venules (11, 12) but not on the subtle alteration of retinal capillaries due to the limitations of imaging technology. Recently, optical coherence tomography angiography (OCTA) technology has emerged as a promising new technology for better visualization and quantitative analysis of retinal capillaries (13). Previous studies have reported the wide use of OCTA not only in the assessment of many retinal diseases (14, 15) but also in systemic vascular diseases, such as hypertension (16), stroke (17), coronary artery disease (18), and chronic kidney disease (19). Numerous studies have shown that OCTA-derived vascular metrics, such as the retinal capillary plexus (RCP) vessel density, are useful to evaluate retinal capillary alternations and microvascular pathologic features (20), which may provide new insight into SUA-related effects on the microvasculature.

The relationship between uric acid and retinal microvascular alternations is still unclear. Additionally, close linkages of diabetic retinopathy and hypertensive retinopathy with SUA have been reported previously (21, 22). However, other previous epidemiological reports have failed to demonstrate these relationships (23, 24). Previously, only two relevant studies analyzed the association between higher SUA and retinal vasculature, focusing on retinal arterioles and venules (11, 12). Findings from these studies were inconsistent and contradictory. There is still a lack of studies on the subtle alterations of vessel density in the retinal capillary plexus. In view of this and considering the close linkage between SUA and sex, this community-based study aimed to investigate the sex-specific association of SUA with RCP using OCTA.

MATERIALS AND METHODS

Design and Population of the Study

Our study was a substudy of the Jidong Eye Cohort Study (JECS). The data used for this study were obtained from JECS participants. Details of the JECS have been previously described (25). A total of 3377 participants were recruited from Jidong communities (Tangshan, Hebei, China) between August 2019 and January 2020. The following participants were removed from the analyzed sample due to the predetermined exclusion criteria: 31 individuals had missing SUA data; 113 individuals had ocular diseases; 163 individuals had suboptimal OCTA images; 11 individuals had low best corrected visual acuity (BCVA); 208 individuals had refraction above +2.00 or under -6.00 diopters; and 121 individuals had missing axial length data (**Figure 1**).

This study was approved by the Ethics Committee of the Staff Hospital of Jidong oil-field of Chinese National Petroleum (China national petroleum corporation Jidong oilfield branch staff hospital approval document of the medical ethics committee, 2018 YILUNZI 1) and followed the Declaration of Helsinki guidelines. We obtained written informed consent forms from all participants.

Assessment of General Variable

In this study, basic information on the participants was obtained using clinical examinations, laboratory tests, and standardized questionnaires for demographic characteristics, current smoking status, current alcohol consumption status, and medical history (26, 27). The average monthly income levels were divided into "< ¥3,000" and "≥ ¥3,000". The education levels were categorized as "illiteracy, primary or middle school" and "college graduate or above". In this study, diabetes was determined by either fasting blood glucose (FBG) ≥ 7.0 mmol/L, self-reported diabetes history, or current antidiabetic medication use; while hypertension was defined as either systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, self-reported hypertension history, or current use of antihypertensive medications. Dyslipidemia was defined as either low-density lipoprotein (LDL-C) ≥ 3.3 mmol/L, high-density lipoprotein (HDL-C) < 1.04 mmol/L, total cholesterol (TC) ≥ 5.17 mmol/L, triglyceride (TG) ≥ 1.7 mmol/L, current use of lipid-lowering medications, or self-reported history of dyslipidemia. We calculated the estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation and adjusted it by a coefficient of 1.1 for the Asian population (28, 29).

Assessment of Serum Uric Acid

Fasting elbow venous blood samples were obtained in the morning after refraining from food and drinking for at least 8 hours and they were stored in vacuum tubes containing ethylenediaminetetraacetic acid. SUA levels were measured using an autoanalyzer (Hitachi, Tokyo, Japan) with the uricase-peroxidase method in the Central Laboratory of Jidong Oil-Field Hospital (25, 30). Participants in this study were stratified into quartiles based on sex-specific SUA levels (male, Q1: ≤ 335 μmol/L, Q2: 336 - 385 μmol/L, Q3: 386 - 443 μmol/L, Q4: ≥ 444 μmol/L; female, Q1: ≤ 244 μmol/L, Q2: 245 - 278 μmol/L, Q3: 279 - 322 μmol/L, Q4: ≥ 323 μmol/L). Hyperuricemia was defined as an SUA level ≥ 360 μmol/L (6.0 mg/dL) in women and ≥ 420 μmol/L (7.0 mg/dL) in men (31).

Ophthalmic Examination

Participants in our study underwent a comprehensive eye examination including best-corrected visual acuity (BCVA) by a standard logarithmic visual acuity chart and refractive status by an autorefractometer (KR800; Topcon; Tokyo, Japan). Refraction was calculated as the spherical equivalent (spherical value and half of the cylindrical value). Measurements of axial length (AL) were obtained using a Lenstar 900 (Haag-Streit; Koeniz, Switzerland). Digital fundus photographs were obtained using a 45° nonmydriatic fundus camera (CR2AF; Canon; Tokyo, Japan). All examination results were reviewed by at least two ophthalmologists. Participants with ocular disease, low BCVA (worse than 0.5 logMAR), or high refraction error

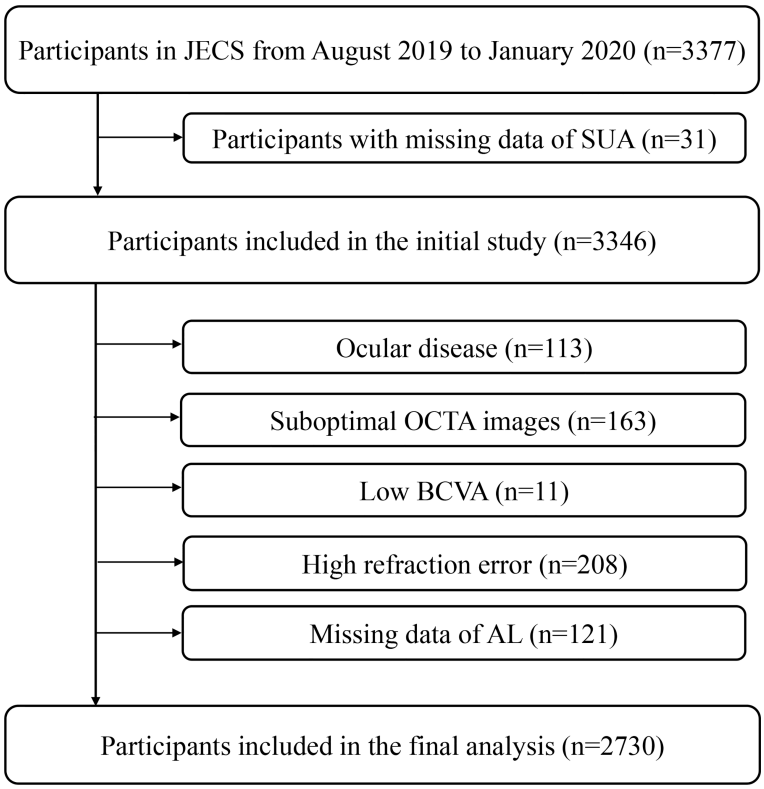

FIGURE 1 | Flow Chart of the Study Participant. JECS, Jidong Eye Cohort Study; OCTA, optical coherence tomography angiography; BCVA, best corrected visual acuity; AL, axial length.

(spherical equivalent < -6.00 D/spherical equivalent > +2.00 D) were excluded from the analyses.

Assessment of OCTA

We obtained OCTA images using a spectral-domain OCTA device (RTVue XR Avanti with AngioVue; Optovue; Fremont, CA, USA). OCTA images were acquired using a 3 × 3 mm^2 scan with a scan density of 304×304 A-scans centered on the macula. The superficial (between the internal limiting membrane and inner plexiform layer) and deep (between the inner plexiform layer and outer plexiform layer) RCPs were automatically segmented according to the built-in software (AngioAnalytics, version 2017.1.0.155) (25). An algorithm incorporated into the device (optovue, Inc) automatically removes the 3D projection artifacts to reduce the motion artifacts and increase the image quality (32). Superficial and deep OCTA images were exported and then corrected using Bennett's formula with AL magnification (33). The vessel density (the proportion of the flow signals) of the superficial and deep RCP was automatically generated by a custom algorithm operating on MATLAB (version 2017b; MathWorks, Inc.; Natick, MA, USA). Details of the processing and analysis methods have been previously described (33, 34). The processing algorithm based on a macula map was as follows: two concentric circles (0.6 and 2.5 mm diameters) divided into five quadrants (parafovea, superior, inferior, nasal, and temporal). In this report, the quadrant of the parafovea served as a representative of the average RCP due to the special structure of the foveal area, and the other quadrants were also presented.

Only OCTA scans with a signal strength index ≥ 7 were included for quantitative analysis and images with defects were excluded from the study. We used the measurement of the right eye if it was available, whereas the left eye was only analyzed in the absence of eligible scans for the right eye.

Statistical Analysis

We expressed continuous variables as the means and standard deviations (SD) and categorical valuables as frequencies and percentages. We examined the differences between the different SUA quartile groups using a one-way ANCOVA test for normally distributed continuous variables and chi-square tests or Fisher's exact test for categorical valuables.

We used multivariable generalized linear models to estimate the association between the SUA quartile and the vessel density in the RCP. We tested for trends by considering the SUA quartile as a continuous ordinal variable. We adjusted all multivariable generalized linear models for age, current drinking status, hypertension, diabetes, body mass index (BMI), TC, TG, HDL-C, LDL-C, and eGFR. Moreover, associations of a 1 standard deviation change in SUA and the presence of hyperuricemia

with RCP vessel density were also tested, and we examined whether the associations between SUA and RCP differed by sex by including interaction terms in the adjusted models.

Associations were measured as βs and 95% confidence intervals (CIs). For all analyses, statistical significance was considered as a 2-tailed P value < 0.05. All statistical analyses were undertaken using SAS software (version 9.4; SAS Institute Inc., Cary, NC, USA).

RESULTS

Baseline Characteristics

A total of 2730 participants from Jidong communities were eventually included in the analyses. The mean age of the included participants was 44.0 ± 11.6 years, and there were 1463 (53.6%) women. Baseline characteristics by different quartiles of serum SUA levels are summarized in **Table 1**. Participants with higher SUA levels were younger (P = 0.006), more likely to be drinkers (p = 0.01), have a higher BMI (P < 0.001), have a lower eGFR (P < 0.001), and have more prevalent hypertension (P < 0.001) and dyslipidemia (P < 0.001).

RCP Vessel Density in Sex-Specific SUA Quartile Groups

Table 2 shows the RCP characteristics in different SUA quartile groups on the baseline survey. For the male participants stratified into quartiles, the vessel density of the superficial RCP decreased from Q1 to Q4 from 51.1% to 50.6% in the parafovea. For the vessel density in other quadrants of RCP, see **Table 2**. However, we did not observe a significant difference in deep RCP in men or superficial and deep RCP in women. **Figure 2** shows the representative OCTA images of male participants in Q1 and Q4.

Association Between SUA and RCP by Sex

We show the relationships between SUA quartile and RCP vessel density for men in **Table 3**. Male participants in the highest SUA quartile had a significant decrease in vessel density in the superficial RCP, even after adjusting for potential confounding factors. Compared to the lowest quartile, the multivariable βs and 95% Cis for the male participants in the second through fourth SUA quartiles were -0.27 (-0.56 – 0.03), -0.30 (-0.60 – 0.01), and -0.46 (-0.78 – -0.14) (P for trend = 0.007) in the parafovea. The βs in other quadrants of RCP are also shown.

TABLE 1 | Baseline characteristics of participants by serum uric acid quartiles.

Characteristics	Total	SUA				P	P for Trend
	(n=2730)	Q1 (n=692)	Q2 (n=682)	Q3 (n=679)	Q4 (n=677)		
Age, y, mean (SD)	44.0 (11.6)	45.1 (11.5)	43.9 (11.1)	43.6 (11.8)	43.4 (12.0)	0.03	0.006
Sex, n (%)						0.99	0.96
Male	1267 (46.4)	320 (46.2)	319 (46.8)	312 (46.0)	316 (46.7)		
Female	1463 (53.6)	372 (53.8)	363 (53.2)	367 (54.1)	361 (53.3)		
Educational level, n (%)						0.69	0.77
lliteracy/Primary/Middle School	849 (31.1)	225 (32.5)	205 (30.1)	204 (30.0)	215 (31.8)		
College/University	1881 (68.9)	467 (67.5)	477 (69.9)	475 (70.0)	462 (68.2)		
Income, n (%)						0.31	0.94
< ¥3,000	216 (7.9)	62 (9.0)	43 (6.3)	55 (8.1)	56 (8.3)		
≥ ¥3,000	2514 (92.1)	630 (91.0)	639 (93.7)	624 (91.9)	621 (91.7)		
Current Smoking, n (%)	532 (19.6)	139 (20.3)	116 (17.1)	132 (19.5)	145 (21.6)	0.20	0.36
Current Drinking, n (%)	377 (14.0)	83 (12.2)	85 (12.5)	98 (14.5)	111 (16.6)	0.07	0.01
Hypertension, n (%)	716 (26.2)	157 (22.7)	157 (23.0)	170 (25.0)	232 (34.3)	< 0.001	< 0.001
Diabetes, n (%)	229 (8.4)	71 (10.3)	55 (8.1)	47 (6.9)	56 (8.3)	0.16	0.13
Dyslipidemia, n (%)	1831 (67.1)	386 (55.8)	429 (62.9)	461 (67.9)	555 (82.0)	< 0.001	< 0.001
SBP, mmHg, mean (SD)	123.7 (16.8)	122.0 (17.1)	121.6 (16.2)	123.3 (15.9)	127.9 (17.1)	< 0.001	< 0.001
DBP, mmHg, mean (SD)	78.8 (12.6)	77.2 (12.6)	77.5 (12.2)	78.9 (12.2)	81.5 (12.7)	< 0.001	< 0.001
FBG, mmol/L, mean (SD)	5.5 (1.4)	5.6 (1.7)	5.5 (1.4)	5.4 (1.2)	5.5 (1.1)	0.13	0.49
BMI, kg/m^2, mean (SD)	24.4 (3.5)	23.3 (3.2)	2.8 (3.2)	24.5 (3.4)	26.0 (3.6)	< 0.001	< 0.001
TC, mmol/L, mean (SD)	5.0 (1.0)	4.8 (0.9)	4.9 (0.9)	5.0 (0.9)	5.3 (1.0)	< 0.001	< 0.001
Triglycerides, mmol/L, mean (SD)	1.7 (1.4)	1.4 (1.0)	1.6 (1.3)	1.7 (1.3)	2.2 (1.8)	< 0.001	< 0.001
HDL-C, mmol/L, mean (SD)	1.2 (0.3)	1.3 (0.3)	1.2 (0.3)	1.2 (0.2)	1.2 (0.2)	< 0.001	< 0.001
LDL-C, mmol/L, mean (SD)	2.1 (0.8)	1.9 (0.7)	2.0 (0.7)	2.1 (0.7)	2.3 (0.8)	< 0.001	< 0.001
AL, mm, mean (SD)	24.1 (1.2)	24.0 (1.2)	24.1 (1.2)	24.1 (1.3)	24.1 (1.2)	0.08	0.07
OCT signal index, mean (SD)	8.5 (0.7)	8.5 (0.7)	8.5 (0.6)	8.4 (0.7)	8.5 (0.6)	0.06	0.14
eGFR, ml/min*1.73m^2, mean (SD)	114.7 (14.9)	117.2 (12.7)	116.0 (13.7)	114.5 (14.6)	111.2 (17.6)	< 0.001	< 0.001
Serum uric acid, umol/L, mean (SD)	336.9 (91.2)	252.9 (47.8)	308.9 (52.1)	351.5 (58.8)	436.2 (83.3)	< 0.001	< 0.001
Serum uric acid, range	129 - 758	129 - 335	245 - 385	279 - 443	323 - 758		

Data were presented as number (percentage) for category variables and mean (SD) for continuous variables.

P for trend tested by considering the SUA quartile as continuous ordinal variables.

The quartiles of SUA levels were calculated by sex respectively. Q1, quartile 1 (n=692): male ≤ 335 umol/L and female ≤ 244 umol/L; Q2, quartile 2 (n=682): male 336 -385 umol/L and female 245 – 278 umol/L; Q3, quartile 3 (n=679): male 386 – 443 umol/L and female 279 - 332 umol/L; Q4, quartile 4 (n=677): male ≥ 444 umol/L and female ≥ 323 umol/L.

SUA, Serum Uric Acid; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; BMI, body mass index; TC, total cholesterol; HDL-C, high density liptein cholesterol; LDL-C, low density lipoprotein cholesterol; AL, axial length; OCT, Optical coherence tomography; eGFR, estimated glomerular filtration rate.

TABLE 2 | Ocular characteristics of participants by serum uric acid quartiles in males and females.

Characteristics	Total	SUA				P	P for Trend
		Q1	Q2	Q3	Q4		
Male	**n=1267**	**n=320**	**n=319**	**n=312**	**n=316**		
Superficial RCP, %, mean (SD)							
Parafovea	50.8 (1.9)	51.1 (2.0)	50.8 (1.8)	50.7 (2.0)	50.6 (1.7)	0.02	0.003
Inferior	50.5 (2.0)	50.8 (2.1)	50.5 (1.9)	50.5 (2.0)	50.3 (1.8)	0.07	0.01
Nasal	50.7 (2.0)	51.0 (2.1)	50.7 (2.0)	50.6 (2.1)	50.4 (1.9)	0.008	0.001
Superior	50.8 (2.0)	51.1 (2.2)	50.8 (1.9)	50.7 (2.0)	50.7 (1.8)	0.12	0.03
Temporal	51.2 (2.1)	51.5 (2.2)	51.2 (2.1)	51.1 (2.2)	51.0 (1.9)	0.02	0.001
Deep RCP, %, mean (SD)							
Parafovea	54.0 (2.9)	54.2 (3.0)	54.0 (3.0)	54.0 (3.0)	53.8 (2.6)	0.53	0.15
Inferior	54.0 (3.0)	54.2 (3.1)	54.0 (3.1)	54.0 (3.1)	53.9 (2.7)	0.47	0.14
Nasal	53.8 (2.9)	53.9 (3.1)	53.8 (3.0)	53.8 (2.9)	53.5 (2.7)	0.43	0.12
Superior	54.2 (3.2)	54.4 (3.3)	54.2 (3.2)	54.2 (3.3)	54.2 (2.8)	0.72	0.41
Temporal	53.9 (3.0)	54.1 (3.0)	54.0 (3.1)	53.9 (3.1)	53.7 (2.8)	0.39	0.08
Female	**n=1463**	**n=372**	**n=363**	**n=367**	**n=361**		
Superficial RCP, %, mean (SD)							
Parafovea	50.3 (1.9)	50.4 (1.9)	50.2 (2.0)	50.3 (1.9)	50.5 (2.0)	0.12	0.33
Inferior	50.1 (2.0)	50.2 (1.9)	50.0 (2.0)	50.1 (2.0)	50.3 (2.0)	0.18	0.40
Nasal	50.1 (2.0)	50.2 (2.0)	50.0 (2.1)	50.0 (2.0)	50.3 (2.0)	0.10	0.57
Superior	50.4 (2.0)	50.3 (2.1)	50.3 (2.1)	50.3 (1.9)	50.5 (2.0)	0.41	0.22
Temporal	50.7 (2.2)	50.8 (2.1)	50.6 (2.2)	50.6 (2.1)	51.0 (2.2)	0.04	0.30
Deep RCP, %, mean (SD)							
Parafovea	54.2 (2.8)	54.3 (2.9)	54.1 (2.8)	54.2 (2.7)	54.2 (2.7)	0.70	0.86
Inferior	54.3 (3.0)	54.4 (3.2)	54.2 (3.0)	54.3 (2.9)	54.5 (2.9)	0.52	0.85
Nasal	53.9 (2.9)	53.9 (3.1)	53.7 (2.8)	53.8 (2.7)	53.9 (2.8)	0.83	0.98
Superior	54.6 (3.0)	54.6 (3.0)	54.5 (3.0)	54.6 (2.9)	54.5 (2.9)	0.93	0.80
Temporal	54.0 (2.9)	54.2 (2.9)	53.9 (2.9)	53.9 (2.8)	54.1 (2.8)	0.38	0.53

Data were presented as mean (SD)SD for continuous variables.

P for trend tested by considering the SUA quartile as continuous ordinal variables.

The quartiles of SUA levels were calculated by sex respectively. In males: Q1, quartile 1 (n=320): ≤ 335 umol/L; Q2, quartile 2 (n=319): 336 - 385 umol/L; Q3, quartile 3 (n=312): 386 - 443 umol/L; Q4, quartile 4 (n=316): ≥ 444 umol/L. In females: Q1, quartile 1 (n=372): ≤ 244 umol/L; Q2, quartile 2 (n=363): 245 - 278 umol/L; Q3, quartile 3 (n=367): 279 - 322 umol/L; Q4, quartile 4 (n=361): ≥ 323 umol/L; n, number.

SUA, Serum Uric Acid; RCP, retinal capillary plexus.

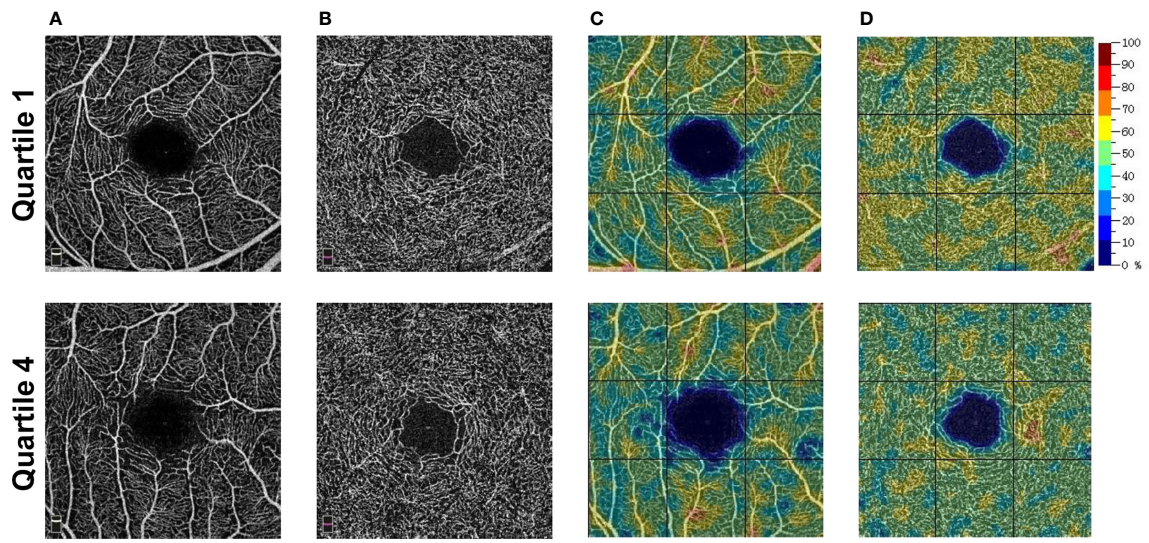

FIGURE 2 | Representative OCTA images of male participants. **(A)** The superficial OCT angiograms. **(B)** The deep OCT angiograms. **(C)** The color-coded superficial RCP vessel density maps. **(D)** The color-coded deep RCP vessel density maps. Quartile 1, SUA level ≤335 umol/L; Quartile 4, SUA level ≥444 umol/L. OCTA, optical coherence tomography angiography; OCT, optical coherence tomography; SUA, serum uric acid; RCP, retinal capillary plexus.

TABLE 3 | Association between serum uric acid and retinal capillary plexus in men.

Characteristics	SUA				P for Trend
	Q1 (n=320)	Q2 (n=319)	Q3 (n=312)	Q4 (n=316)	
Superficial RCP					
Parafovea	Referent	-0.27 (-0.56 – 0.03)	-0.30 (-0.60 – 0.01)	-0.46 (-0.78 – -0.14)	0.007
Inferior	Referent	-0.24 (-0.55 – 0.06)	-0.24 (-0.56 – 0.07)	-0.41 (-0.74 – -0.08)	0.02
Nasal	Referent	-0.30 (-0.62 – 0.01)	-0.29 (-0.62 – 0.03)	-0.55 (-0.89 – -0.21)	0.003
Superior	Referent	-0.27 (-0.58 – 0.05)	-0.30 (-0.62 – 0.02)	-0.36 (-0.70 – -0.03)	0.04
Temporal	Referent	-0.25 (-0.57 – 0.08)	-0.36 (-0.70 – -0.02)	-0.51 (-0.86 – -0.16)	0.004
Deep RCP					
Parafovea	Referent	-0.19 (-0.64 – 0.26)	-0.18 (-0.65 – 0.28)	-0.31 (-0.79 – 0.17)	0.25
Inferior	Referent	-0.24 (-0.71 – 0.23)	-0.21 (-0.69 – 0.27)	-0.41 (-0.91 – 0.10)	0.15
Nasal	Referent	-0.08 (-0.54 – 0.38)	-0.10 (-0.57 – 0.37)	-0.31 (-0.80 – 0.19)	0.24
Superior	Referent	-0.31 (-0.81 – 0.19)	-0.26 (-0.76 – 0.25)	-0.21 (-0.74 – 0.32)	0.50
Temporal	Referent	-0.12 (-0.58 – 0.35)	-0.17 (-0.65 – 0.31)	-0.31 (-0.81 – 0.18)	0.22

Adjusted for age, current drinking status, hypertension, diabetes, BMI, TC, TG, HDL-C, LDL-C, and eGFR.
P for trend tested with generalized linear models by considering the SUA quartile as continuous ordinal variables.
Q1, quartile 1 (n=320): ≤ 335 umol/L; Q2, quartile 2 (n=319): 336 - 385 umol/L; Q3, quartile 3 (n=312): 386 - 443 umol/L; Q4, quartile 4 (n=316): ≥ 444 umol/L.
SUA, Serum Uric Acid; RCP, retinal capillary plexus.

TABLE 4 | Association between serum uric acid and retinal capillary plexus in women.

Characteristics	SUA				P for Trend
	Q1 (n=372)	Q2 (n=363)	Q3 (n=367)	Q4 (n=361)	
Superficial RCP					
Parafovea	Referent	-0.24 (-0.52 – 0.04)	-0.24 (-0.52 – 0.05)	-0.16 (-0.46 – 0.14)	0.29
Inferior	Referent	-0.25 (-0.54 – 0.04)	-0.24 (-0.53 – 0.05)	-0.21 (-0.52 – 0.11)	0.20
Nasal	Referent	-0.31 (-0.60 – -0.01)	-0.28 (-0.58 – 0.01)	-0.19 (-0.51 – 0.13)	0.24
Superior	Referent	-0.12 (-0.41 – 0.18)	-0.10 (-0.40 – 0.19)	-0.10 (-0.41 – 0.22)	0.56
Temporal	Referent	-0.30 (-0.61 – 0.02)	-0.31 (-0.63 – 0.00)	-0.15 (-0.49 – 0.19)	0.34
Deep RCP					
Parafovea	Referent	-0.29 (-0.70 – 0.11)	-0.14 (-0.55 – 0.27)	-0.11 (-0.55 – 0.33)	0.76
Inferior	Referent	-0.34 (-0.77 – 0.10)	-0.13 (-0.57 – 0.31)	-0.02 (-0.49 – 0.45)	0.90
Nasal	Referent	-0.26 (-0.68 – 0.16)	-0.10 (-0.52 – 0.32)	-0.10 (-0.56 – 0.35)	0.81
Superior	Referent	-0.18 (-0.62 – 0.25)	-0.00 (-0.44 – 0.44)	-0.07 (-0.54 – 0.39)	0.96
Temporal	Referent	-0.40 (-0.82 – 0.02)	-0.32 (-0.74 – 0.10)	-0.25 (-0.71 – 0.20)	0.32

Adjusted for age, current drinking status, hypertension, diabetes, BMI, TC, TG, HDL-C, LDL-C, and eGFR.
P for trend tested with generalized linear models by considering the SUA quartile as continuous ordinal variables.
Q1, quartile 1 (n=372): ≤ 244 umol/L; Q2, quartile 2 (n=363): 245 - 278 umol/L; Q3, quartile 3 (n=367): 279 - 322 umol/L; Q4, quartile 4 (n=361): ≥ 323 umol/L.
SUA, Serum Uric Acid; RCP, retinal capillary plexus.

However, for deep RCP vessel density, we observed no significant association.

We show the relationships between SUA quartile and RCP vessel density for women in **Table 4**. No significant associations were found between SUA levels and RCP vessel density in women.

We observed a significant moderating effect of sex on the association between SUA and RCP. SUA levels were relatively more strongly associated with low superficial RCP vessel density (parafovea, interaction P=0.02) in men than in women (**Table 5**).

Sensitivity Analysis

We show the adjusted associations between hyperuricemia and RCP in **Table 6**. After adjusting for the confounders mentioned above, we found significant associations between hyperuricemia and superficial RCP vessel density (parafovea: β = -0.24, 95% CI, -0.47 to -0.01) in men but not in women. However, no significant association was found between hyperuricemia and deep RCP in either sex. Moreover, associations between 1 standard deviation altered in SUA and the RCP vessel density were also tested, as shown in **Table 7**. We observed similar associations.

DISCUSSION

In this OCTA study, we evaluated the detrimental effect of high SUA levels on RCP in a relatively large community-based population. The multivariable generalized linear model analysis showed that the male participants with SUA levels in the highest quartile were significantly associated with lower RCP vessel density after adjusting for confounders.

Collectively, the studies to date have not shown a clear relationship between SUA and retinal vascular metrics (11, 12). In our study, we showed that higher SUA levels are associated with

TABLE 5 | Impact of serum uric acid on retinal capillary plexus according to sex.

Characteristics	Sex		P for
	Male (n=1267)	Female (n=1463)	interaction
Superficial RCP			
Parafovea	-0.14 (-0.24 – -0.04)	-0.05 (-0.15 – 0.04)	0.02
Inferior	-0.12 (-0.23 – -0.02)	-0.06 (-0.16 – 0.03)	0.07
Nasal	-0.16 (-0.27 – -0.05)	-0.06 (-0.16 – 0.04)	0.02
Superior	-0.11 (-0.22 – -0.01)	-0.03 (-0.13 – 0.07)	0.05
Temporal	-0.16 (-0.28 – -0.05)	-0.05 (-0.16 – 0.05)	0.02
Deep RCP			
Parafovea	-0.09 (-0.25 – 0.06)	-0.02 (-0.16 – 0.12)	0.13
Inferior	-0.12 (-0.28 – 0.04)	0.01 (-0.14 – 0.16)	0.08
Nasal	-0.09 (-0.25 – 0.06)	-0.02 (-0.16 – 0.13)	0.10
Superior	-0.06 (-0.23 – 0.11)	-0.00 (-0.15 – 0.14)	0.25
Temporal	-0.10 (-0.26 – 0.06)	-0.07 (-0.22 – 0.07)	0.23

Adjusted for age, current drinking status, hypertension, diabetes, BMI, TC, TG, HDL-C, LDL-C, and eGFR.
The SUA quartile were considered as continuous ordinal variables.
Interaction effect was calculated from models that included interaction terms of factor x continuous SUA quartiles, and were adjusted for age, current drinking status, hypertension, diabetes, BMI, TC, TG, HDL-C, LDL-C, and eGFR.
RCP, retinal capillary plexus.

TABLE 6 | Association between hyperuricemia and retinal capillary plexus.

Characteristics	Sex		P for
	male (n=1267)	female (n=1463)	interaction
Superficial RCP			
Parafovea	-0.24 (-0.47 – -0.01)	0.03 (-0.29 – 0.35)	0.02
Inferior	-0.21 (-0.45 – 0.04)	0.02 (-0.31 – 0.35)	0.04
Nasal	-0.30 (-0.55 – -0.05)	0.13 (-0.20 – 0.47)	0.004
Superior	-0.15 (-0.40 – 0.10)	-0.07 (-0.40 – 0.27)	0.20
Temporal	-0.32 (-0.58 – -0.06)	0.01 (-0.35 – 0.36)	0.02
Deep RCP			
Parafovea	-0.11 (-0.46 – 0.25)	0.27 (-0.19 – 0.73)	0.04
Inferior	-0.13 (-0.50 – 0.24)	0.36 (-0.14 – 0.85)	0.04
Nasal	-0.13 (-0.50 – 0.23)	0.34 (-0.14 – 0.81)	0.02
Superior	-0.02 (-0.41 – 0.37)	0.18 (-0.31 – 0.68)	0.22
Temporal	-0.15 (-0.52 – 0.22)	0.21 (-0.27 – 0.69)	0.05

Adjusted for age, current drinking status, hypertension, diabetes, BMI, TC, TG, HDL-C, LDL-C, and eGFR.
Hyperuricemia was considered as SUA ≥ 420 μmol/L in males and ≥ 360 μmol/L in females.
Interaction effect was calculated from models that included interaction terms of factor x hyperuricemia, and were adjusted for age, current drinking status, hypertension, diabetes, BMI, TC, TG, HDL-C, LDL-C, and eGFR.
RCP, retinal capillary plexus.

lower vessel density only in men. In supporting of our findings, YuanZhi et al. (11) previously showed an association between an elevated SUA and a smaller retinal arteriolar caliber and larger retinal venular caliber, and the associations were more pronounced in men than in women. However, a study in a Chinese coastal population showed that a higher SUA was associated with a larger retinal arteriolar caliber and larger retinal venular caliber only in women (12). This pattern of inconsistent findings may be explained by different SUA levels, different characteristics of the participants, and different imaging methods.

As reported in previous studies, the loss of blood flow or hypoperfusion in retinal vasculature leads to several ocular diseases, such as hypertensive retinopathy (22) and diabetic retinopathy (35, 36). Findings from our studies may help explain why people with higher SUA levels are more likely to develop ocular disorders and visual impairment (21, 37). However, it is important to point out that higher SUA levels are associated with only a small reduction in RCP vessel density, which may not reach clinical relevance, although it was statistically significant. Potentially, the reduced RCP in participants with higher SUA may be explained by the underlying physiological mechanism by which uric acid induces endothelial dysfunction (38, 39) and stimulates endothelial cell proliferation (40) by reducing nitric oxide and activating the renin-angiotensin system (41) and eventually leading to microvascular damage (42).

In our study, significant sex differences in SUA levels and their association with RCP vessel density were observed. We found that SUA levels were associated with RCP vessel density in men but not in women. It is important to point out that the man sex is a significant risk factor for high SUA levels, as man are up to four times more likely to be affected (43). Our findings suggest that retinal microvasculature in man are more possible to be

TABLE 7 | Association between continuous serum uric acid and retinal capillary plexus.

Characteristics	Sex		P for
	Male (n=1267)	Female (n=1463)	interaction
Superficial RCP, per 1 SD increase.			
Parafovea	-0.19 (-0.32 – -0.06)	-0.04 (-0.19 – 0.11)	0.01
Inferior	-0.17 (-0.30 – -0.03)	-0.05 (-0.21 – 0.10)	0.03
Nasal	-0.21 (-0.35 – -0.08)	-0.04 (-0.19 – 0.12)	0.007
Superior	-0.17 (-0.30 – -0.04)	-0.02 (-0.18 – 0.13)	0.02
Temporal	-0.22 (-0.36 – -0.08)	-0.06 (-0.23 – 0.11)	0.01
Deep RCP, per 1 SD increase.			
Parafovea	-0.14 (-0.33 – 0.05)	0.09 (-0.13 – 0.31)	0.02
Inferior	-0.17 (-0.37 – 0.03)	0.16 (-0.07 – 0.39)	0.01
Nasal	-0.16 (-0.35 – 0.04)	0.11 (-0.10 – 0.33)	0.03
Superior	-0.10 (-0.31 – 0.11)	0.07 (-0.16 – 0.30)	0.08
Temporal	-0.12 (-0.32 – 0.08)	0.02 (-0.20 – 0.25)	0.05

Adjusted for age, current drinking status, hypertension, diabetes, BMI, TC, TG, HDL-C, LDL-C, and eGFR.
The SUA alternations were defined as per each SD increase.
Interaction effect was calculated from models that included interaction terms of factor x SUA, and were adjusted for age, current drinking status, hypertension, diabetes, BMI, TC, TG, HDL-C, LDL-C, and eGFR.
RCP, retinal capillary plexus.

affected by high SUA levels than women. Our study emphasized the importance of modulating SUA for men. The sex differences in this study may be attributed to menopause and estrogen (10), as we observed a significant fluctuation in SUA levels around the period of menopause in women. The studies mentioned above showed inconsistent findings (11, 12). In addition, a study in Japan reported an association between SUA levels and diabetic retinopathy only in men (44). Nevertheless, other studies previously showed that an increase in SUA can be more detrimental in women (10). The discrepancy may be attributed to age, SUA levels, hormone levels, and other cohort differences. Further research is still required.

Surprisingly, we observed that SUA levels were associated with vessel density only in the superficial RCP but not in the deep RCP. OCTA imaging in the deep retinal OCT angiogram, in contrast to superficial imaging, is more likely to be affected by motion artifacts, and the quantification of flow density in deep RCP is more challenging. Previous studies have shown that the repeatability of deep retinal OCT angiograms is weaker than that of superficial retinal OCT angiograms (45–47).

It has been well-documented that higher SUA levels may lead to hypertension (41). As a matter of fact, OCTA metrics may also be affected by hypertension (16) It is interesting to note that participants with higher SUA levels had more prevalent hypertension in our study. Findings from our studies may help explain why people with higher SUA levels are more likely to develop systemic microvascular disease (17, 18).

To our knowledge, this was the first study to identify a sex-specific association between SUA and RCP in a large community-based population using OCTA. The main strengths of this study include the use of detailed ophthalmic examination in a relatively large community-based study, adjustments for several potential confounding factors, a standardized quantitative system of retinal vascular plexus including magnification correction, and investigation using sensitivity analyses to ensure the robustness of the results.

However, several limitations in our study should also be discussed. First, we could not draw a causative association between SUA and RCP due to limitations of the cross-sectional nature of this study. There is no doubt that it is of great interest to explore the alterations of RCP in relation to high SUA levels over time, and it may be a future study objective as a follow-up to the JECS. Second, the study participants were all individuals from the Jidong community. This may not adequately represent other populations, and the applicability of our results to other racial/ethnic groups might be limited. More studies in other populations are required to further determine the effect of SUA on RCP. Finally, some potential confounders, such as hormone levels, cell factors that may affect SUA, retinal vasculature, and residual confounders, were not included in the analysis.

CONCLUSION

In conclusion, we found that higher SUA levels were associated with lower superficial RCP vessel density in men. Given that the retinal microvasculature is an ideal window to observe the alternations of the microcirculation, our findings help validate the detrimental effect of high SUA levels on the retinal microvasculature and imply the importance of modulating SUA to prevent the microvascular alternation especially for men.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Staff Hospital of Jidong

oil-field of Chinese National Petroleum. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ML, LC, JQ, and FL designed and conceptualized the study and interpreted the data. KY analyzed the data. KY, XZ, YX, BS, CL, KS, and YJ had a major role in the acquisition of data. KY drafted the manuscript. ML, LC, JQ, and FL revised the manuscript for intellectual content. All authors read and approved the final manuscript.

FUNDING

This study was supported by the National Natural Science Foundation of China, No. 81900903 (to ML); National Key R&D Program of China, No. 2020YFC2008200 (to FL) and 2019YFC0840708 (to LC); Zhejiang Provincial Natural Science Foundation of China, No. LY22H120007 (to LC); the Medical and Health Science and Technology Program of Zhejiang Province, No. 2017KY113 (to ML), No. 2018KY543 (to LC); Wenzhou Science and Technology Program, No. Y20210984 (to LC). The funding bodies played no role in the study design, collection, analysis, and interpretation of data.

ACKNOWLEDGMENTS

The authors are grateful to the Jidong community for its collaboration, especially the dedicated participants and all research staff involved in the study. We thank Dr. Xianwei Wang who provided insightful methodological advice and wisdom throughout the study.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Endocrinology

CLINICAL TRIAL
published: 27 May 2022
doi: 10.3389/fendo.2022.899241

Association Between Serum Uric Acid and Carotid Intima-Media Thickness in Different Fasting Blood Glucose Patterns: A Case-Control Study

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Edited by:
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Specialty section:
This article was submitted to Cardiovascular Endocrinology, a section of the journal Frontiers in Endocrinology

Received: *18 March 2022*
Accepted: *07 April 2022*
Published: *27 May 2022*

Citation:
Gao Y, Xu B, Yang Y, Zhang M, Yu T, Zhang Q, Sun J and Liu R (2022) Association Between Serum Uric Acid and Carotid Intima-Media Thickness in Different Fasting Blood Glucose Patterns: A Case-Control Study. Front. Endocrinol. 13:899241. doi: 10.3389/fendo.2022.899241

Our objective was to analyze the correlation between serum uric acid (SUA) levels and carotid intima-media thickness (CIMT) and explore the relationship between SUA and carotid atherosclerosis in different glucose metabolism patterns. A total of 614 patients were enrolled in this case-control study, including 406 in the normouricemia group and 208 in the hyperuricemia group. The two groups were each divided into three groups according to fasting blood glucose (FBG) level: normal, impaired fasting glucose (IFG), and diabetes mellitus (DM). CIMT and the CIMT thickening rate in the hyperuricemia group were significantly higher than those in the normouricemia group: 0.17 (0.11–0.24) cm vs. 0.12 (0.08–0.15) cm and 73.56% vs. 51.97% ($p < 0.001$). Pearson's correlation analysis showed that age, systolic blood pressure (SBP), diastolic blood pressure, FBG, triglyceride, SUA, creatinine, and blood urea nitrogen were positively correlated with CIMT, whereas high-density lipoprotein cholesterol and total cholesterol were negatively correlated with CIMT. Multiple linear regression analysis showed that age, SUA, FBG, and SBP were independent factors that affected CIMT. Furthermore, age and SBP were independent factors in the normouricemia group, and FBG was an independent factor that affected CIMT in the hyperuricemia group ($p < 0.05$). In the hyperuricemia group, CIMT in the DM group was significantly higher than that in the normal group [0.20 (0.14–0.25)cm vs. 0.15 (0.1–0.25); $p < 0.05$], and the CIMT thickening rate in the DM group was significantly higher than those in the IFG and normal groups (90.38% vs. 78.38%, 90.38% vs. 65.81%; $p < 0.05$). The ROC curve analysis showed that uric acid combined with age, SBP, and FBG had the highest area under the curve (AUC) for predicting CIMT thickening [0.855 (95% confidence interval (CI): 0.804–0.906)], followed by uric acid combined with FBG [AUC: 0.767 (95% CI: 0.726–0.808)]. In conclusion, SUA was closely associated with an increase in CIMT in patients with specific FBG metabolic patterns and may be an independent risk factor for carotid atherosclerosis. SUA, especially in combination with other factors (such as age,

SBP, FBG), may serve as a specific model to help predict the incidence of CIMT thickening.
Clinical Trial Registration: http://www.chictr.org.cn, identifier ChiCTR2000039124.

Keywords: serum uric acid, carotid atherosclerosis, carotid intima-media thickness, fasting blood glucose, case-control study

INTRODUCTION

Stroke is currently the second leading cause of death worldwide, accounting for 11.8% of all deaths (1). In China, cardiovascular and cerebrovascular diseases are the most common causes of death, and there are approximately 250 million new stroke patients each year (2, 3). With the growing older adult population, the incidence of such events will likely continue to increase, most of which will be ischemic stroke (4). Carotid atherosclerosis plays an important role in the development of stroke, 18%–25% of ischemic strokes are attributed to thromboembolism due to carotid atherosclerotic disease (5–7). Approximately 28% of the global general population aged 30–79 years had an intima-media thickness abnormality of 1.0 mm or greater in 2020, which suggests that the number of people with an intima-media thickness abnormality could be as high as 1 billion (8). In China, the number of people affected by carotid atherosclerosis and carotid plaques was subsequently anticipated to reach 267.25 million and 199.83 million, respectively, by 2020 (9). Early identification of risk factors and diagnosis of carotid vascular diseases are clinically significant for the prevention of stroke. The carotid artery provides a "window" that reflects systemic arteriosclerosis, which is directly related to the development of cerebrovascular disease (10). CIMT measured using arterial ultrasound is a common clinical indicator of the degree of atherosclerosis, and increased CIMT is significantly associated with an increased risk of stroke (10). Thus, CIMT can be used to clinically assess the overall risk of stroke (11).

Hyperuricemia is a metabolic disease caused by purine metabolism or uric acid excretion disorders. Elevated uric acid levels are associated with numerous recognized risk factors for cardiovascular disease, which include age, hypertension, hyperlipidemia, obesity, and diabetes (12–16). The prevalence of hyperuricemia (serum uric acid [SUA] level > 7 mg/dl) in the adult population in the United States is 11.9% based on the United States National Health and Nutrition Examination Survey (17). A recent study showed that the incidence of hyperuricemia in China is 18.4% (18). Since the 1950s, the correlation between uric acid and cardiovascular and cerebrovascular diseases has continued to attract considerable attention (19). Similarly, several studies reported that SUA levels were independently associated with the development of cardiovascular and cerebrovascular diseases, especially myocardial infarction and stroke; therefore, SUA is a strong predictor of subsequent cardiovascular diseases and all-cause death (20–23). The result of a recent meta-analysis showed that patients with hyperuricemia had a higher incidence of CIMT thickening than the normal population (24).

Hyperuricemia is typically accompanied by a state of hyperinsulinemia or diabetes mellitus (DM); abnormal glucose metabolism is accompanied by abnormal renal function, which results in impaired excretion of uric acid in the body and ultimately hyperuricemia (25). A study in a Chinese population showed that fasting blood glucose (FBG) was an independent risk factor for CIMT, whereby CIMT levels increase significantly with changes in glucose metabolism (26). However, there have not been any studies examining whether the relationship between SUA and CIMT is consistent under different patterns of glucose metabolism. Therefore, we conducted this clinical study to explore the relationship between SUA and carotid atherosclerosis under different glucose metabolic conditions toward the early detection of risk factors and the active prevention of strokes.

MATERIALS AND METHODS

Inclusion and Exclusion Criteria

From October 1, 2020, to November 20, 2021, medical histories and examination results of inpatients were obtained from the China-Japan United Hospital of Jilin University and the First Hospital of Jilin University. Inclusion criteria were as follows: 1) ability to understand and willingness to provide written informed consent and 2) aged over 18 years. Exclusion criteria were as follows: 1) severely impaired liver and kidney function, 2) use of diuretics in the past one month, 3) history of malignant tumors or received radiotherapy within the past 3 months, 4) acute stroke, 5) autoimmune diseases, 6) blood system diseases, 7) development of a serious infection in the past month, 8) acute complications of diabetes, 9) cognitive disorders, 10) acute respiratory failure, 11) acute myocardial infarction, and 12) administered antituberculous drugs within the past month. The study was approved by the Ethics Committee of the China-Japan Union Hospital of Jilin University (2020032509) and the Ethics Committee of the First Hospital of Jilin University (2020-420). The clinical trial registration number is ChiCTR2000039124.

Clinical and Laboratory Evaluation

Basic information, such as gender, age, height, weight, and blood pressure were collected, and body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). All patients fasted for at least 10 hours. Blood and urine were collected the following morning to assess FBG, triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), SUA, creatinine (Cr), blood urea nitrogen (BUN), and urine pH levels. SUA levels were detected using the uricase-peroxidase method with a Beckman Coulter biochemical analysis system (Beckman Coulter Inc., Brea, CA, USA). Patients were divided into normouricemia and hyperuricemia groups according to the SUA cut off level of 420 μmol/L (27). A total of 614 patients participated in the case-control study, including

TABLE 1 | Characteristics of the study population.

	Normouricemic group (n=400)				*p* value	Hyperuricemic group (n=206)				*P* value
	Total (n=400)	Nomal (n=205)	IFG (n=45)	DM (n=150)		Total (n=206)	Nomal (n=117)	IFG (n=37)	DM (n=52)	
Age (years)	55.00 (44.00,64.00)	50.00 (38.00,62.00)	61.00 (55.00,67.00)	57.00 (51.00,65.00)	<0.05	56.00 (46.00,64.75)	56.00 (43.00,64.00)	58.00 (48.00,65.00)	55.00 (50.00,63.75)	> 0.05
Male%	48.52	41.46	40.00	58.00	<0.05	84.13	87.18	78.38	80.77	<0.05
BMI (kg/m2)	24.45 (22.70,26.96)	23.20 (21.30,25.93)	24.80 (23.10,27.03)	25.10 (23.68,27.83)	<0.05	25.40 (23.70,27.70)	25.40 (23.38,27.30)	25.45 (23.85,27.95)	26.55 (23.68,28.48)	> 0.05
SBP (mmHg)	133.00 (121.00,146.00)	138.00 (114.00,142,00)	142.00 (130.75,150.25)	135.00 (126.00,146.00)	<0.05	139.00 (128.00,150.00)	135.00 (128.00,145.00)	143.00 (130.00,155.50)	137.00 (126.50,152.00)	> 0.05
DBP (mmHg)	80.00 (70.00,88.00)	79.00 (69.00,86.00)	84.00 (74.75,90.00)	80.00 (72.00,87.00)	> 0.05	82.00 (77.00,93.00)	80.00 (76.00,90.00)	85.00 (80.00,94.50)	82.00 (79.50,96.00)	> 0.05
FBG (mmol/L)	5.97 (5.12,8.30)	5.15 (4.77,5.45)	6.64 (6.46,6.85)	9.38 (7.89,11.92)	<0.05	5.80 (5.12,7.02)	5.24 (4.87,5.60)	6.50 (6.27,6.63)	8.54 (7.70,10.89)	<0.05
TG (mmol/L)	1.51 (1.09,2.20)	1.30 (0.95,1.78)	1.89 (1.13,2.43)	1.72 (1.33,2.54)	<0.05	2.18 (1.46,3.55)	1.89 (1.41,3.01)	2.39 (1.57,3.93)	2.80 (1.95,4.13)	<0.05
TC (mmol/L)	5.10 (4.28,5.92)	5.02 (4.34,5.84)	5.20 (4.10,6.08)	5.16 (4.37,6.06)	> 0.05	5.32 (4.55,6.01)	5.29 (4.55,5.85)	5.37 (4.35,6.54)	5.26 (4.80,6.12)	> 0.05
HDL-C (mmol/L)	1.23 (1.04,1.46)	1.33 (1.14,1.55)	1.18 (0.99,1.46)	1.10 (0.98,1.30)	<0.05	1.09 (0.93,1.26)	1.11 (0.97,1.27)	1.82 (0.93,1.26)	2.19 (0.90,1.22)	> 0.05
LDL-C (mmol/L)	3.00 (2.37,3.56)	2.76 (2.32,3.35)	3.08 (2.33,3.79)	3.11 (2.53,3.76)	<0.05	3.15 (2.68,3.67)	3.04 (2.66,3.51)	3.38 (2.69,4.10)	3.23 (2.72,3.71)	> 0.05
Cr (umol/L)	65.40 (57.86,76.62)	66.51 (60.25,79.84)	67.61 (57.80,78.79)	62.22 (54.49,71.62)	<0.05	80.70 (67.92,93.41)	80.70 (67.93,93.19)	79.68 (65.60,87.51)	79.30 (65.18,91.55)	> 0.05
BUN (umol/L)	5.16 (4.30,5.94)	4.88 (4.02,5.69)	5.61 (4.65,6.69)	5.41 (4.69,6.33)	<0.05	5.65 (4.66,6.89)	5.40 (4.56,6.31)	6.02 (5.40,6.75)	5.90 (4.72,7.42)	> 0.05

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TG, triglycerides; TC, cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BUN, blood urea nitrogen; Cr, creatinine. Statistical methods: Chi-square test was used for gender comparison between groups. Age, BMI, SBP, DBP, FBG, TG, TC, HDL-C, LDL-C, Cr, and BUN were compared between groups by rank-sum test.

406 (66.12%) in the normouricemia group and 208 (33.88%) in the hyperuricemia group. All subjects were aged between 22 and 89 years. The proportions of males in the normouricemia and hyperuricemia groups were 48.52% and 84.13%, respectively. Patients in the normouricemia and hyperuricemia groups were each divided into three groups according to FBG levels: normal (FBG < 6.1 mmol/L; n = 205 and 117, respectively), impaired fasting glucose (IFG; FBG 6.1–7.0 mmol/L; n = 45 and 37, respectively), and DM (FBG ≥ 7.0 mmol/L or used antidiabetic drugs in patients with diabetes) (28) (n = 150 and 52, respectively). Eight patients were excluded from the blood glucose subgroup analysis due to missing FBG values.

Evaluation of Carotid Atherosclerosis

Experienced physicians used high-resolution real-time B-ultrasound (Philips EPIQ 7; Philips, Amsterdam, Netherlands) to examine the neck vessels. CIMT measurements were performed 10 mm proximal to the bifurcation of both carotid arteries. In the absence of plaques, the thickest CIMT was used. If plaques were present, the maximum thickness diameter of the plaque was used for statistical analysis. Measurements were taken three times, and an average value was obtained. CIMT < 1.0 mm was defined as normal intima, CIMT ≥ 1.0 mm was regarded as thickened, and localized CIMT ≥ 1.5 mm was defined as a plaque (8, 29). The CIMT thickening rate is defined as the percentage of the population with CIMT ≥ 1.0 mm.

Statistical Analysis

Statistical analysis was performed using SPSS 25.0. Quantitative variables were described as means ± standard deviations or medians (interquartile ranges). T-tests and rank-sum tests were used to compare groups. Pearson's correlation was used for correlation analysis. Using CIMT as the dependent variable, a multiple linear regression model was used to adjust for influencing factors and evaluate the relationship between SUA and CIMT. The area under the receiver operating characteristic (ROC) curve (AUC) indicated the specificity of the risk factors in predicting CIMT thickening. If necessary, logarithms were used for statistical correlation analysis. A $p < 0.05$ was considered statistically significant.

RESULTS

Basic Characteristics of the Population

In the normouricemia group, there were significant differences under different FBG metabolism patterns in gender, age, BMI, systolic blood pressure (SBP), TG, LDL-C, HDL-C, Cr, and BUN ($p < 0.05$), whereas there were no significant differences in diastolic blood pressure (DBP) and TC ($p > 0.05$). In the hyperuricemia group, there were differences under different FBG metabolism in gender and TG level ($p < 0.05$) but not in age, BMI, SBP, DBP, TC, LDL-C, HDL-C, Cr, and BUN levels ($p > 0.05$; **Table 1**). CIMT and the CIMT thickening rate in the hyperuricemia group were significantly higher than those in the normouricemia group: 0.17 (0.11–0.24) cm vs. 0.12 (0.08–0.15) cm and 73.56% vs. 51.97% ($p < 0.001$), respectively (**Figure 1**).

SUA as an Independent Influencing Factor of CIMT

Pearson correlation analysis showed that age (r = 0.552, $p < 0.001$), SBP (r = 0.317, $p < 0.001$), DBP (r = 0.195, $p < 0.001$), FBG (r = 0.250, $p < 0.001$), TG (r = 0.177, $p < 0.001$), SUA (r = 0.255, $p < 0.001$), Cr (r = 0.146, $p < 0.001$), and BUN (r = 0.265, $p < 0.001$) were positively correlated with CIMT, whereas HDL-C (r = −0.245, $p < 0.001$) and TC (r = −0.094, $p = 0.021$) were negatively correlated with CIMT (**Table 2**). Age had the strongest correlation with CIMT, followed by SBP, SUA, and FBG.

Multivariate linear regression analysis showed that after adjusting for age, SBP, DBP, SUA, FBG, TG, TC, HDL-C, Cr, and BUN levels, the factors that independently influenced CIMT were age [β = 0.37, 95% confidence interval (CI): 0.62–0.98, $p < 0.001$], SUA (β = 0.25, 95% CI: 0.25–0.55, $p < 0.001$), SBP (β = 0.15, 95% CI: 0.14–0.86, $p = 0.007$), and FBG (β = 0.13, 95% CI: 0.07–0.30, $p = 0.002$). Age and SUA were the most independent (**Table 3**).

SUA and CIMT in Different FBG Patterns

Multivariate analysis showed that age ($p < 0.001$) and SBP ($p = 0.041$) were independent risk factors for CIMT in the normouricemia group, whereas FBG was an independent risk factor for CIMT in the hyperuricemia group ($p = 0.033$; **Table 4**). In the normal, IFG, and DM groups, CIMTs in the hyperuricemia group were significantly higher than that in the normouricemia group: 0.15 (0.10–0.25) cm vs. 0.08 (0.07–0.12) cm, 0.15 (0.12–0.22) cm vs. 0.12 (0.11–0.16) cm, and 0.20 (0.14–0.25) cm vs. 0.14 (0.11–0.21) cm ($p < 0.05$), respectively (**Figure 2A**). Similarly, the CIMT thickening rates in the hyperuricemia group were significantly higher than that in the normouricemia group across all three FBG groups: 65.81% vs. 32.68%, 78.38% vs. 68.89%, and 90.38% vs. 74.67% ($p < 0.05$), respectively (**Figure 2B**). In the hyperuricemia group, results showed that CIMT in the DM group was significantly higher than that in the normal group [0.2 (0.14–0.25) cm vs. 0.15 (0.1–0.25); $p < 0.05$; **Figure 2A**], and the CIMT thickening rate in the DM group was significantly higher than that in the IFG and normal groups (90.38% vs. 78.38% and 90.38% vs. 65.81%, respectively; $p < 0.05$; **Figure 2B**). Under different FBG metabolism patterns, CIMT and the CIMT thickening rate in the hyperuricemia group were higher than those in the normouricemia group. Moreover, CIMT and the CIMT thickening rate in the hyperuricemia group showed a trend gradual increase with the increase in FBG.

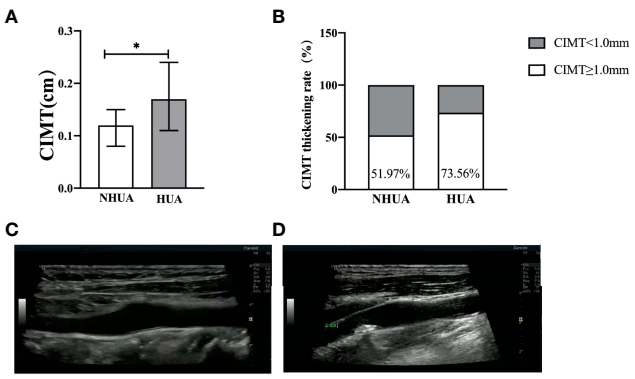

FIGURE 1 | **(A, B)** Comparison of CIMT and CIMT thickening rate between the normouricemia and hyperuricemia groups. CIMT and the CIMT thickening rate in the hyperuricemia group were significantly higher than those in the normouricemia group ($p < 0.001$). **(C, D)** The B-ultrasound image of the normal carotid intima-media thickness and carotid intima-media thickness thickening. NHUA: normouricemia group (n = 406); HUA, hyperuricemia group (n = 208). *$p < 0.05$.

TABLE 2 | Correlation analysis of CIMT with general data and biochemical indexes.

	r	*P* value
Age	0.552	<0.001
BMI	0.073	0.109
SBP	0.317	<0.001
DBP	0.195	<0.001
SUA	0.255	<0.001
FBG	0.250	<0.001
U-PH	-0.550	0.182
TG	0.177	<0.001
TC	-0.094	0.021
HDL-C	-0.245	<0.001
LDL-C	0.045	0.263
Cr	0.146	<0.001
BUN	0.265	<0.001

Pearson correlation analysis showed that age (r = 0.552, p < 0.001), SBP (r = 0.317, p < 0.001), DBP (r = 0.195, p < 0.001), FBG (r = 0.250, p < 0.001), TG (r = 0.177, p < 0.001), SUA (r = 0.255, p < 0.001), Cr (r = 0.146, p < 0.001), and BUN (r = 0.265, p < 0.001) were positively correlated with CIMT, whereas HDL-C (r = –0.245, p < 0.001) and TC (r = –0.094, p = 0.021) were negatively correlated with CIMT.

TABLE 3 | Multiple linear regression analysis of CIMT as dependent variable.

	β	SE	β(95%CI)	*P* value
Age	0.37	0.09	(0.62,0.98)	<0.001
SUA	0.25	0.08	(0.25,0.55)	<0.001
SBP	0.15	0.19	(0.14,0.86)	0.007
FBG	0.13	0.06	(0.07,0.30)	0.002

Take CIMT as the dependent variable, multivariate linear regression analysis showed that after adjusting for age, SBP, DBP, SUA, FBG, TG, TC, HDL-C, Cr, and BUN levels, the factors that independently influenced CIMT were age (β = 0.37, 95% CI: 0.62–0.98, p < 0.001), SUA (β = 0.25, 95% CI: 0.25–0.55, p < 0.001), SBP (β = 0.15, 95% CI: 0.14–0.86, p = 0.007), and FBG (β = 0.13, 95% CI: 0.07–0.30, p = 0.002).

SUA Combined With Age, FBG, and SBP as the Best Index for Diagnosing CIMT Thickening

The ROC curve analysis showed that the AUCs for using age, SBP, FBG, and SUA to predict CIMT were 0.854 (95% CI: 0.820–0.888), 0.749 (95% CI: 0.691–0.807), 0.746 (95% CI: 0.705–0.787), and 0.581 (95% CI: 0.533–0.629), respectively (**Figures 3A–D**). SUA combined with age, SBP, and FBG had the highest AUC for predicting the thickening of CIMT [AUC: 0.855 (95% CI: 0.804–0.906)] (**Figure 3E**), followed by SUA combined with FBG [AUC: 0.767 (95% CI: 0.726–0.808); **Figure 3F**]. Age was the most significant factor, and the inclusion of factors such as SBP, FBG, and SUA helped improve diagnostic efficiency.

TABLE 4 | Determinants of traditional risk factors for CIMT in different SUA groups in a multivariate analysis.

	Normouricemic group				Hyperuricemic group			
	β	SE	(95%CI)	*P* value	β	SE	(95%CI)	*P* value
Age	0.35	0.12	(0.48,0.95)	<0.001	–	–	–	–
BMI	0.05	0.19	(-0.21,0.53)	0.383	–	–	–	–
SBP	0.12	0.19	(0.02,0.74)	0.041	–	–	–	–
FBG	0.09	0.07	(0.25,0.80)	0.148	0.156	0.13	(0.02,0.54)	0.033
TG	-0.06	0.05	(-0.15,0.05)	0.349	0.01	0.06	(-0.12,0.13)	0.905
HDL-C	-0.06	0.11	(-0.32,0.12)	0.360	–	–	–	–
LDL-C	-0.02	0.08	(-0.18,0.14)	0.790	–	–	–	–
Cr	0.03	0.08	(-0.11,0.19)	0.623	–	–	–	–
BUN	0.03	0.09	(-0.14,0.21)	0.672	–	–	–	–

Take CIMT as the dependent variable, multivariate analysis showed that age ($p < 0.001$) and SBP ($p = 0.041$) were independent risk factors for CIMT in the normouricemia group, whereas FBG ($p = 0.033$) was an independent risk factor for CIMT in the hyperuricemia group.

DISCUSSION

In this case-control study, we evaluated the relationship between SUA and CIMT in the Chinese population and the correlation between SUA and CIMT in different glucose metabolism states. We found that patients with high uric acid had higher CIMT and CIMT thickening rates than those with normal uric acid. Meanwhile, CIMT and the CIMT thickening rate in the hyperuricemia group showed a trend of gradual increase with the increase in FBG. By examining cross-sectional data of the population, there was a significant association between SUA and CIMT, which persisted even after adjusting for traditional confounding factors, such as age, blood pressure, lipids, and FBG. Serum uric acid can be used as an independent risk factor for CIMT thickening. Furthermore, in addition to uric acid level, age, SBP, and FBG were independently correlated with CIMT too. An evaluation of SUA combined with other factors (such as age, SBP, FBG) may provide a more accurate prediction of CIMT thickening.

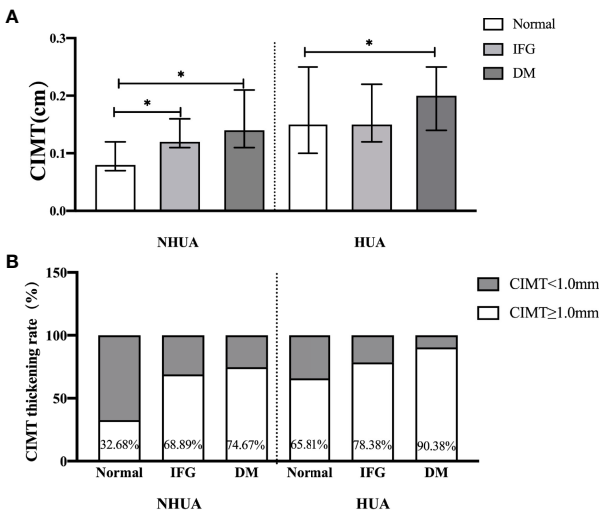

FIGURE 2 | CIMT and CIMT thickening rate for different FBG metabolism patterns. Patients were divided into three groups according to fasting blood glucose metabolism patterns: normal, impaired fasting glucose (IFG), and diabetes mellitus (DM). Under different FBG metabolism patterns, CIMT and the CIMT thickening rate in the hyperuricemia group were higher than those in the normouricemia group ($p < 0.05$). CIMT and CIMT thickening rate in the hyperuricemia group showed a trend gradual increase with the increase in FBG ($p < 0.05$). NHUA, normouricemia group (Normal, n=205; IFG, n=45; DM, n=150); HUA, hyperuricemia group (Normal, n=117; IFG, n=37; DM, n=52). *$p < 0.05$.

Stroke is a serious health hazard with high mortality and disability rates and has gradually become the leading cause of death in humans (30, 31). Approximately 5.5 million stroke-related deaths occur each year (32). Around 30% of patients with an initial onset of acute cardio-cerebrovascular disease exhibit no clinical symptoms (33). Most strokes are caused by arterial occlusion due to the formation of an embolus due to carotid plaque rupture (34). Changes in CIMT occur earlier than the formation of plaques during the development of carotid atherosclerosis. SUA acts as an antioxidant scavenger that can provide powerful free radical scavenging capacity in the plasma, so SUA offers certain benefits, but there is also evidence from animal models and epidemiological studies of an association between the increase in SUA concentration and adverse cardiovascular and cerebrovascular risk factors (35, 36). In a study in hospitalized older adults in Japan, CIMT and the prevalence of carotid atherosclerosis were shown to significantly increase with an increase in the uric acid quartile in both men and women without metabolic syndrome, which suggests that SUA was an independent risk factor for carotid atherosclerosis (37). Meanwhile a clinical trial in the United States reported that SUA levels were positively correlated with CIMT and associated with significant vascular stenosis in patients with ischemic stroke, which indicated that SUA played a key role in the pathogenesis of atherosclerosis and participates in the development of ischemic stroke (21). In China, a study by Song et al. in middle-aged and older Chinese adults also confirmed a linear relationship between SUA and CIMT (38). Indeed, the independent risk of cardiovascular disease in a general Italian population significantly increases when uric acid levels exceed 5.6 mg/dl (39). However, several studies have shown that the incidence of cardiovascular and cerebrovascular diseases does not increase in patients with hyperuricemia without gout (40, 41). According to National Health and Nutrition Examination Survey III, the relationship

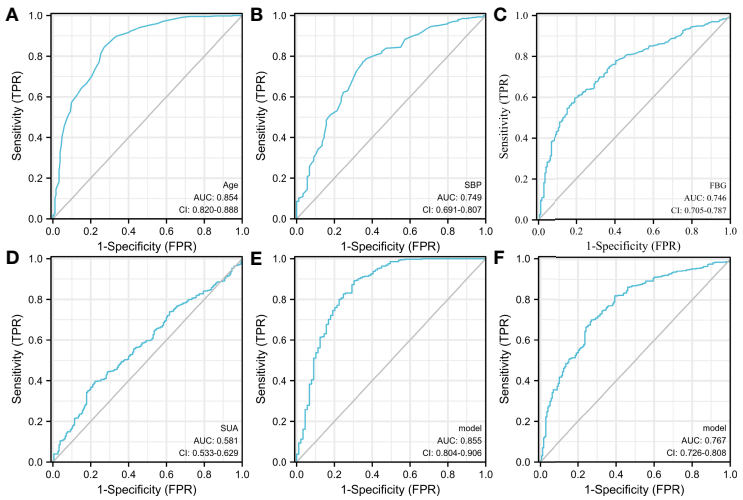

FIGURE 3 | The receiver operating characteristic (ROC) curve. **(A–D)** Specificity of age, SBP, FBG, and SUA for predicting the thickening of CIMT. **(E)** Specificity of SUA combining age, SBP, and FBG for predicting the thickening of CIMT. **(F)** Specificity of SUA combined with FBG for predicting the thickening of CIMT. SUA combined with age, SBP, and FBG had the highest AUC for predicting the thickening of CIMT, followed by SUA combined with FBG.

between SUA level and cardiovascular disease mortality was u-shaped (42). Both low and high uric acid levels may be independent risk factors for cardiovascular disease; moreover, uric acid levels over 7 mg/dl were an independent risk factor for stroke (42). Our study further confirmed SUA can be used as an independent risk factor for carotid atherosclerosis in Chinese people.

Mendelian randomized analysis showed that elevated levels of SUA lead to elevated blood pressure, which in turn, increased the risk of cardiovascular diseases, such as coronary heart disease and stroke (43). A study in Chinese patients with type 2 diabetes found that elevated SUA levels were strongly associated with carotid atherosclerosis (44). Diabetes is associated with an increased risk of atherosclerotic disease, and people with diabetes have a higher risk of stroke than those without diabetes (45, 46). Previous genome-wide studies have shown that impaired glucose tolerance is significantly associated with CIMT, and a genome-wide study on uric acid salt found that transcription factors involved in urate metabolism may be associated with various metabolic processes of synergy between adjustment, such as blood glucose and other cardiovascular risk factors, which may increase the likelihood of confusion regarding causality (47). We found that Age, SBP, FBG, and SUA played important roles in carotid atherosclerosis. However, because age is an uncontrollable factor for cardiovascular disease, more attention should be directed toward controllable factors, such as SBP, FBG, and SUA. FBG and SBP play crucial roles in the development of stroke (48–50), and our study demonstrated that the effect of SUA on carotid atherosclerosis should not be ignored. SUA, in combination with other factors, may serve as a specific model to help predict the incidence of CIMT thickening. Previous studies have shown that LDL-C causes atherosclerosis. However, we did not observe a correlation between LDL-C and CIMT. We speculate that this discrepancy is related to the administration of lipid-lowering drugs to some patients. Given the correlation between SUA level and CIMT, uric acid could be considered an independent risk factor for carotid arteriosclerosis as well as a potential intervention target. Several studies have shown that reducing uric acid by administering allopurinol, febuxostat, and other drug treatments can significantly improve local and systemic endothelial function, peripheral vasodilation capacity, and blood flow and delay the progression of CIMT (51–53). However, determining its impact on cardiovascular and cerebrovascular diseases requires prospective studies to be conducted using reliable clinical endpoints.

Uric acid is a damage-related molecule that is released during tissue ischemia and cell death. When uric acid crystallizes, it activates nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP-3) inflammasomes, which leads to apoptosis-associated speck-like protein-containing speck formations, caspase-1 activation, and interleukin (IL)-1β production. NLRP-3 and IL-1β are associated with plaque instability and atherogenesis. Urate crystals trigger a series of inflammatory reactions by activating the NLRP-3 pathway, promoting an increase in CIMT, which leads to plaque formation and ultimately, cardiovascular and cerebrovascular events (54, 55). However, the mechanism of increased blood uric acid leading to CIMT remains controversial. In general, researchers worldwide agree that blood uric acid leads to the development of atherosclerosis *via* the following mechanisms: 1) elevated blood uric acid level promotes low-density lipoprotein oxidation and lipid peroxidation, which in turn, contributes to the development of atherosclerosis (56); 2) when blood uric acid concentration increases, arteriosclerotic uric acid microcrystals precipitate easily, are deposited in the vascular intima, and cause

local inflammatory reactions, which directly damages vascular endothelial cells, eventually resulting in lipid deposition (57); 3) an increase in blood uric acid is often accompanied by the aggregation of reactive oxygen species, such as oxygen free radicals and hydrogen peroxide, which leads to vascular inflammatory reactions (58); 4) urate, as an inflammatory substance, directly promotes platelet aggregation and thrombosis, whereas cytokines released by platelets cause vascular smooth muscle hyperplasia (51); and 5) elevated blood uric acid level has been linked to obesity, insulin resistance, dyslipidemia, and hypertension, all of which are associated with an increased risk of cardiovascular disease. Drop uric acid treatment is the main method used to promote uric acid excretion, and studies have shown that drop uric acid treatment can reduce blood pressure. Patients with high uric acid hematic disease who have high blood pressure, especially young patients without a long history of high blood pressure; otherwise, high uric acid hematic disease patients with a prolonged period of high blood pressure eventually develop chronic kidney disease due to uric acid excretion dysfunction. This, in turn, forms a vicious cycle of hyperuricemia and subsequently triggers or aggravates cardiovascular disease (59). Moreover, several studies have confirmed that SUA-lowering therapy can improve outcomes of patients with a cardiovascular or cerebrovascular disease to a certain extent (60).

Our study had several limitations. First, the participants in the study were recruited from only two hospitals, and the number of analyzed cases in the study was small. Thus, the study population may not represent the current situation of patients with hyperuricemia across China. Moreover, the study lacked reliable comprehensiveness to clarify certain relationships. Further prospective studies with larger and more representative samples are needed to confirm the association between SUA level and cerebrovascular disease. Second, we only evaluated FBG levels of the participants, and postprandial blood glucose and hemoglobin A1c levels were not evaluated, which may impact the identification of glucose metabolic conditions. Finally, whether uric acid-lowering treatment influences the outcomes of patients with cardiovascular and cerebrovascular diseases requires further study.

Our findings suggested that SUA was an independent risk factor for carotid atherosclerosis and that an elevated SUA level promoted thickening of the carotid intima depending on FBG patterns. SUA, combined with age, SBP, FBG, could be used as a specific model to help predict the incidence of CIMT thickening. An in-depth study of the specific underlying mechanism would be valuable for the early prevention of carotid vascular diseases.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the China-Japan Union Hospital of Jilin University (2020032509) and the Ethics Committee of the First Hospital of Jilin University (2020-420). The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

YG and BX were involved in data collection and article writing; RL designed the project and was responsible for article revisions; YY and MZ were involved in measuring CIMT; TY and YG were responsible for literature retrieval; QZ and JS were responsible for chart construction. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by grants from the Department of Science and Technology of Jilin Province (20210204217YY), the Interdisciplinary Innovation Project of the First Hospital of Jilin University (JDYYJCHX2020014), and the Scientific Research Project of the Jilin Provincial Department of Education (JJKH202 11162KJ).

ACKNOWLEDGMENTS

We would like to thank all patients and participants who contributed to this study.

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frontiers | Frontiers in Endocrinology

ORIGINAL RESEARCH
published: 13 June 2022
doi: 10.3389/fendo.2022.890305

Association Between Serum Uric Acid Level and Carotid Atherosclerosis and Metabolic Syndrome in Patients With Type 2 Diabetes Mellitus

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Background: Serum uric acid (SUA) is associated with many cardiovascular risk factors, such as metabolic syndrome (MetS) and subclinical atherosclerosis. However, the relationship of SUA with carotid atherosclerosis remains controversial. We aimed to investigate whether elevated SUA levels are associated with a high risk of carotid atherosclerosis and MetS in patients with type 2 diabetes mellitus (T2DM).

Methods: This cross-sectional study was performed with a sample of 1,947 hospitalized patients with T2DM. Carotid intima-media thickness and carotid artery plaques were measured *via* Doppler ultrasound.

Results: Uric acid levels were negatively associated with HbA1C, eGFR, and HDL-C (all $P < 0.001$) and positively associated with WBC, BMI, ACR, creatinine, total cholesterol, triglycerides, LDL-C, systolic blood pressure, and diastolic blood pressure (all $P < 0.001$). After adjusting for multiple potential confounders, the risks were substantially higher for MetS in the highest quartile of SUA levels (odds ratio: 2.91, 95% confidence interval: 1.54–5.51, $P = 0.003$ for trend) than in the lowest quartile of SUA levels. Furthermore, a significant increase was observed in the prevalence of overweight/

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Edited by:
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Reviewed by:
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Specialty section:
This article was submitted to Cardiovascular Endocrinology, a section of the journal Frontiers in Endocrinology

Received: *05 March 2022*
Accepted: *04 May 2022*
Published: *13 June 2022*

Citation:
Li W, Wang Y, Ouyang S, Li M, Liu R, Zhang Y, Liu X, Li T and Liu S (2022) Association Between Serum Uric Acid Level and Carotid Atherosclerosis and Metabolic Syndrome in Patients With Type 2 Diabetes Mellitus. Front. Endocrinol. 13:890305. doi: 10.3389/fendo.2022.890305

obesity, hypertension, and dyslipidemia across the SUA quartiles independent of confounders. However, no significant association was found between SUA quartile with the presence of carotid atherosclerosis.

Conclusions: In patients with T2DM, SUA levels were closely associated with MetS and its components but not with carotid atherosclerosis.

Keywords: uric acid, metabolic syndrome, carotid atherosclerosis, intima-media thickness, type 2 diabetes mellitus

BACKGROUND

Accumulating epidemiological and clinical evidence demonstrated that serum uric acid (SUA) levels are strongly associated with many cardiovascular risk factors, such as obesity, hypertension, hyperlipidemia, diabetes, metabolic syndrome (MetS), and subclinical atherosclerosis (1–3). Among these risk factors, the associations of SUA with atherosclerosis and MetS have been observed in several studies in both general and type 2 diabetic mellitus (T2DM) populations (4, 5).

Uric acid is the end metabolic product of purine in humans. Hyperuricemia can lead to various diseases, and it is most notably involved in the pathogenesis of gouty arthritis (3). Previous studies have suggested that hyperuricemia is a risk factor for cardiovascular disease (CVD) in the general population (6, 7). Ultrasound of the carotid artery to identify carotid intima-media thickness (c-IMT) and carotid artery plaques (CAP) can predict the risk of CVD. As a surrogate of atherosclerosis diseases, CAP accounts for approximately a fifth of the risk of stroke and coronary artery diseases (8, 9). However, the associations between SUA concentration and carotid atherosclerosis, as reflected by c-IMT and CAP, have previously been studied but produced conflicting results. A population-based cross-sectional survey demonstrated that SUA level is associated with MetS and an independent risk factor for carotid atherosclerosis in patients with T2DM (4). Another study showed that SUA levels are closely associated with hypertension and MetS but not with atherosclerosis in people with diabetes (10). Some authors considered that the role of uric acid in atherosclerosis might be attributed to other cardiovascular risk factors, such as hypertension, obesity, MetS, and chronic kidney disease (11, 12). Furthermore, uric acid-induced inflammatory pathway may play an important role in the pathogenesis of MetS, increased uric acid levels have been founded in inflammatory conditions (13), the role of inflammation in the association between SUA and carotid atherosclerosis should be examined.

Although previous studies have showed that the independence of relationship between SUA and MetS and atherosclerosis. However, few studies have examined the relationship between SUA and components of MetS, as well as the association between SUA and carotid atherosclerosis in patients with T2DM. Therefore, this study aimed to investigate the association between SUA level and MetS and carotid atherosclerosis in T2DM populations.

Abbreviations: ACR, Albumin/creatinine ratio; BMI, Body mass index; CAP, Carotid artery plaques; CI, Confidence interval; c-IMT, Carotid intima-media thickness; CVD, Cardiovascular disease; DBP, Diastolic blood pressure; eGFR, Estimated glomerular filtration rate; FBG, Fasting plasma glucose; HbA1c, Glycosylated hemoglobin; HDL-C, High-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; MetS, metabolic syndrome; OR, Odds ratio; SBP, Systolic blood pressure; TC, Total cholesterol; TG, Triglyceride; T2DM, Type 2 diabetes mellitus; SUA, Serum uric acid.

METHODS

Study Subjects

This cross-sectional study evaluated the prevalence of MetS and carotid atherosclerosis in patients with T2DM aged over 18 who were hospitalized at the First Affiliated Hospital of Zhengzhou University from January 2018 to December 2020. Patients who were taking any drug that might interfere with uric acid metabolism, such as allopurinol, furosemide, and thiazides, etc, were excluded (N = 85). Patients who did not undergo carotid ultrasound examination and without complete clinical and SUA data were also excluded (N = 368). In total, 1,947 patients, including 1,335 males, were included in the final analyses. All patients underwent an interview and provided a history of hypertension, CVD, duration of diabetes, use of lipid-lowering drugs and antihypertensive agents, alcohol consumption, and smoking habits. Body mass index (BMI) was calculated by body weight (kg) divided by height squared (m^2). Blood pressure was measured by using an automatic blood-pressure meter after the participants sat for at least 10 min. The average of three measurements was recorded for further analysis. This study was approved by the Institution Review Board of the First Affiliated Hospital of Zhengzhou University.

Laboratory Measurements

The patients were asked to fast overnight, and then blood samples were obtained for further analysis. Total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), fasting blood glucose (FBG), insulin, SUA, creatinine, white blood cells (WBC), and C-reactive protein (CRP) were measured. HbA1c level was measured *via* high-performance liquid chromatography. A sterile, random-spot urine sample was used to measure the albumin/creatinine ratio (ACR). The estimated glomerular filtration rate (eGFR) was calculated using the simplified Modification of Diet in Renal Disease formula: $eGFR = 186.3 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female})$.

Assessment of CAP and c-IMT

Carotid ultrasonography was performed using a color Doppler ultrasonic diagnostic instrument. Trained and certified sonographers conducted the examination. c-IMT was determined at the point approximately 1.5 cm away from the distal part of the bifurcation of common carotid artery. c-IMT was calculated as the mean of the intima-media thicknesses of the left and right common carotid arteries. CAP was defined as a focal region with a thickness of ≥1.5 mm as measured from the media adventitia interface to the lumen–intima interface or as the presence of focal wall thickening that was at least 50% greater than that of the surrounding vessel wall.

Definition of MetS

MetS was defined on the basis of the updated National Cholesterol Education Program Adult Treatment Panel III criteria for Asian-Americans as presenting at least three of the following components: 1) waist circumference 90 cm or greater in men or 80 cm or greater in women; 2) TG 1.7 mmol/L or greater; 3) HDL-C less than 1.03 mmol/L in men or less than 1.30 mmol/L in women; 4) blood pressure 130/85 mmHg or greater or current use of antihypertensive medications; or 5) fasting plasma glucose 5.6 mmol/L or greater or previously diagnosed with T2DM or on oral antidiabetic agents or insulin (14).

Statistical Analysis

Continuous variables were checked for the normal distribution using Kolmogorov–Smirnov statistics. Normally distributed data were expressed as means ± SD, whereas variables with a skewed distribution were reported as median (interquartile range, IQR). Categorical variables were represented by frequency and percentage. Kruskal–Wallis test was used to analyze groups differences for continuous variables, and Chi-square test was used for categorical variables. Spearman correlation coefficients between SUA and metabolic features were calculated by partial correlation analysis on ranks. Multivariate logistic regression models were used to estimate the odds ratios (ORs) for CAP and MetS according to SUA quartiles. Potential confounding variables, including age, gender, smoking, alcohol drinking, duration of diabetes, self-reported CVD, eGFR, FBG, HbA1C, CRP, and BMI, were controlled in the regression models. All statistical analyses were performed using SPSS version 26.0 (SPSS, Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

RESULTS

Characteristics of the Participants According to SUA Quartiles

We identified 1,947 patients with T2DM with a mean age of 49.6 ± 11.9 years. The population studied herein was stratified into

TABLE 1 | Characteristics of study participants according to uric acid quartiles.

	Q1 N = 485 (< 242)	Q2 N = 485 (242-293)	Q3 N = 489 (293-353)	Q4 N = 488 (≥ 353)	P value
Male, n (%)	213 (43.9)	299 (61.6)	384 (78.5)	439 (90)	0
Age, years	54 (47–62)	53 (45–60)	50 (42–58)	46 (35–54)	0
DD, years	5 (1–10)	5 (0.9–10)	5 (2–11)	3 (0.3–10)	0.049
CVD, n (%)	46 (9.5)	60 (12.4)	40 (8.2)	41 (8.4)	0.1
Hypertension, n (%)	171 (35.3)	221 (45.6)	206 (42.1)	252 (51.6)	0
Smoking, n (%)	75 (15.5)	124 (25.6)	141 (28.8)	157 (32.2)	0
Alcohol, n (%)	60 (12.4)	102 (21)	125 (25.6)	129 (26.4)	0
BMI, kg/m^2	24 (22–26.2)	24.4 (22.9–27.7)	26 (23.9–28)	26.9 (24.7–30)	0
HbA1C, %	9 (7.5–10.6)	8.6 (7.3–10.2)	8.5 (7.4–10.1)	8.1 (6.7–10.4)	0
FBG, mmol/L	7.8 (6.2–10.6)	7.8 (6.0–10.0)	7.8 (6.5–10.3)	7.4 (6.0–10.8)	0.199
Insulin, μU/mL	4.54 (2.1–8.1)	4.9 (2.5–8.6)	5.5 (2.8–11.1)	7.0 (3.7–13.8)	0
CRP, mg/L	0.85 (0.49–2.16)	0.96 (0.51–2.54)	1.09 (0.53–2.43)	1.78 (0.86–3.82)	0
WBC	6 (5.1–7.4)	6.1 (5.1–7.4)	6.37 (5.5–7.6)	6.6 (5.6–8.0)	0
ACR, mg/mmoL	0.67 (0.38–1.43)	0.68 (0.4–2.19)	0.8 (0.34–3.74)	1.29 (0.47–5.82)	0
Creatinine, μmol/L	54 (47.7–65.5)	61 (53–69.7)	67 (58–76.4)	71 (62–81)	0
SUA, μmol/L	206 (181–223)	268 (256–282)	319 (305–337)	410 (381–459)	0
eGFR, $ml/min/1.73^2$	105.7 (99.2–115.0)	104.3 (98.1–113.9)	105.3 (94.6–114.2)	106.1 (90.9–118.8)	0.418
SBP, mmHg	129 (120–143)	131 (120–141)	135 (126–145)	133 (126–143)	0.004
DBP, mmHg	80 (73–87)	81 (74–89)	84 (79–92)	85 (79–92)	0
MetS, n (%)	277 (57.1)	353 (72.8)	392 (80.2)	429 (87.9)	0
CAP, n (%)	275 (56.7)	258 (53.2)	244 (49.9)	238 (48.8)	0.058
c-IMT, mm	1.3 (1.1–1.3)	1.2 (1.1–1.3)	1.2 (1.1–1.3)	1.2 (1.1–1.3)	0.179
TC, mmol/L	4.43 (3.8–5.1)	4.34 (3.6–5.2)	4.38 (3.8–5.1)	4.44 (3.8–5.2)	0.012
TG, mmol/L	1.26 (0.9–2.0)	1.68 (1.1–2.6)	1.88 (1.2–3.0)	2.09 (1.4–3.9)	0
HDL-C, mmol/L	1.13 (0.9–1.4)	1.03 (0.9–1.3)	0.99 (0.8–1.2)	0.95 (0.8–1.2)	0
LDL-C, mmol/L	2.69 (2.1–3.3)	2.51 (1.9–3.5)	2.61 (2.0–3.2)	2.48 (1.8–3.1)	0.189

ACR, albumin/creatinine ratio; BMI, body mass index; c-IMT, carotid intima-media thickness; CAP, carotid artery plaques; CRP, C-reactive protein; DBP, diastolic blood pressure; DD, duration of diabetes; eGFR, estimated glomerular filtration; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; SBP, systolic blood pressure; SUA, serum uric acid; TC, total cholesterol; TG, total triglycerides; WBC, white blood cells.

quartiles according to SUA levels. The baseline demographic and medical characteristics for SUA quartiles are provided in **Table 1**. The cut-off SUA values for Q1, Q2, Q3, and Q4 were <242, 242–293, 293–353, and ≥353 μmol/L, respectively. When analyzed by quartiles of SUA levels, the patients with higher uric acid levels were more likely to be male, smokers, drinker, and younger (all P < 0.001). With respect to metabolic parameters, the patients in the higher uric acid quartiles exhibited higher levels of systolic blood pressure (SBP) and diastolic blood pressure (DBP), BMI, CRP, creatinine, insulin, ACR, TG, and TC than those in the lower uric acid quartiles (all P < 0.05). By contrast, the patients with higher uric acid levels displayed shorter duration of diabetes and lower levels of HbA1C and HDL-C than those with lower uric acid levels (all P < 0.05). However, no difference in c-IMT and CAP was observed between the SUA quartile groups.

TABLE 2 | Correlation between SUA and other parameters.

Variable	Correlation coefficient	P value
BMI, kg/m^2	0.325	0
CRP, mg/L	0.019	0.514
WBC	0.129	0
HbA1C, %	-0.173	0
ACR, mg/mmoL	0.152	0
FBG, mmol/L	-0.044	0.056
Creatinine, μmol/L	0.292	0
eGFR, ml/min/1.73^2	-0.33	0
TC, mmol/L	0.105	0
TG, mmol/L	0.184	0
HDL-C, mmol/L	-0.148	0
LDL-C, mmol/L	0.013	0.56
SBP, mmHg	0.092	0
DBP, mmHg	0.099	0
c-IMT, mm	-0.06	0.355

All correlation coefficients were calculated after adjustment for age, gender, and diabetes duration.

Correlation Between SUA and Other Parameters

Partial correlation analysis revealed close correlation between SUA levels and BMI, HbA1C, ACR, creatinine, eGFR, SBP, DBP, TC, TG, and HDL-C among various metabolic features after adjusting for age, gender, and duration of diabetes (**Table 2**). Remarkably, SUA levels gradually increased with increasing number of MetS components. The mean values of SUA concentrations significantly increased for those with one, two, three, four, and five components of MetS; the mean values were 244.3 ± 62.7, 266.9 ± 75.5, 298.7 ± 92.5, 322.2 ± 94.3, and 337.7 ± 98.2 μmol/L, respectively (P < 0.001, **Figure 1A**). Furthermore, the prevalence of MetS was higher with increasing SUA quartiles; 57.10%, 72.80%, 80.20%, and 87.90% for Q1, Q2, Q3, and Q4, respectively (P < 0.001 for trend, **Figure 1B**).

Comparison of MetS and CAP Between the SUA Quartile Groups

As presented in **Table 3**, the OR for MetS was higher with increasing SUA quartiles after adjusting for age and gender (OR: 5.132, 95% CI: 3.63–7.25, P < 0.001 for trend). In the highest uric acid quartile, the OR was 2.91 (95% CI: 1.54–5.51, P = 0.003 for trend) for MetS after further adjusting for alcohol drinking, smoking, duration of diabetes, self-reported CVD, BMI, CRP, HbA1C, FBG, eGFR, TC, and LDL-C. A comparison of CAP between the SUA quartile groups after adjusting for multiple potential confounders is given in **Table 3**. However, no significant differences were observed in the prevalence of CAP across the four groups.

Association Between SUA Quartiles and Other MetS Components

The associations of the SUA quartiles with different MetS components in all patients with T2DM are summarized in **Table 4**. After controlling for multiple confounding factors, the SUA quartiles were found to be independently associated with increased prevalence of hypertension in T2DM populations. The OR for hypertension increased with increasing SUA quartiles. In

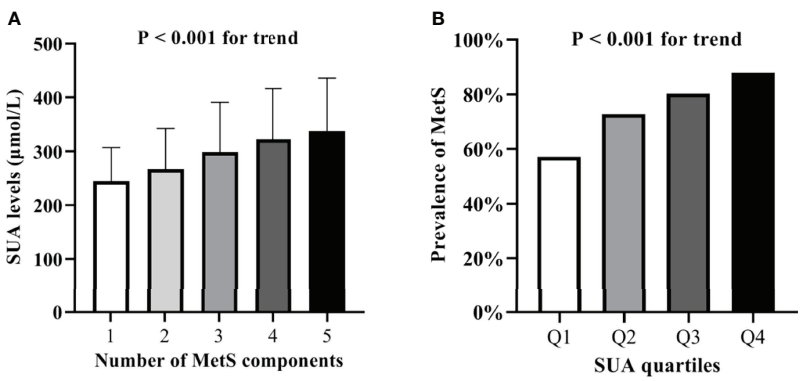

FIGURE 1 | **(A)** Serum uric acid levels according to the number of MetS components. **(B)** Comparison of the prevalence of MetS among the four SUA quartile groups.

TABLE 3 | Adjusted ORs and 95% CIs for MetS and CAP according to SUA quartiles.

	Q1	Q2	Q3	Q4	P value
			OR (95% CI)		
CAP					
Model 1	1	0.85 (0.64–1.14)	0.90 (0.67–1.21)	1.07 (0.78–1.47)	0.408
Model 2	1	0.77 (0.58–1.04)	0.82 (0.60–1.11)	0.90 (0.65–1.25)	0.332
Model 3	1	0.80 (0.59–1.08)	0.85 (0.62–1.16)	0.97 (0.69–1.37)	0.38
Model 4	1	0.82 (0.54–1.24)	0.87 (0.56–1.35)	1.07 (0.65–1.76)	0.559
MetS					
Model 1*	1	2.00 (1.52–2.63)	2.94 (2.18–3.96)	5.13 (3.63–7.25)	0
Model 2*	1	1.96 (1.49–2.58)	2.94 (2.18–3.97)	5.17 (3.65–7.32)	0
Model 3*	1	1.41 (1.01–1.97)	1.69 (1.18–2.42)	2.66 (1.77–4.01)	0
Model 4*	1	2.01 (1.24–3.25)	1.99 (1.17–3.37)	2.91 (1.54–5.51)	0.003

Model 1 adjusted for age and gender.
Model 2 further adjusted for alcohol drinking, smoking, duration of diabetes, hypertension, and history of CVD.
Model 3 further adjusted for BMI.
Model 4 further adjusted for eGFR, CRP, FBG, HbA1C, TG, TC, HDL-C, and LDL-C.
Model 1 adjusted for age and gender.*
Model 2 further adjusted for alcohol drinking, smoking, duration of diabetes, and history of CVD.*
Model 3 further adjusted for BMI.*
Model 4 further adjusted for eGFR, CRP, FBG, HbA1C, TC, and LDL-C.*

the highest SUA quartile, the OR was 2.13 (95% CI: 1.34–3.38, P = 0.015) for hypertension. Similarly, in the highest SUA quartile, the OR was 3.45 (95% CI: 2.25–5.28, P < 0.001) for overweight/obesity (BMI ≥ 25 kg/m^2). Dyslipidemia was defined as TC ≥ 6.2 mmol/L, or TG = 1.7 mmol/L or greater, or HDL-C < 1.03 mmol/L in men or < 1.30 mmol/L in women. In our patients with T2DM, after controlling for confounding factors, the SUA quartiles were still independently associated with increased prevalence of dyslipidemia. In the highest SUA quartile, the OR for dyslipidemia (TG ≥ 1.7 mmol/L) was 2.71 (95% CI: 1.73–4.25, P < 0.001), and the OR for dyslipidemia (TC ≥ 6.2 mmol/L) was 2.51 (95% CI: 1.17–5.38, P = 0.013). However, no significant differences were found in the prevalence of dyslipidemia (HDL-C abnormality) across the four SUA quartile groups.

DISCUSSION

SUA levels were strongly associated with the presence of MetS but not with the presence of carotid atherosclerosis in the patients with T2DM. In the highest SUA quartile, the ORs were 2.91 (95% CI: 1.54–5.51) for MetS after further adjusting for other atherosclerotic risk factors, such as age, gender, BMI, eGFR, and other lipid and glycemic parameters. However, SUA quartile was not associated with the presence of carotid artery plaque. Furthermore, the prevalence of hypertension, dyslipidemia, and overweight/obesity, substantially increased across the SUA quartiles independent of potential confounders.

Many studies have evaluated the associations between uric acid and MetS (15, 16). Consistent with the results of previous studies (4, 10), we observed a strong relationship between SUA and MetS. The ORs were substantially higher for MetS (OR: 2.91, 95% CI 1.54–5.51, P = 0.003 for trend) in the highest SUA quartile than those in the lowest SUA quartile. We also observed that SUA concentration increased with the number of MetS components (P < 0.001 for trend). Moreover, we found that the patients in the higher SUA quartiles had greater numbers of MetS components than the patients in the lower SUA quartiles. However, the underlying mechanisms of the association between SUA and MetS remain largely unknown. Previous studies indicated that hyperuricemia may be partially responsible for the inflammatory process in adipose tissues and vascular endothelial cells that will lead to a chronic low-grade inflammation and insulin resistance in subjects with MetS (17, 18). A recent study showed that higher SUA levels present higher levels of CRP and increased serum levels of inflammatory cytokines, indicating that SUA may be an inductor of subclinical inflammation (13). Consistent with this supposition, we observed that the acute phase biomarkers, including WBC and CRP levels, gradually increased with SUA quartiles (P < 0.001). Therefore, given that low-grade inflammation and insulin resistance are two major risks factors for MetS, uric acid-induced inflammatory pathway may play an important role in the pathogenesis of MetS. Interestingly, previous studies have demonstrated that reducing uric acid substantially improves systemic inflammation, endothelial function, and peripheral vasodilator capacity (19, 20). Results of studies from the URRAH database further strengthen the role of uric acid in CVD, the identified cut-off values support clinicians consider uric acid as an additional cardiovascular risk factor (21). Thus, SUA may be a promising candidate for risk assessment and a potential intervention target for MetS and CVD (17).

Numerous studies have demonstrated that SUA levels are independently associated with the presence of hypertension (22, 23). In previous retrospective cohort study showed that elevated SUA levels could be associated with poor blood

TABLE 4 | Association of SUA quartiles with MetS components.

	Q1	Q2	Q3	Q4	P value
			OR (95% CI)		
Overweight/Obesity	1	1.56 (1.08–2.23)	2.56 (1.74–3.76)	3.45 (2.25–5.28)	0
Hypertension	1	1.40 (0.94–2.08)	1.41 (0.93–2.15)	2.13 (1.34–3.38)	0.015
Dyslipidemia (TG)	1	1.61 (1.09–2.37)	2.56 (1.70–3.85)	2.71 (1.73–4.25)	0
Dyslipidemia (TC)	1	0.71 (0.32–1.57)	1.41 (0.68–2.94)	2.51 (1.17–5.38)	0.013
Dyslipidemia (HDL-C)	1	1.45 (0.99–2.12)	1.36 (0.91–2.03)	1.52 (0.98–2.37)	0.195

Adjusted for age, sex, alcohol drinking, smoking, duration of diabetes, self-reported CVD, BMI, CRP, HbA1C, FBG, eGFR.

pressure and diabetic control (24, 25). A recent study suggested that uric acid has independent effects on the development of hypertension and MetS but is not an independent risk factor for atherosclerosis in patients with T2DM (10). Our results were in agreement with these findings. The ORs for hypertension increased with increasing SUA quartiles. In the highest SUA quartile, the OR was 2.13 (95% CI: 1.34–3.38, $P < 0.015$) for hypertension. Experimental studies have also suggested the potential roles of uric acid in the pathogenesis of hypertension. The mechanism by which uric acid causes hypertension may be due to the inhibition of the release of endothelial nitric oxide and the activation of the rennin–angiotensin system, which lead to oxidative stress, endothelial dysfunction, and smooth muscle cell proliferation, and ultimately to elevated blood pressure (26, 27).

In the past decades, several studies have assessed the relationship between SUA and the components of MetS in different selected populations. Multiple clinical and epidemiological studies have also demonstrated the strong association among SUA and obesity, hypertension, and MetS (28, 29). A previous study reported that the dyslipidemia components of serum TC, TG, and LDL-C levels are positively associated with SUA levels, whereas serum HDL-C levels are inversely related with SUA (30). Our analysis was consistent with these findings. A notable increase in the risk of overweight/obesity, hypertension, and dyslipidemia was observed across the SUA quartiles after adjusting for known potential confounders. However, the issue of whether hyperuricemia is a downstream result of MetS, or it may play an upstream role in MetS development remains unclear. The Mendelian randomization (MR) technique enables their use as instrumental variables for testing causality by exploiting the random distribution of genetic variants (31). An MR investigation suggested that SUA may augment the risk of MetS by increasing blood pressure and TC levels and lowering HDL-C levels but not by accumulating fat or hyperglycemia. Obesity may be a causal agent for all the components of MetS, including hyperuricemia (32). Meanwhile, a recent study of obese adults indicated that SUA has no apparent association with hypertension, dyslipidemia, T2DM, and cardiovascular events (33). Thus, further complementary studies on the causal relationship and the potential mechanism between SUA and components of MetS are warranted.

However, the results regarding the associations of SUA with atherosclerosis and CVD from different studies remains controversial (4, 34). Several clinical studies have reported that elevated SUA levels are independent predictors of atherosclerosis, CVD, and mortality in different populations (5). However, other epidemiological studies have failed to confirm such associations and argued that these relationship are not causal but rather a result of a coexistence with other cardiovascular risk factors, such as obesity, MetS, and chronic kidney disease (10, 11). A recent study indicated that SUA appears to be strongly correlated with c-IMT but not with the prevalence of carotid plaques or aortic stiffness (26). The present study did not observe any association between SUA and c-IMT and carotid atherosclerotic plaques in T2DM populations despite adjusting for all known confounders. Thus, these results demonstrated that SUA may not be a risk factor for CAP and that the association between SUA and carotid atherosclerosis is not truly independent. Additionally, the methodological differences and the different characteristics of study populations might account for the discrepancies reported in the literature and by the present study. Therefore, given that the SUA levels were strongly associated with MetS and its components, SUA may play an indirect role in the pathogenesis of atherosclerosis *via* other CVD factors, such as obesity, hypertension, dyslipidemia, and MetS in some selected populations.

Owing to the cross-sectional nature of this study, it has several limitations. The mechanisms underlying these associations remain to be explored. The study findings are inherently limited in the ability to eliminate causal effect relationships between SUA and MetS. The participants of the present study were Chinese patients with T2DM. Therefore, the present results might not be representative of the general population. Moreover, many cardiovascular risk factors, such as glucose and lipid metabolic disorders, can accumulate in patients with T2DM and might affect the role of SUA in the development of carotid atherosclerosis and CVD.

CONCLUSION

In summary, the findings of this study strongly suggested that SUA has independent association with the prevalence of hypertension, obesity, dyslipidemia and MetS but not with carotid atherosclerosis in T2DM populations. Our findings demonstrated that the role of uric acid in atherosclerosis might be attributed to other cardiovascular risk factors, such as MetS and its components. Prospective studies are required to clarify further the causal associations of SUA with MetS and carotid atherosclerosis in patients with T2DM.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institution Review Board of the First Affiliated Hospital of Zhengzhou University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

WL, YW, TL, XL, and SL contributed to the conception and design of the study. WL, YW, SL, YZ, ML, and RL recruited the subjects and supervised the study. WL, YW and SO analyzed the data. WL and SL wrote the initial draft of the paper. WL, YW, TL, XL, and SL contributed to the writing, reviewing, and revising of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

WL is funded by the National Natural Science Foundation of China (82000831).

ACKNOWLEDGMENTS

We would like to thank the participants in this study.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 19 December 2022
DOI 10.3389/fendo.2022.1022031

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Cardiovascular Endocrinology, a section of the journal Frontiers in Endocrinology

RECEIVED 18 August 2022
ACCEPTED 23 November 2022
PUBLISHED 19 December 2022

CITATION
Su Y, Ding N, Zhou Y, Yang G and Chai X (2022) The relationship between uric acid and total femur bone mineral density in hypertensive and non-hypertensive populations. *Front. Endocrinol.* 13:1022031. doi: 10.3389/fendo.2022.1022031

The relationship between uric acid and total femur bone mineral density in hypertensive and non-hypertensive populations

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Objective: This study aimed to explore the association between uric acid (UA) and total femur bone mineral density (BMD) in hypertensive and non-hypertensive groups.

Methods: We conducted a cross-sectional study of 13,108 participants in the NHANES database, including 4,679 hypertensive and 8,429 non-hypertensive subjects. A weighted multiple linear regression analysis was conducted to explore the association between UA and total femur BMD.

Results: In the hypertensive group, the relationship between UA and total femur BMD was positive [β, 3.02 (95% CI, -0.44 to 6.48), p = 0.0962). In the non-hypertensive group, the association was significantly positive [β, 5.64 (95% CI, 2.06–9.22), p = 0.0038]. In gender-stratified analysis, UA was analyzed as a continuous variable and a categorical variable (quartile). The significantly positive association was present in both the hypertensive male group [β, 5.10 (95% CI, 0.98–9.21), p for trend = 0.0042] and non-hypertensive male group [β, 10.63 (95% CI, 6.32–14.94), p for trend = 0.0001]. A smooth curve fitting showed that in the hypertensive male group, the relationship between UA and total femur BMD was an inverted U-shaped curve. In the hypertensive female group, the relationship was basically negative. In the non-hypertensive population, the relationship between UA and total femur BMD was an inverted U curve in both men and women.

Conclusion: In the hypertensive male group, the association between UA and total femur BMD was an inverted U-shaped curve. As to women, the relationship was basically negative. In the non-hypertensive group, the association between UA and total femur BMD was an inverted U-shaped curve in different genders.

KEYWORDS

uric acid, bone mineral density, hypertension, NHANES, epidemiology

Introduction

Hyperuricemia has been proven to be associated with a variety of clinical diseases, such as hypertension, heart failure, insulin resistance, diabetes, osteoporosis, and chronic renal disease (1–7). Previous studies have shown that both blood pressure and hypertension tend to increase with elevated uric acid (UA) levels (8–10). According to NHANES 2015–2016 data, in the US population, the prevalence of hyperuricemia in women was 20.2%, and that in women was 20.0% (11). In recent years, the relationship between UA and bone mineral density (BMD) or osteoporosis has also been discussed a lot. A meta-analysis of 55,859 subjects showed that UA levels were positively associated with BMD and negatively associated with new fractures (12). A meta-analysis of five prospective studies including 29,110 participants showed that UA levels were inversely associated with fracture risk, with an overall hazard ratio of 0.79 (95% CI, 0.69–0.89) in the highest group compared to the lowest group after tertiary grouping of UA levels (13). High oxidative stress levels and weak antioxidant capacity may be the underlying mechanisms leading to osteoporosis (14, 15). The antioxidant effect of UA may be used to explain the protective effect on BMD (16).

Inversely, few studies have investigated the relationship between UA and BMD in hypertensive and non-hypertensive populations. In this population, especially the hypertensive population, whether there is a correlation between low UA levels and decreased BMD is a question that deserves the attention of clinicians. As consequence, a cross-sectional study of 13,108 participants was used to investigate the relationship between UA and total femur BMD. The data on these participants were derived from the NHANES database.

Methods

Study population

NHANES was a research program to investigate the health and nutritional status of the US population. It was counted on a 2-year cycle. A certain number of people are included in each cycle, and their sociology, lifestyle, diet, disease, blood testing, and other relevant indicators were collected. In our research, we collected data from four cycles of 2007–2008, 2009–2010, 2013–2014, and 2017–2018 for analysis (2011–2012, 2015–2016 without femoral BMD examinations). A total of 18,893 subjects completed femoral BMD scans during these four cycles, and we excluded 5,785 participants for the following reasons: 1) missing UA data (n = 2362); 2) missing data on the diagnosis of hypertension; 3) bilateral oophorectomy or hysterectomy or malignancy or thyroid disease (n = 3211); and 4) taking prednisone or cortisone or estrogen or progesterone. Finally, 13,108 participants were included in the study, including 4,679 in the hypertensive group and 8,429 in the non-hypertensive group (Figure 1).

Bone mineral density and hypertension

In our study, total femur BMD was obtained by measuring the femur by dual energy X-ray absorptiometry (DXA). DXA was widely used in the measurement of BMD and has the advantages of fast speed, convenience, and low radiation (17). Three Hologic QDR-4500A fan-beam densitometers were used for total femur BMD scans, which were performed by trained and certified radiologic technicians. Longitudinal monitoring of the instrument by weekly scanning of the Hologic Femur Phantom was conducted according to the manufacturer's requirements. Participants meeting one of the following four criteria will be defined as having hypertension: 1) systolic blood pressure (SBP) ≥140 mmHg, 2) diastolic blood pressure (DBP) ≥90 mmHg, 3) having been told by a doctor to have high blood pressure, and 4) taking antihypertensive medication. The SBP and DBP were obtained by the following method: All participants had their blood pressure measured by trained and certified personnel after a 5-min rest in a seated position. Three consecutive blood pressure readings were obtained by auscultation, and if blood pressure measurement was not completed successfully, a fourth measurement was taken. SBP and DBP are averages of all available measurements.

Sociodemographic and lifestyle factors

We included three demographic variables: gender, age, and race. Lifestyle included smoking status, alcohol consumption, and total physical activity (TPA). Smoking status was classified according to multiple questions in the smoking questionnaire: current smoking, former smoking, non-smoking, and unrecorded. Lifetime smoking of less than 100 cigarettes was defined as non-smoking. Alcohol consumption was classified as drinking, non-drinking, and unrecorded according to questions on the drinking questionnaire. Among them, drinking more than or equal to 12 times per year was defined as drinking. TPA data were based on the Global Physical Activity Questionnaire, which includes three types of physical activity: recreational, occupational, and transportation, and were divided into vigorous and moderate categories according to the intensity of each physical activity. TPA is the sum of the three types of physical activity (multiplied by two if the physical activity was vigorous) (18, 19). According to the 2018 Physical Activity Guidelines for Americans, subjects were defined as active participants if their TPA minutes were ≥150 min (20).

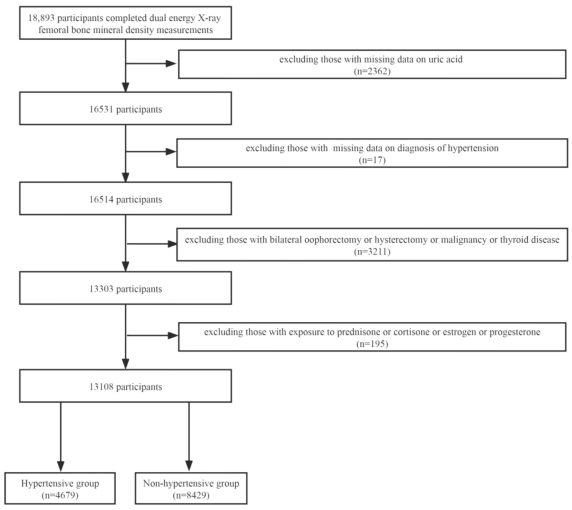

FIGURE 1
Flowchart of the study design and participants excluded from the study.

Metabolic factors, clinical laboratory indicators, and dietary factors

Metabolic factors and clinical laboratory indicators include diabetes, body mass index (BMI), total cholesterol, glomerular filtration rate (GFR), serum vitamin D2 + D3, and UA. Participants meeting one of the following four criteria will be defined as having diabetes:1) taking hypoglycemic agent or insulin, 2) fasting blood sugar ≥126 mg/dl, 3) 2-h Oral Glucose Tolerance Test blood sugar ≥200 mg/dl, and 4) glycohemoglobin ≥6.5%. BMI was calculated as weight in kilograms divided by height in meters squared. The Modification of Diet in Renal Disease (MDRD) equation was used to calculate GFR: $186 \times SC^{-1.154} \times Age^{-0.203} \times (0.742$ if female) (21). Dietary variables incorporate daily total protein and total calcium intake. Two 24-h dietary recall recordings were conducted by trained dietary interviewers. Total protein and total calcium intakes were the mean of protein and calcium intakes recorded from two dietary recalls. In the hypertensive group, whether antihypertensive treatment was administered was also included in the data analysis.

Statistical analysis

Appropriate weights, stratification, and clustering were used in the data analysis in order for the findings to be representative of the US population. In hypertensive and non-hypertensive groups, the correlation between UA and total femur BMD was determined by the Pearson correlation test. We use a weighted mean [95% confidence intervals (CI)] representation for continuous variables and weighted percentage (95% CI) representation for categorical variables. Continuous and categorical clinical characteristics were compared using survey-weighted linear regression and survey-weighted chi-square tests, respectively. The independent relationship between UA and total femur BMD in the hypertensive and non-hypertensive groups was conducted by applying the multiple linear regression model. At the same time, the linear trend test was performed after grouping the UA into quartiles. To discover the nonlinear relationship between UA and total femur BMD, we performed smooth curve fittings. All variables were incorporated into the model to adjust for potential confounding, and analyses were stratified by gender. Data analysis was performed using the statistical packages R (http://www.R-project.org) and EmpowerStats (http://www.empowerstats.com). Differences were considered statistically significant when p-value <0.05.

Results

Subjects characteristics

The baseline characteristics of participants were illuminated in Table 1. In the hypertensive group (n = 4679), there was a significantly positive correlation between UA and total femur BMD (r = 0.2081, p < 0.0001). The ratios of men and women were 59.62% and 40.38%, respectively; 66.56% were non-Hispanic white. The proportions of smoking, drinking, active participants, and diabetes were 18.70%, 49.21%, 58.44%, and 24.38% respectively; 11.33% people have a GFR <60 ml/min/1.73 m^2. The mean value for age, total cholesterol, BMI, serum vitamin D2 + D3, protein intake, calcium intake, total femur

BMD, and UA were 56.54 years, 5.09 mmol/L, 29.93 kg/m^2, 68.95 nmol/L, 82.52 g/day, 938.74 mg/day, 976.56 mg/cm^2, and 5.83 mg/dl, respectively; 59.12% of the population received antihypertensive therapy. In the non-hypertensive group (n = 8429), there was a significantly positive correlation between UA and total femur BMD (r = 0.2735, p < 0.0001). The ratios of men and women were 54.00% and 46.00%, respectively; 65.48% were non-Hispanic white. The proportions of smoking, drinking, active participants, and diabetes were 18.56%, 47.89%, 72.72%, and 5.82% respectively; 1.74% people have a GFR <60 ml/min/1.73 m^2. The mean value for age, total cholesterol, BMI, serum vitamin D2 + D3, protein

TABLE 1 Description of participants based on the presence or absence of hypertension.

	Hypertension(yes) N = 4679	Hypertension(no) N = 8429	p-Value
Gender			<0.0001
Male	59.62 (57.99,61.23)	54.00 (52.74,55.26)	
Female	40.38 (38.77,42.01)	46.00 (44.74,47.26)	
Age(years)	56.54 (56.02,57.05)	38.95 (38.34,39.55)	<0.0001
Race			<0.0001
Mexican American	6.73 (5.12,8.81)	10.87 (8.58,13.68)	
Other Hispanic	5.13 (4.03,6.50)	6.27 (4.83,8.10)	
Non-Hispanic White	66.56 (62.11,70.73)	65.48 (61.35,69.38)	
Non-Hispanic Black	13.68 (11.41,16.32)	9.67 (8.41,11.10)	
Other Race	7.90 (6.64,9.37)	7.72 (6.42,9.24)	
Smoking status			<0.0001
Current-smoking	18.70 (16.91,20.64)	18.56 (17.19,20.00)	
Former smoking	29.41 (27.62,31.27)	17.94 (16.52,19.46)	
Non-smoking	51.19 (48.67,53.71)	47.54 (45.14,49.95)	
Not recorded	0.70 (0.53,0.92)	15.96 (15.05,16.91)	
Alcohol consumption			<0.0001
No drinking	35.61 (33.13,38.17)	24.60 (23.16,26.10)	
Drinking	49.21 (46.73,51.69)	47.89 (46.05,49.73)	
Not recorded	15.18 (13.83,16.64)	27.51 (26.15,28.91)	
Total physical activity			<0.0001
Inactive participants	41.56 (39.52,43.62)	27.28 (25.84,28.78)	
Active participants	58.44 (56.38,60.48)	72.72 (71.22,74.16)	
Diabetes			<0.0001
No	75.62 (73.59,77.55)	94.18 (93.35,94.91)	
Yes	24.38 (22.45,26.41)	5.82 (5.09,6.65)	
GFR(ml/min/1.73 m^2)			<0.0001
<60	11.33 (10.05,12.75)	1.74 (1.37,2.21)	
60-90	49.71 (47.52,51.91)	35.23 (33.54,36.97)	
≥90	38.96 (36.64,41.33)	63.03 (61.19,64.83)	
Total Cholesterol (mmol/L)	5.09 (5.04,5.13)	4.89 (4.86,4.93)	<0.0001
BMI (kg/m^2)	29.93 (29.70,30.17)	26.60 (26.41,26.79)	<0.0001
Serum vitamin D2 + D3 (nmol/L)	68.95 (67.45,70.44)	68.87 (67.41,70.32)	0.9172
Protein intake (g/day)	82.52 (80.86,84.17)	84.43 (83.19,85.66)	0.0343
Calcium intake (mg/day)	938.74 (920.73,956.74)	1010.29 (988.48,1032.10)	<0.0001
Total femur BMD (mg/cm^2)	976.56 (969.87,983.25)	981.54 (976.89,986.19)	0.2118
Uric acid (mg/dl)	5.83 (5.76,5.90)	5.25 (5.21,5.28)	<0.0001
Antihypertensive therapy			
Yes	59.12 (57.02,61.18)		
No	40.88 (38.82,42.98)		

GFR, Glomerular filtration rate; BMD, Bone mineral density; BMI, body mass index.
For continuous variables: survey-weighted mean (95% CI), p-value was by survey-weighted linear regression.
For categorical variables: survey-weighted percentage (95% CI), p-value was by survey-weighted chi-square test.

intake, calcium intake, total femur BMD, and UA were 38.95 years, 4.89 mmol/L, 26.60 kg/m^2, 68.87 nmol/L, 84.43 g/day, 1010.29 mg/day, 981.54 mg/cm^2, and 5.25 mg/dl, respectively.

Association between UA and total femur BMD

Table 2 shows the results of weighted multiple linear regression analyses between UA and total femur BMD in different models. In model I, sociodemographic factors (gender, age, race) were adjusted. The significantly positive association can be found in the hypertensive [β, 11.06 (95% CI, 7.04–15.07)] and non-hypertensive group (β, 23.83 (95% CI, 20.25–27.40)]. In model II, lifestyle factors (smoking status, alcohol consumption, TPA) were adjusted and added into model I. The significantly positive association still presented in the hypertensive [β, 10.73 (95% CI, 6.69–14.77)] and non-hypertensive group [β, 22.68 (95% CI, 19.17–26.20)]. In model III, metabolic, clinical laboratory indicators, and dietary factors (BMI, GFR, total cholesterol, diabetes, serum vitamin D2 + D3, protein intake, calcium intake) were adjusted and added into model II. In the hypertensive group, whether or not to receive antihypertensive therapy was also included in the model to adjust. Although the positive association still presented [β, 3.02 (95% CI, -0.44 to 6.48)], the p-value was >0.05. In the non-hypertensive group, a significantly positive association still existed [β, 5.64 (95% CI, 2.06–9.22)].

Subgroup analysis stratified by gender

In different subgroup analyses, we analyzed UA with continuous and categorical variables (quartile). In the hypertensive group (Figure 2), as to men, the relationship between UA and total femur BMD was significantly positive [β, 5.10 (95% CI, 0.98, 9.21)], and the trend test was significant (p = 0.0042). Paradoxically, this linear relationship and trend test were not significant in women. In the non-hypertensive group (Figure 3), the significantly positive association [β, 10.63 (95% CI, 6.32–14.94)] and trend test (p = 0.0001) still existed in men. In women, this linear relationship and trend test were also not significant. So to explore the nonlinear relationship, we performed a smooth curve fitting. In hypertensive male and female groups (Figure 4), the relationships were an inverted U-shaped curve and negative, respectively. In the non-hypertensive population (Figure 5), the relationship between UA and total femur BMD was an inverted U curve in both men and women.

Discussion

In this study, the association of UA with total femur BMD in hypertensive and non-hypertensive populations was investigated in a large population (n = 13108). In the hypertensive male group, the association between UA and total femur BMD was an inverted U-shaped curve. As for the female, the relationship between the two was basically negative. In the non-hypertensive group, the association between UA and total femur BMD was an inverted U-shaped curve between different genders.

Many studies have reported the relationship between UA and BMD. However, there are some differences in the findings due to the different study groups. A cross-sectional study including 1705 men over 70 years of age suggested that men with serum UA levels above the group median had significantly higher BMD at all sites than men with UA levels below the median (22). Paradoxically, in a prospective cohort study of 1963 older men (age ≥65), high UA levels (≥6.88 mg/dl) were associated with an increased risk of hip fracture (23). In terms of women, in a study including 615 perimenopausal and postmenopausal Japanese women, higher UA levels were linearly associated with higher lumbar spine BMD (24). Inversely, in another recent study of 103,799 women, those with a history of gout had a 38% higher risk of hip fracture than those without a history of gout after 22 years of follow-up (25).

When we explored the relationship between UA and total femur BMD in both hypertensive and non-hypertensive male subgroups, the trend test was significant, and the smooth curve fitting showed an inverted U-shaped curve. The reason for this result was that, according to the quartiles of UA levels, women have lower UA levels than men, resulting in fewer men in the low

TABLE 2 Result of multiple linear regression analysis between UA and total femur BMD in hypertensive and non-hypertensive group.

Model	Hypertensive group (β, 95% CI, p)	Non-hypertensive group (β, 95% CI, p)
Model I	11.06 (7.04, 15.07) <0.0001	23.83 (20.25, 27.40) <0.0001
Model II	10.73 (6.69, 14.77) <0.0001	22.68 (19.17, 26.20) <0.0001
Model III	3.02 (-0.44, 6.48) 0.0962	5.64 (2.06, 9.22) 0.0038

CI, confidence interval; UA, uric acid; BMD, bone mineral density.
For BMD: survey-weighted β (95% CI) p-value.
Model I was adjusted for: gender, age, and race.
Model II was adjusted for: smoking, alcohol consumption, and total physical activity in addition to model I.
Model III was adjusted for: body mass index, glomerular filtration rate, total cholesterol, diabetes, serum vitamin D2 + D3, protein intake, and calcium intake, in addition model II. Antihypertensive treatment variables were adjusted in the hypertensive group.

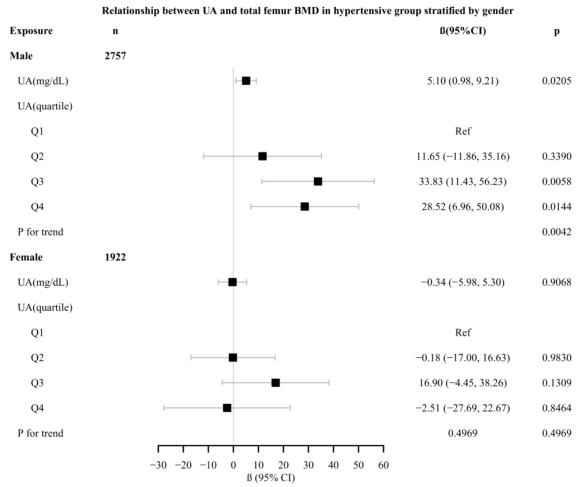

FIGURE 2
Relationship between UA and total femur BMD in the hypertensive group, stratified by gender. Adjusted for: race, age, alcohol consumption, smoke, total physical activity, body mass index, glomerular filtration rate, total cholesterol, diabetes, serum vitamin D2 + D3, protein intake, calcium intake, antihypertensive treatment.

group and a majority of men in the high group. Although the antioxidant effect of UA can prevent the loss of bone mass (16), studies have also shown that the higher the UA level, the lower the testosterone level (26, 27), and the lack of testosterone can lead to osteoporosis (28). This mechanism may be applied to explain the inverted U relationship between UA and total femur BMD in men. There were gender differences in the relationship between UA and BMD in the hypertensive group. Although the prevalence of chronic kidney disease (CKD) was higher among women than men, the rate of functional deterioration is faster in men than in women (29). Animal studies have shown that estrogen has a protective effect on the kidney (30) and that testosterone worsens kidney function (31), while kidney oxidative stress levels are lower in women (32). CKD causes hyperparathyroidism, increased UA levels, and decreased vitamin D activity, while UA decreased vitamin D levels and the parathyroid hormone decreased UA

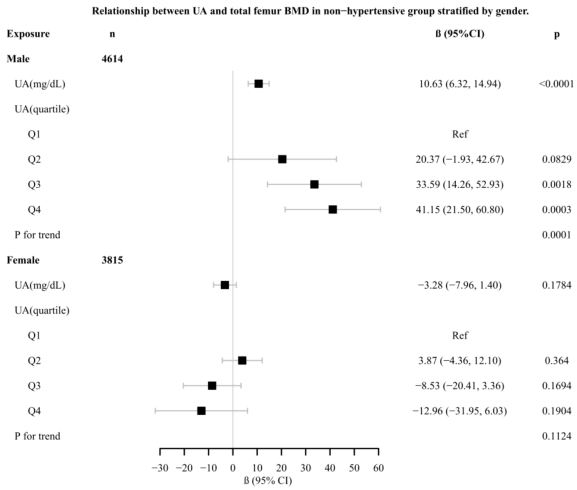

FIGURE 3
Relationship between UA and total femur BMD in the non-hypertensive group, stratified by gender. Adjusted for: race, age, alcohol consumption, smoke, total physical activity, body mass index, glomerular filtration rate, total cholesterol, diabetes, serum vitamin D2 + D3, protein intake, calcium intake.

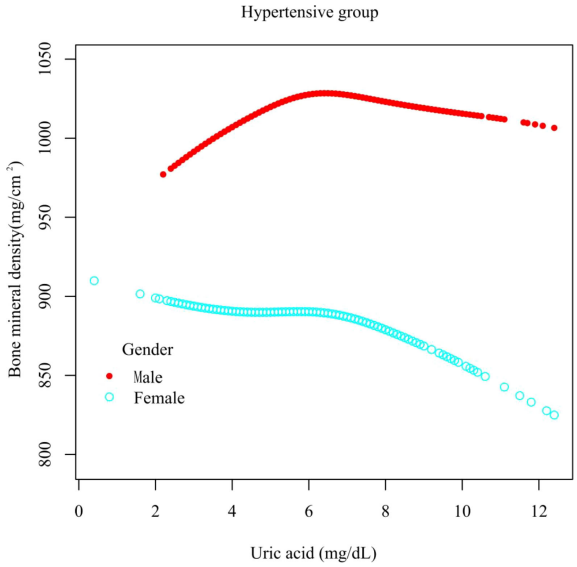

FIGURE 4
A smooth curve fitting for the relationship between UA and total femur BMD in the hypertensive group, stratified by gender. Adjusted for: race, age, alcohol consumption, smoke, total physical activity, body mass index, glomerular filtration rate, total cholesterol, diabetes, serum vitamin D2 + D3, protein intake, calcium intake, antihypertensive treatment.

excretion. The interaction of multiple factors eventually leads to a decrease in bone mass (33) and gender differences in the hypertensive population. In hypertensive and non-hypertensive women, the relationship between UA and total femur BMD was negative and inverted U-shaped, respectively, which could be partly explained by the different levels of sex hormones. The mean ages of the hypertensive and non-hypertensive women in our study were 57.52 and 39.00 years, respectively; so most of the

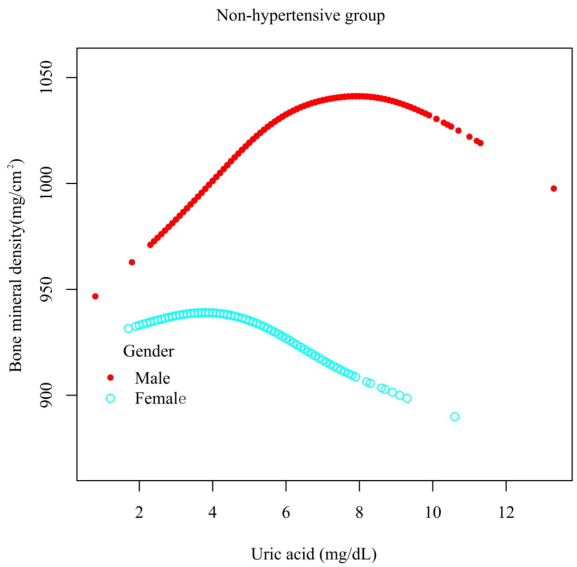

FIGURE 5
A smooth curve fitting for the relationship between UA and total femur BMD in the non-hypertensive group, stratified by gender. Adjusted for: race, age, alcohol consumption, smoke, total physical activity, body mass index, glomerular filtration rate, total cholesterol, diabetes, serum vitamin D2 + D3, protein intake, calcium intake.

hypertensive women in our study were in menopause. After menopause, the lack of sex hormones can lead to decreased bone mass and osteoporosis (34). Nevertheless, the lack of estrogen and progesterone will reduce the function of the kidneys to excrete UA, resulting in an increase in the level of UA (35). Homoplastically, research has also shown that in postmenopausal women, higher levels of UA were associated with lower levels of vitamin D (36).

The significance of our study is to provide clinicians with some hints that appropriate UA-lowering therapy does not necessarily lead to bone loss in both hypertensive and non-hypertensive populations. Prospective studies are needed in the future to verify the effect of UA-lowering therapy on BMD in hypertensive and non-hypertensive populations. Of course, our study also has certain limitations. First, due to the limitations of cross-sectional study, the causal effect of UA on BMD has not been determined. Future prospective studies will be needed to clarify the relationship between them. Second, some variables in the study were based on self-report and may have subjective recall bias. Third, some participants in the hypertensive group were diagnosed based on the measurement of blood pressure multiple times in a short period of time, which may not necessarily reflect the state of blood pressure.

Conclusions

In the hypertensive male group, the association between UA and total femur BMD was an inverted U-shaped curve. As to women, the relationship was basically negative. In the non-hypertensive group, the association between UA and total femur BMD was an inverted U-shaped curve between different genders.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by National Center for Health Statistics. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

Conception and design: YS and ND; Administrative support: XC; Provision of study materials or patients: XC; Collection and assembly of data: YS, YZ, and GY; Data analysis and interpretation: YS and ND. All authors contributed to the article and approved the submitted version.

Funding

Key Research and Development Program of Hunan Province (2019SK2022). Degree and Postgraduate Education Reform Project of Central South University (2022JGB008).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 06 March 2023
DOI 10.3389/fendo.2023.1143458

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Cardiovascular Endocrinology, a section of the journal Frontiers in Endocrinology

RECEIVED 13 January 2023
ACCEPTED 14 February 2023
PUBLISHED 06 March 2023

CITATION
Deng X-l, Yi H-w, Xiao J, Zhang X-f, Zhao J, Sun M, Wen X-s, Liu Z-q, Gao L, Li Z-y, Ge P, Yu Q and Zhang D-y (2023) Serum uric acid: A risk factor for right ventricular dysfunction and prognosis in heart failure with preserved ejection fraction.
Front. Endocrinol. 14:1143458.
doi: 10.3389/fendo.2023.1143458

Serum uric acid: A risk factor for right ventricular dysfunction and prognosis in heart failure with preserved ejection fraction

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Background: Hyperuricemia and right ventricular dysfunction (RVD) are both widespread in heart failure with preserved ejection fraction (HFpEF) patients. RVD is associated with a poor prognosis in HFpEF. The correlation between serum uric acid (UA) levels and right ventricular function is unclear. The prognostic performance of UA in patients with HFpEF needs further validation.

Methods and results: A total of 210 patients with HFpEF were included in the study and divided into two groups according to UA level: the normal UA group (≤7 mg/dl) and the high UA group (>7 mg/dl). The variables examined included clinical characteristics, echocardiography, and serum biochemical parameters. Right ventricular function was assessed by tricuspid annular plane systolic excursion (TAPSE) and tricuspid annular peak systolic velocity (TAPSV). Baseline characteristics were compared between the two groups, and the correlation between baseline UA and RVD was assessed using multifactorial binary logistic regression. Kaplan–Meier curves were used to describe all-cause mortality and heart failure readmission. Results showed that right ventricular function parameters were worse in the high UA group. After adjusting for UA, left ventricular posterior wall thickness (LVPWT), N-terminal B-type natriuretic peptide (NT-proBNP), atrial fibrillation (AF), and low-density lipoprotein cholesterol (LDL-C), UA (odds ratio = 2.028; $p < 0.001$) was independently associated with RVD, and UA >7 mg/dl (HR = 2.98; $p < 0.001$) was associated with heart failure readmission in patients with HFpEF.

Conclusion: Elevated serum UA is closely associated with RVD and significantly associated with the heart failure readmission rate in patients with HFpEF.

KEYWORDS

serum uric acid, right ventricular dysfunction, heart failure with preserved ejection fraction, hyperuricemia, prognosis

10.3389/fendo.2023.1143458

Introduction

Heart failure with preserved ejection fraction (HFpEF) is generally considered a syndrome with pathophysiological heterogeneity, whose prevalence has increased rapidly over the past two decades (1, 2). Factors affecting the prognosis (mortality and hospitalization) of HFpEF include metabolic syndrome, renal insufficiency, and so forth (3). Hyperuricemia is an important comorbidity in heart failure patients and is usually associated with advanced severity of heart failure (4).

As the end product of purine metabolism in the human body, uric acid (UA) is commonly associated with the development and progression of cardiovascular diseases such as peripheral artery disease, coronary artery disease (CAD), hypertension, and atrial fibrillation (AF) (5–7). The prevalence of hyperuricemia ranges from 13.4% to 20.1% in different populations (8–10), and the total number of people with hyperuricemia in China has gradually increased to 170 million (11). Elevated UA was particularly common in people with heart failure in China (12), and previous studies have shown that hyperuricemia may contribute to worse clinical outcomes in patients with cardiovascular diseases (13, 14).

Right ventricular dysfunction (RVD) is one of the common manifestations in the HFpEF population (15). Former studies have demonstrated that RVD leads to a worse clinical prognosis compared to HFpEF patients without RVD. However, the current treatment of RVD has not been as effective as anticipated (16–18). This study aimed to investigate the relationship between UA and RVD in the context of HFpEF and to illustrate the relationship between UA and the prognosis of HFpEF.

Patients and methods

Study design and study population

This is a prospective observational study to assess the association between baseline UA and RVD in patients with HFpEF and to investigate the relationship between elevated UA and patient prognosis. Study patients were enrolled between October 2020 and April 2022. All enrolled patients met the inclusion criteria for a definitive diagnosis of HFpEF according to the HFA-PEFF diagnostic algorithm. The exclusion criteria were (1) acute coronary syndrome or right myocardial infarction history, (2) severe renal impairment (eGFR < 30 ml/min/1.73 m^2, based on CKD-EPI formula), (3) urate-lowering therapy, (4) malignant tumor, (5) severe hepatic impairment (elevated liver enzymes: three times over upper reference limit or liver cirrhosis), and (6) infections. According to Chinese guidelines for the diagnosis and management of hyperuricemia and gout in 2019, hyperuricemia is defined as above 7.0 mg/dl (19). Patients enrolled in the study were divided into two groups: normal UA group (UA ≤7.0 mg/dl) and high UA group (UA >7.0 mg/dl). All the study population signed informed consents that were prospectively registered and agreed to be followed up for the collection of outcome data. Patients were followed up by phone every 4 months, and three patients were lost during the follow-up period. The last follow-up visit ended in August 2022. Ultimately, 210 patients were enrolled in the study (Figure 1). The study was in accordance with the Declaration of Helsinki, approved by the Clinical Research Review Board of the First Affiliated Hospital of Chongqing Medical University (No. 2021-473), and registered on clinicaltrials.gov with an identifier of NCT05053256.

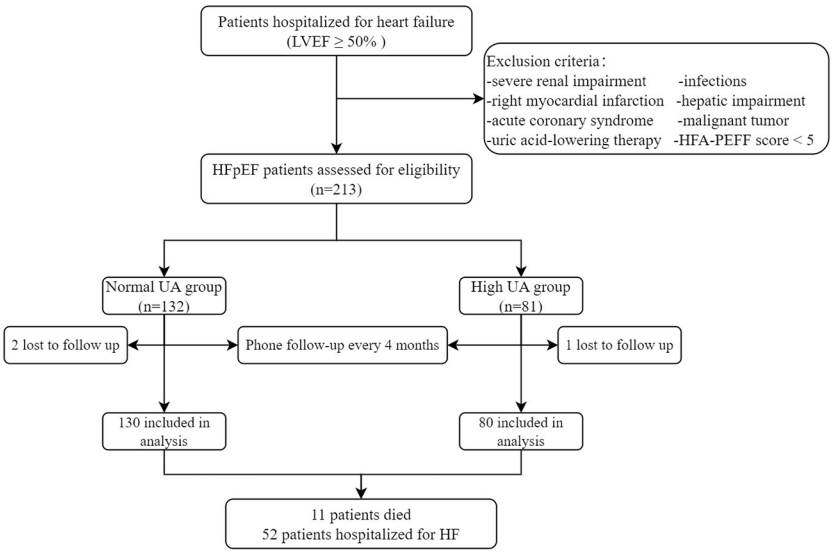

FIGURE 1
The enrollment flowchart. HFpEF, heart failure with preserved ejection fraction; HF, heart failure; LVEF, left ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion; TAPSV, tricuspid annular peak systolic velocity; UA, uric acid.

Data collection

The baseline clinical data collection was conducted by trained researchers following the same protocol at the time of enrollment. Patients' demographics, comorbidities, personal histories, medications, laboratory tests, and echocardiography were collected. Biochemical indexes were detected and analyzed, including albumin (Alb), blood urea nitrogen (BUR), creatinine (Cr), direct bilirubin (DB), hemoglobin (Hb), glycosylated hemoglobin (HbAlc), high-sensitivity C-reactive protein (hs-CRP), LDL-C, N-terminal B-type natriuretic peptide (NT-proBNP), and UA.

Serum uric acid measurement

Blood samples were taken on the second morning after admission. UA was performed through the central laboratory using ABBOTT. Conversion of each UA measurement from micromoles per liter to milligrams per deciliter was conducted by dividing it by 60.

Echocardiography and assessment of right ventricular function

All the echocardiographic examinations were conducted by trained echocardiographers according to the guidelines of the American Society of Echocardiography (ASE) (20). The standard four-chamber method was used to measure the right atrial transverse diameter, right ventricular anteroposterior diameter, tricuspid annular plane systolic excursion (TAPSE), and tricuspid annular peak systolic velocity (TAPSV). We defined RVD as TAPSE <17 mm and TAPSV <9.5 cm/s. Pulmonary systolic pressure (PASP) was calculated as 4 * (peak tricuspid regurgitation velocity (TR))^2 + right atrial pressure, estimated based on the diameter and collapse of the inferior vena cava.

Outcomes and clinical follow-up

Endpoints examined include readmission for heart failure and all-cause mortality. Heart failure readmission was determined by two senior doctors in the heart failure ward. Deaths were confirmed by population management consultations and hospital death certificates. Enrolled patients were followed up by telephone or WeChat every 4 months until the end of August 2022 or death. Postcharge clinical events were obtained through telephone follow-up and medical records from other hospitals.

Statistical analysis

We used percentages for qualitative data. Normally distributed quantitative data were presented as mean ± standard deviation (SD), and abnormally distributed quantitative data were presented as median (interquartile range (IQR)). The receiver operating characteristic (ROC) curve was used to determine the predictive value of UA for RVD. When comparing baseline data for HFpEF patients with UA > 7 mg/dl and UA ≤ 7 mg/dl, independent sample *t*-test, rank sum test, or Chi-square test were selected based on data characteristics. Pearson's or Spearman's tests were used to assess the association of variables with UA, TAPSE, and TAPSV. Based on published data and clinical relevance, we performed a univariate analysis of UA, gender, CAD, diabetes, AF, body mass index (BMI), systolic blood pressure (SBP), heart rate, left ventricular posterior wall thickness (LVPWT), and interventricular septal thickness (IVST). Based on the results of univariate binary logistic analysis, different models were developed to determine the odds ratio (OR) between UA and RVD. The long-term cumulative incidence of all-cause mortality and heart failure readmission was estimated using Kaplan–Meier curves. The predictive value of variables for heart failure readmission was tested by Cox's univariate proportional hazards regression analysis. Variables in univariate Cox regression were included in multivariate Cox regression, and subgroup analysis was performed to demonstrate the potential effects of UA >7 mg/dl. Statistical significance was $p < 0.05$. Results were expressed as a hazard ratio (HR) with 95% confidence intervals (95% CI). All statistical analyses were performed using SPSS version 24.0 (SPSS, Chicago, IL, USA).

Results

Clinical characteristics

In total, 210 eligible HFpEF patients were recruited to the study (59% women), with 80 patients assigned to the high UA group. Compared to the normal UA group, patients in the high UA group were more prevalent with CAD, AF, and higher New York Heart Association (NYHA) class heart failure, higher SBP, diastolic blood pressure (DBP), heart rate, BUR, Cr, NT-proBNP, DB, and hs-CRP, but lower Alb and LDL-C at baseline ($p < 0.05$; Table 1). Except for the higher frequency of diuretics use in the high UA group, there was no difference in medication use or other characteristics, including age, BMI, HbAlc, history of smoking, or alcohol consumption between the two groups (Table 1).

The echocardiographic characteristics of patients are presented in Table 1. Compared with the normal UA group, patients in the high UA group displayed worse right heart structure and function, including larger right ventricular (RV) diameter and right atrium (RA) diameter, higher PASP, and lower TAPSE and TAPSV, but similar left ventricular end-diastolic dimension (LVEDD), left atrial volume index (LAVI), left ventricular mass index (LVMI), and left ventricular ejection fraction (LVEF). In the present study, the prevalence of RVD was 34.3% among all participants, and the prevalence in the high UA group was four times higher than that in the normal UA group (66.3% vs. 14.6%; $p < 0.001$; Table 1).

The association among UA, TAPSE, TAPSV, and selected variables

Spearman's correlations among UA, TAPSE, TAPSV, and selected variables are summarized in Table 2. UA was positively

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TABLE 1 Baseline characteristics of the study population according to serum uric acid.

	Total (*n* = 210)	Normal UA (≤7 mg/dl, *n* = 130)	High UA (>7 mg/dl, *n* = 80)	*p*-value
Demographics				
Age (years)	74 (67, 81)	72 (67, 79)	77 (66, 82)	0.132
Gender/men (*n*, %)	86 (41.0%)	45 (34.6%)	41 (51.2%)	0.017
BMI (kg/m^2)	23.6 (21.1, 26.4)	23.6 (21.5, 25.9)	23.6 (20.6, 26.7)	0.668
SBP (mmHg)	125 ± 15.6	121 ± 12.5	132 ± 17.5	<0.001
DBP (mmHg)	73 ± 9.7	70 ± 7.7	77 ± 11.1	<0.001
Heart rate	76 (66, 89)	74 (65, 85)	84 (71, 98)	0.001
Comorbidities				
CAD (*n*, %)	94 (44.8%)	45 (34.6%)	49 (61.3%)	<0.001
Hypertension (*n*, %)	136 (64.8%)	83 (63.8%)	53 (66.3%)	0.723
Diabetes (*n*, %)	74 (35.2%)	49 (37.7%)	25 (31.3%)	0.343
AF (*n*, %)	84 (40.0%)	39 (30.0%)	45 (56.3%)	<0.001
NYHA class				
II	106 (50.5%)	81 (62.3%)	25 (31.3%)	<0.001
III	92 (43.8%)	46 (35.4%)	46 (57.5%)	0.002
IV	12 (5.7%)	3 (2.3%)	9 (11.3%)	0.007
Personal history				
Smoking (*n*, %)	54 (25.7%)	31 (23.8%)	23 (28.7%)	0.430
Drinking (*n*, %)	41 (19.5%)	20 (15.4%)	21 (26.3%)	0.054
Medications				
Diuretics (*n*, %)	141 (67.1%)	78 (60%)	63 (78.8%)	0.005
ACEI/ARB/ARNI (*n*, %)	132 (62.9%)	83 (63.8%)	49 (61.3%)	0.705
Statins (*n*, %)	158 (75.2%)	103(79.2%)	55(68.8%)	0.087
Laboratory values				
UA (mg/dl)	6.14 (5.05, 7.60)	5.24 (4.67, 5.92)	8.10 (7.48, 9.12)	<0.001
BUR (mmol/L)	6.8 (5.6, 9.1)	6.4 (5.3, 7.9)	8 (6.1, 9.9)	<0.001
Cr (μmol/L)	79 (63, 96)	69 (60, 85)	94 (79, 115)	<0.001
NT-proBNP (pmol/L)	114.8 (52.8, 262.4)	83.3 (50.5, 164.7)	220.6 (109.3, 344.1)	<0.001
hs-CRP (mg/L)	2.03(0.74, 6.94)	1.40 (0.67, 4.69)	2.91 (1.39, 9.79)	0.001
Hb (g/L)	130 (119, 143)	128 (120, 141)	131 (120, 146)	0.177
LDL-C (mmol/L)	2.13 (1.63, 2.59)	2.20 (1.71, 2.64)	1.97 (1.46, 2.47)	0.020
TB (μmol/L)	11.9 (8.4, 17.6)	11.0 (8.0, 14.4)	14.4 (9.5, 20.7)	0.001
DB (μmol/L)	5.1 (3.4, 7.2)	4.4 (3.2, 6.0)	6.2 (4.4, 9.9)	<0.001
Alb (g/L)	40 (38, 43)	42 (39, 44)	39 (37, 41)	<0.001
HbAlc (%)	5.6 (6, 6.4)	6.0 (5.6, 6.4)	5.9 (5.7, 6.4)	0.687
Echocardiography				
TAPSE (mm)	17.9 ± 3.7	18.9 ± 3.3	16.2 ± 3.7	<0.001
TAPSV (cm/s)	10.5 (9.0, 12.8)	11.6 (10.2, 13.2)	9.1 (7.9, 9.8)	<0.001
PASP (mmHg)	42 (34, 49)	39 (32, 45)	45 (36, 56)	0.002

(Continued)

TABLE 1 Continued

	Total (n = 210)	Normal UA (≤7 mg/dl, n = 130)	High UA (>7 mg/dl, n = 80)	p-value
RA diameter (mm)	39 (35, 45)	37 (33, 42)	43 (37, 50)	<0.001
RV diameter (mm)	21 (20, 24)	20 (19.22)	22 (20, 26)	<0.001
LA diameter (mm)	36 (32, 41)	36 (32, 40)	38 (32, 42)	0.133
LVEDD (mm)	47 ± 5.9	46 ± 5.8	47 ± 6.2	0.264
LAVI (ml/m^2)	40 (33, 54)	40 (33, 53)	44 (33, 56)	0.147
LVMI (kg/m)	112 (96, 140)	113 (96, 140)	111(96, 140)	0.894
LVPWT (mm)	10.0 (10.0, 11.0)	10.0 (10.0, 11.0)	10.0 (10.0, 12.0)	0.723
IVST (mm)	11.0 (10.0, 12.0)	11.0 (10.0, 12.0)	10.5 (10.0, 12.0)	0.979
LVEF (%)	61 (58, 65)	62 (58, 65)	60 (57, 64)	0.108
H2FPEF score	4 (3, 5)	3 (3, 5)	5 (3, 6)	0.004
HFA-PEFF score	6 (5, 6)	6 (5, 6)	6 (5, 6)	0.088
RVD (n, %)	72 (34.3%)	19 (14.6%)	53 (66.3%)	<0.001

Values are mean ± standard deviation, number (%), or median (interquartile range). AF, atrial fibrillation; Alb, albumin; BMI, body mass index; BUR, blood urea nitrogen; CAD, coronary artery disease; Cr, creatinine; DB, direct bilirubin; DBP, diastolic blood pressure; HbA1c, glycosylated hemoglobin; Hb, hemoglobin; hs-CRP, high-sensitivity C-reactive protein; IVST, interventricular septal thickness; LA, left atrium; LAVI, left atrial volume index; LDL-C, low-density lipoprotein cholesterol; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; LVPWT, left ventricular posterior wall thickness; LVMI, left ventricular mass index; NT-proBNP, N-terminal B-type natriuretic peptide; PASP, pulmonary artery systolic blood pressure; RV, right ventricular; RVD, right ventricular dysfunction; SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion; TAPSV, tricuspid annular peak systolic velocity; TB, total bilirubin; UA, uric acid.

correlated with PASP, heart rate, SBP, Cr, NT-proBNP, hs-CRP, and DB ($p < 0.05$) but negatively correlated with TAPSE, TAPSV, LDL-C, and Alb ($p < 0.05$). In addition, TAPSE and TAPSV had positive associations with IVST, LVPWT, LDL-C, and Alb, but were negatively associated with PASP, heart rate, Cr, NT-proBNP, hs-CRP, and DB ($p < 0.05$; Table 2). The correlation between UA and echocardiographic characteristics representing right heart dysfunction is indicated in Supplementary Figure S1.

ROC curve for the prediction of RVD

ROC curves are shown in Figure 2 to demonstrate the diagnostic UA value for the prediction of RVD, which was defined as TAPSE < 17 mm and TAPSV < 9.5 cm/s. The area under the curve (AUC) for RVD was 0.825 (95% CI, 0.764–0.886; $p < 0.001$). The best cutoff value of UA for predicting RVD was 7.15 mg/dl, yielding sensitivity and specificity of 69.4% and 85.5%, respectively (Figure 2).

Univariate and multiple logistic regression analysis with RVD

In univariate binary logistic regression analysis, RVD was significantly associated with UA (OR = 2.061; 95% CI, 1.654–2.568; $p < 0.001$), AF (OR = 3.508; 95% CI, 1.933–6.366; $p < 0.001$), IVST (OR = 0.807; 95% CI, 0.658–0.990; $p = 0.040$), LVPWT (OR = 0.742; 95% CI, 0.593–0.928; $p = 0.009$), and other biochemical indexes including NT-proBNP, Cr, DB, and Alb (Table 3).

Multivariable binary logistic regression analysis was performed using variables that were significant in univariate binary logistic regression, and four separate models were developed by the stepwise regression analysis method. Variables of the same type or related were included in one model. Variables that were significant in the first three models were taken into model 4. The results showed that UA was independently associated with RVD in all models (Figure 3). Details of the OR and p-value are listed in Supplementary Table S1.

The correlation between UA and the prognosis of HFpEF

During a median follow-up period of 278 (190–443) days, 52 (24.8%) patients were readmitted for heart failure, and 11 (5.2%) patients died. Kaplan–Meier curves for heart failure readmission and all-cause mortality are displayed in Figure 4. The rate of heart failure readmission was higher in the high UA group ($p = 0.001$) compared to the normal UA group, and all-cause mortality also trended to be higher without statistical significance ($p = 0.062$). The rate of heart failure readmission was higher in both male ($p = 0.002$) and female ($p = 0.018$) patients in the high UA group (Supplementary Figure S2A). To better understand the effect of UA on heart failure readmission, univariate and multivariate Cox regression analyses were performed. In univariate Cox regression, high UA (>7 mg/dl), RVD, and NT-proBNP were related to heart failure readmission ($p < 0.05$). Indicators in univariate Cox regression were taken into multivariate Cox regression, and high UA (HR = 3.027; $p = 0.002$) and NT-proBNP (HR = 1.002 for 1 pmol/L increase; $p = 0.01$) were independently related to heart failure readmission rate after

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TABLE 2 Correlation analysis among UA, TAPSE, TAPSV, and other variables.

	TAPSE		TAPSV		UA	
	r	*p*-value	*r*	*p*-value	*r*	*p*-value
TAPSE (mm)	–	–	0.711	<0.001	−0.441	<0.001
TAPSV (cm/s)	0.711	<0.001	–	–	−0.495	<0.001
UA (mg/dl)	−0.441	<0.001	−0.495	<0.001	–	–
PASP (mmHg)	−0.290	<0.001	−0.249	<0.001	0.250	<0.001
LVPWT (mm)	0.216	0.002	0.187	0.007	−0.010	0.867
IVST (mm)	0.209	0.001	0.160	0.016	−0.050	0.581
Age (year)	−0.113	0.104	−0.164	0.018	0.088	0.203
Heart rate	−0.230	0.001	−0.193	0.005	0.214	0.002
SBP (mmHg)	0.081	0.242	0.005	0.940	0.277	0.001
LDL-C (mmol/L)	0.202	0.003	0.225	0.001	−0.155	0.025
Creatinine (μmol/L)	−0.165	0.017	−0.245	<0.001	0.514	<0.001
hs-CRP (mg/L)	−0.205	0.005	−0.151	0.040	0.255	<0.001
NT-proBNP (pmol/L)	−0.473	<0.001	−0.473	<0.001	0.381	<0.001
DB (μmol/L)	−0.343	<0.001	−0.327	<0.001	0.339	<0.001
Alb (g/L)	0.217	0.002	0.195	0.005	−0.297	<0.001

Alb, albumin; hs-CRP, high-sensitivity C-reactive protein; IVST, interventricular septal thickness; LDL-C, low-density lipoprotein cholesterol; LVPWT, left ventricular posterior wall thickness; NT-proBNP, N-terminal B-type natriuretic peptide; PASP, pulmonary artery systolic blood pressure; SBP, systolic blood pressure; TAPSE, tricuspid annular plane systolic excursion; TAPSV, tricuspid annular peak systolic velocity; UA, uric acid.

adjusting of high UA, gender, NYHA class, CAD, AF, RVD, NT-proBNP, and Cr (Supplementary Table S2). To gain further insight into the role of UA in patients with HFpEF, a subgroup analysis was also conducted. The results indicated that UA > 7 mg/dl might be a risk factor for heart failure readmission regardless of gender, NT-proBNP, TAPSE, PASP, LVPWT, Alb, and DB values (Supplementary Figure S3). The association between high UA and heart failure readmission was stronger in male than in female patients (male (HR 3.88) and female (HR 2.43) patients).

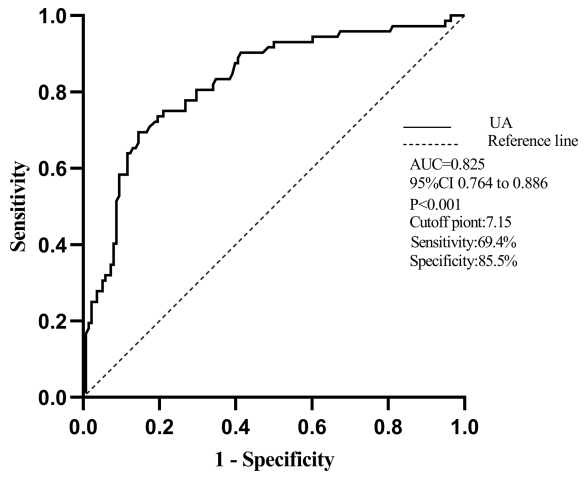

FIGURE 2
The receiver operator characteristic (ROC) curve of UA for predicting RVD. Notes: The area under the curve (AUC) for RVD was 0.825(95% CI, 0.764–0.886). The best cutoff of serum UA to predict RVD was 7.15 mg/dl with a sensitivity of 69.4% and a specificity of 85.5%.

Discussion

The results of this prospective cohort analysis showed that UA levels were associated with the adverse change in right ventricular function in HFpEF patients, with RVD measured by TAPSE and TAPSV. Patients in the high UA group had a higher rate of heart failure readmission, but no statistical difference in all-cause mortality between the two groups was detected.

The European Society of Cardiology (ESC) guidelines highlight UA measurement as an additional marker for the stratification of cardiovascular risk (21), although hyperuricemia is common in patients with chronic heart failure with a prevalence of 50% (22), in HFpEF (26%) (23), and in our research (38%). Limited data are available regarding the relationships of UA levels in HFpEF, especially between UA and right ventricular function. In the present study, we found that hyperuricemia was independently associated with right ventricular function in HFpEF. There are few reports about whether UA correlates with right ventricular function in patients with HFpEF, but some information from previous studies suggests that correlations may exist. A previous study in asymptomatic patients with type 2 diabetes demonstrated an independent relationship between UA and biventricular systolic function, regardless of renal function or diabetic control (24). In patients with idiopathic pulmonary artery hypertension, higher UA levels were suggested to be associated with a

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TABLE 3 Univariate binary logistic regression on the absolute value of right ventricular dysfunction.

	OR	95% CI	*p*-value
UA (mg/dl)	2.061	1.654–2.568	<0.001
Gender (*n*)	1.244	0.699–2.216	0.458
CAD (*n*)	1.068	0.603–1.893	0.822
AF (*n*)	3.508	1.933–6.366	<0.001
Diuretics (*n*)	3.099	1.555–6.179	0.001
SBP (mmHg)	0.992	0.974–1.011	0.397
Heart rate	1.023	1,009–1.037	0.001
LVPWT (mm)	0.742	0.593–0.928	0.009
IVST (mm)	0.807	0.658–0.990	0.040
Cr (μmol/L)	1.021	1.010–1.032	<0.001
NT-proBNP (pmol/L)	1.006	1.004–1.008	<0.001
hs-CRP (mg/L)	0.999	0.992–1.006	0.711
LDL-C (mmol/L)	0.538	0.362–0.800	0.002
DB (μmol/L)	1.174	1.084–1.271	<0.001
Alb (g/L)	0.842	0.774–0.916	<0.001

Alb, albumin; CAD, coronary artery disease; Cr, creatinine; DB, direct bilirubin; hs-CRP, high-sensitivity C-reactive protein; IVST, interventricular septal thickness; LDL-C, low-density lipoprotein cholesterol; LVPWT, left ventricular posterior wall thickness; NT-proBNP, N-terminal B-type natriuretic peptide; UA, uric acid.

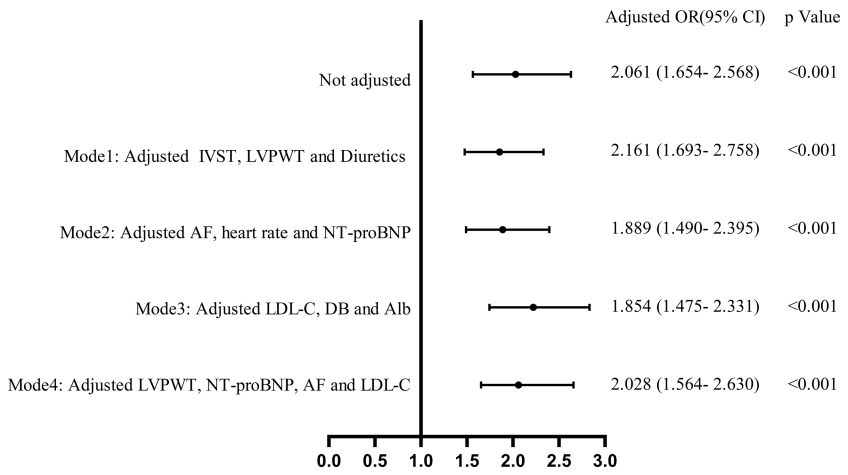

FIGURE 3
Multivariate binary logistic regression analysis of the effect of UA on the absolute value of right ventricular dysfunction.

lower cardiac index and higher pulmonary vascular resistance (25, 26). Another study in patients with ischemic heart disease or dilated cardiomyopathy showed hyperuricemia was associated with elevated right atrial pressures (27). According to those reports and our results, UA levels might correlate with pulmonary artery, right atrial pressure, and right ventricular function.

Variables frequently used to assess RV function in patients with heart failure include RV ejection fraction, the longitudinal strain of the RV, TAPSE, and TAPSV. In the current study, TAPSE and TAPSV were used to assess right ventricular function, which is recommended by ASE to improve the accuracy of RVD (20). They are negatively associated with PASP and TR, the latter two being used in HFpEF diagnosis by the diagnostic algorithm of the HFA-PEFF (28, 29). The relationship between TAPSE and UA has rarely been reported. In our study, we declared high UA levels were significantly related to lower TAPSE, which is consistent with previous reports in type 2 diabetes patients (24), suggesting that UA might be a biomarker of RVD in patients with HFpEF.

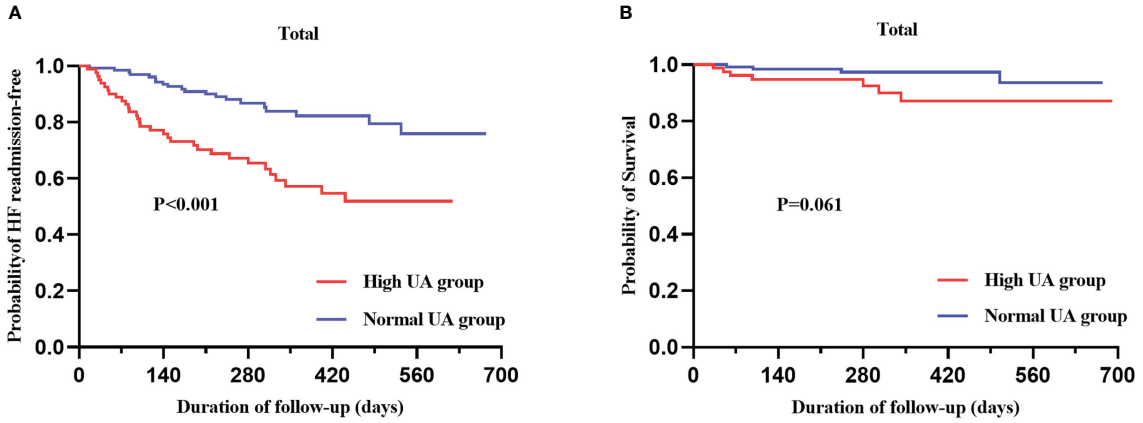

FIGURE 4
Kaplan–Meier analysis for heart failure readmission **(A)** and all-cause mortality **(B)** categorized by serum UA level.

The mechanisms to account for elevated UA and RVD in HFpEF patients appear to be unclear and remain to be elucidated. The possible explanations for the findings are as follows: Firstly, increased UA production due to the upregulation of xanthine oxidase and decreased UA excretion owing to lactic acid accumulation and reduced renal perfusion resulted in a high prevalence of hyperuricemia in heart failure patients (30, 31). Secondly, animal and cell experiments have demonstrated that elevated UA may lead to an increase in cytokine activation, insulin resistance, and oxidative stress, impairing endothelial function and activating the renin–angiotensin system (32–35), which may promote pulmonary vascular remodeling. Meanwhile, the right ventricle is very sensitive to increased pulmonary vascular resistance (36). Increased PASP promotes right ventricular remodeling. Further studies are still needed to demonstrate whether UA evolves in the development of RVD or is only a risk factor for RVD in HFpEF patients.

Previous studies in China did not report gender differences in UA levels in HFpEF patients, so we grouped patients according to Chinese hyperuricemia guidelines: the normal UA group (UA ≤ 7.0 mg/dl) and the high UA group (UA > 7.0 mg/dl). However, the enrolled population showed that gender differences in UA levels did exist. In addition, several studies have shown that the effect of gender on the prognosis of HFpEF is still controversial (37–39). In our study, we performed a gender-specific adjusted analysis and found that hyperuricemia was associated with heart failure readmissions in all patients, more prominently in men. This is in line with the higher comorbidity burden in male heart failure patients (40, 41). For our results, it is important to carefully consider the gender difference in UA levels and the impact of hyperuricemia on the clinical outcomes of patients with HFpEF.

It is widely accepted that UA is an independent predictor of heart failure morbidity and worse outcomes in heart failure population (42–44). However, previous studies demonstrated that the relationship between UA and all-cause mortality or cardiovascular death was controversial both in HFpEF and heart failure with reduced ejection fraction (HFrEF). In the DAPA-HF trial, UA per 1 mg/dl unit increase was not associated with cardiovascular death (HR, 1.06 (0.99–1.14); p = 0.07) or all-cause mortality (HR, 1.03 (0.97–1.1); p = 0.25) in patients with HFrEF (45). In the EMPEROR-reduced trial, serum UA was an independent predictor of increased mortality (all-cause and cardiovascular mortality) and hospitalization for heart failure when the highest serum UA tertile was compared to the lowest serum UA tertile (4). In addition, the PARAGON-HF trial and the RELAX trial displayed inconsistent results regarding the relationship between elevated UA and all-cause mortality in HFpEF (23, 46). Multiple studies in HFrEF have shown that UA-lowering treatment with benzbromarone or allopurinol failed to improve clinical outcomes, exercise capacity, quality of life, and left ventricular systolic function (47, 48). Research in patients with hyperuricemia and HFpEF showed that UA was a predictor for the composite of all-cause mortality and HF rehospitalization and that lowering UA may improve prognosis (49). This suggests that UA-lowering therapy might help improve the prognosis of the patient. To date, there has been no study on the relationship between UA-lowering treatment and RV function in HFpEF. Therefore, whether reducing UA would improve RV function in patients with HFpEF need to be demonstrated by designing specific studies.

Limitations

Our study has the following drawbacks: First, the sample size is limited, and the follow-up time is not long enough. Second, we did not collect the dynamic changes of UA and evaluate the prognostic effects of UA reduction. Third, improvement or deterioration of RVD was not assessed during follow-up, so the effect of UA on changes in RVD outcomes could not be obtained. Fourth, as a prospective observational study, we cannot evaluate the potential role of UA in the development and progression of HFpEF.

Conclusion

Overall, elevated UA levels are associated with RVD in HFpEF patients and may be related to heart failure readmission in patients with HFpEF.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Clinical Research Review Board of the First Affiliated Hospital of Chongqing Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

X-LD contributed to the study design, data analysis, and manuscript preparation. H-WY, JX, X-FZ, JZ, MS, X-SW, Z-QL, LG, Z-YL, and PG were involved in the acquisition of data. D-YZ and QY worked on the study concept, design, and final proof. All authors read and approved the final manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (number 82270406, 81970203), the Chongqing Health Commission (number 2022MSXM028), and the China Cardiovascular Health Alliance-Access Research Found (number 2021-CCA-ACCESS-130).

Acknowledgments

The authors thank Dong Qian (Chongqing Medical University) for help in performing echocardiography and analysis.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1143458/full#supplementary-material

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frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 16 March 2023
DOI 10.3389/fendo.2023.1140093

OPEN ACCESS

EDITED BY
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SPECIALTY SECTION
This article was submitted to Cardiovascular Endocrinology, a section of the journal Frontiers in Endocrinology

RECEIVED 08 January 2023
ACCEPTED 28 February 2023
PUBLISHED 16 March 2023

CITATION
Chen X, Jin H, Wang D, Liu J, Qin Y, Zhang Y, Zhang Y and Xiang Q (2023) Serum creatinine levels, traditional cardiovascular risk factors and 10-year cardiovascular risk in Chinese patients with hypertension.
Front. Endocrinol. 14:1140093.
doi: 10.3389/fendo.2023.1140093

Serum creatinine levels, traditional cardiovascular risk factors and 10-year cardiovascular risk in Chinese patients with hypertension

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Background: Serum creatinine is associated with cardiovascular risk and cardiovascular events, however, the relationship between serum creatinine levels and cardiovascular risk is not well established in hypertensive population in Jiangsu Province. We aimed to evaluate the association of serum creatinine levels with traditional cardiovascular risk factors and 10-year cardiovascular risk in a Chinese hypertensive population.

Methods: Participants were patients with hypertension registered and enrolled in health service centers in 5 counties or districts from January 2019 to May 2020 in Jiangsu Province of China followed strict inclusion and exclusion criteria, demographics as well as clinical indicators and disease history and lifestyle were collected. Participants were divided into four groups according to quartiles of serum creatinine levels, then the China-PAR model was used to calculate 10-year cardiovascular risk for each individual.

Results: A total of 9978 participants were enrolled in this study, 4173(41.82%) were males. The blood pressure level and prevalence of dyslipidemia, elderly, current smokers and drinking as well as obesity were higher in the Q4 group than the Q1 group (all $P < 0.05$). Multivariable logistic regression showed that serum creatinine in the Q4 group compared with that in the Q1 group was positively associated with overweight and obesity (OR=1.432, 95% CI 1.237-1.658, $P<0.001$), while negatively associated with physical activity (OR=0.189, 95%CI 0.165-0.217, $P<0.001$), and so on. Multiple linear regression showed 10-year cardiovascular risk is positively associated with serum creatinine levels after adjusting for multiple risk factors (β=0.432, $P< 0.001$).

Conclusion: Serum creatinine was associated with several traditional cardiovascular risk factors and the 10-year cardiovascular risk in hypertensive patients. Creatinine-reduction and kidney-sparing therapy are essential for patients with hypertension to optimize control of cardiovascular risk.

KEYWORDS

serum creatinine, cardiovascular disease, risk factor, China-PAR model, hypertension patients

1 Introduction

Serum creatinine (Scr) is the anhydride form of creatine and serves a marker of renal function, which mainly comes from muscle metabolism (1). In clinical studies, elevated serum creatinine levels are generally considered as an adverse events or outcomes, often indicating renal impairment (2, 3), meanwhile, studies have shown that impaired renal function is often accompanied by increased cardiovascular risk (4). Serum creatinine levels are not only a contributor to the development cardiovascular events, but also strongly associated with longitudinal risk for cardiovascular disease (CVD) and mortality (5, 6).

Previous studies have shown that slight changes in serum creatinine incrementally associated with increased risk for CVD such as coronary heart disease and heart failure (6, 7), but their association with 10-year cardiovascular risk has not been evaluated in patients with essential hypertension in China. It has been reported that serum creatinine is significantly correlated with pre-inflammatory markers such as Lipoprotein (a)(Lp(a)) and high sensitive C Reactive Protein (hs-CRP) (8, 9), however, the relationship between serum creatinine levels and traditional cardiovascular risk factors such as diabetes and dyslipidemia remains controversial.

The prediction model for atherosclerotic cardiovascular disease (ASCVD) risk in China (China-PAR) has been validated in several Chinese population cohort, which is considered to be a suitable cardiovascular risk prediction model for Asians (10–12). Based on the risk score calculated by the China-PAR risk prediction model, participants were classified into different risk levels and then subsequently treated with corresponding intervention measures. Because of the interaction between serum creatinine and cardiovascular events, we suspected that serum creatinine might be associated with the predicted 10-year cardiovascular risk. However, the data on the association between serum creatinine and predicted 10-year cardiovascular risk is fairly limited.

Therefore, the aim of our study is to estimate the association between serum creatinine levels and traditional cardiovascular risk factors and 10-year cardiovascular risk based on data from a hypertensive population in Jiangsu Province of China, in order to provide references for the prevention of CVD in hypertensive patients with higher creatinine levels.

2 Method

2.1 Data source and participants

Five representative counties or districts in Jiangsu province were selected by multistage stratified random sampling method according to the characteristics of regional economic development (north, midland and south Jiangsu Province), population distribution and lifestyle to ensure the representativeness of research participants. Participants with essential hypertension were registered and enrolled from 50 towns or communities (10 towns or communities were randomly selected according the Random number table method from each counties or districts) in health service centers from January 2019 to May 2020 in Jiangsu Province of China followed strict inclusion and exclusion criteria. Participants aged 40-70 years old, continued residence in registration location for more than half a year, and voluntarily signed informed consent were included. The exclusion criteria were lacking of basic information, diagnosed with secondary hypertension or coronary heart disease, stroke and heart failure and other CVD, used serum creatinine-lowering agents or other drugs that may affect creatinine levels and inability or unwillingness to participate in the survey. A total of 9978 participants with essential hypertension were included in the final analysis (Figure 1). Traditional cardiovascular risk factors such as height and weight, blood pressure and waist circumference (WC), as well as disease history such as diabetes and dyslipidemia, and lifestyle factors such as smoking, drinking, levels of vegetables and fruits intake were collected. Participants were divided into four groups according to quartiles of serum creatinine levels: quartile1 (Q1) group (Scr ≤ 68.00 μmol/l, n=2414), quartile 2 (Q2) group (Scr 68.01-78.00 μmol/l, n=2470), quartile 3 (Q3) group (Scr 78.01-89.99μmol/l, n=2540), and quartile 4 (Q4) group (Scr ≥ 90.00μmol/l, n = 2554). The procedures followed in this study were approved by the Ethics Review Board of Jiangsu Center for Disease Control and Prevention (SL2015-B004-01). Informed consent was obtained from all participants, and all study procedures were conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines, and complied with the principles of the Declaration of Helsinki (1975, revised 2013).

2.2 Serum creatinine measurement

The participants are required to control diet and not to over eat meat or do strenuous exercise within three days prior to the measurement. Blood samples were obtained from an antecubital vein after fasting for at least 8 hours and then aliquoted within 2 hours and frozen at −80°C, then transported in dry ice to the central laboratory in Jiangsu Province Center for Disease Control and Prevention, which was certificated by The National Laboratory

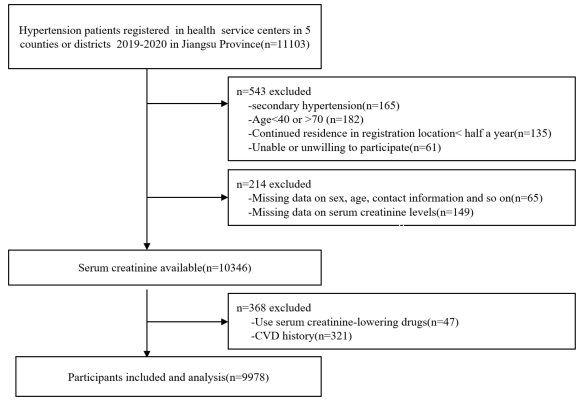

FIGURE 1
Flow chart of participants. CVD, cardiovascular disease.

Certification of China. The serum creatinine was measured by automatic biochemical analyzer (Abbott Laboratories, USA) within one week, and the whole process of laboratory testing was strictly controlled by professionals.

2.3 Definition of traditional cardiovascular risk factors

In our study, hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg or with anti-hypertensive treatment or participants had a reported history of hypertension (13). Hypertension treatment was defined as regularly taking antihypertensive drugs within two weeks before investigation. Diabetes was defined as fasting plasma glucose (FPG)≥7.0 mmol/L or participants are taking hypoglycemic drugs or have a history of diabetes (14). Dyslipidemia was defined as total cholesterol (TC)≥6.22 mmol/L and/or triglyceride (TG)≥2.26 mmol/L and/or high density lipoprotein-cholesterol (HDL-C) <1.04 mmol/L and/or low density lipoprotein-cholesterol (LDL-C) ≥4.14 mmol/L, or participants reported a history of dyslipidemia or were taking lipid-lowering drugs (15). Body mass index (BMI) is calculated as weight divided by the square of height and then be divided into four grades: <18.5 kg/m^2 as the underweight group; 18.5–23.9 as the normal group; 24.0–27.9 as the overweight group; ≥28.0 kg/m^2 as the obesity group (16, 17). Smoking was defined as participants smoked one or more cigarettes per day during the 30 days prior to the survey (18). Drinking was defined as having consumed alcohol in the 30 days before the survey and at least once a week (19).

2.4 Risk estimation model

The China-PAR model was adopted to calculate the 10-year cardiovascular risk for each individual, which is available online (https://www.cvdrisk.com.cn/ASCVD/ Articles/Index/52). The China-PAR risk score included sex, age, SBP, WC, smoking, diabetes, geographic region, urbanization, family history of CVD, and treatment for hypertension. Based on the calculated risk score, the participants were divided into three risk categories: <5% as low risk group, 5-9.9% as moderate risk group, and ≥10% as high risk group (10).

2.5 Statistical analysis

Continuous variables meeting the normal distribution were expressed using the mean ± standard deviation (SD) and use F-test. Categorical variables are expressed as counts and percentages and were compared using x^2-test. Multivariate logistic regression analysis was used to determine the association of serum creatinine with cardiovascular risk factors. Sensitivity analysis excluded the participants receiving hypertension treatment and diabetes, and multiple linear regression analysis was used to study the relationship between serum creatinine level and 10-year cardiovascular risk. Statistical analyses were performed using SPSS version 27.0(IBM, Armonk, NY, United States), and two-sided *P* values of <0.05 were considered statistically significant.

3 Results

3.1 Characteristics of participants

The general characteristics of the 9978 participants enrolled in this study by serum creatinine levels are presented in Table 1. Among all participants, the average age was 58.58 years, with male gender distribution of 41.82%. Results of the study grouped by serum creatinine quartiles were indicated that the blood pressure level and prevalence of dyslipidemia, elderly, current smokers and drinking as well as obesity were higher in the Q4 group than the Q1 group (all $P<0.05$).

3.2 Association between serum creatinine levels and cardiovascular risk factors

Multivariable logistic regression was performed to study the relationship between serum creatinine and cardiovascular risk factors, as shown in Table 2, in total participants, the odds ratio (OR) for age, overweight and obesity, drinking, physical exercise, and intake of vegetables and fruits and so on, were 1.403(95% CI 1.237-1.592, $P<0.001$), 1.432(95%CI 1.237-1.658, $P<0.001$), 1.336 (95% CI 1.080-1.653, $P=0.008$), 0.189(95%CI 0.165-0.217, $P<0.001$) and 0.727(95%CI 0.637-0.829, $P<0.001$) in the Q4 group compared with that in the Q1 group respectively, which suggests that serum creatinine levels are positively correlated with age, obesity and alcohol consumption, but negatively correlated with fruits and vegetables intake.

3.3 Association between serum creatinine and cardiovascular risk factors according gender stratification

Results further analyzed according to gender stratification was shown in Figure 2, the OR for age, drinking and physical exercise was 1.389 (95% CI 1.126-1.714, $P < 0.05$), 1.385(95% CI 1.098-1.747, $P< 0.05$), 0.194(95% CI 0.149-0.251, $P<0.05$) in the Q4 group compared with that in the Q1 group in men, respectively.

As for women, the OR for age, hypertension treatment, physical exercise and intake of vegetables and fruits was 1.492(95% CI 1.255-1.773, $P < 0.05$), 1.310(95% CI 1.024-1.677, $P<0.05$), 0.258(95%CI 0.216-0.308, $P<0.05$), 0.704(95%CI 0.590-0.839, $P<0.05$) in the Q4 group compared with that in the Q1 group, respectively. The results

10.3389/fendo.2023.1140093

TABLE 1 Characteristics of participants according to quartiles of serum creatinine.

Variables	All the participants (n=9978)	Quartiles of Serum creatinine (Scr)				*P* value
		Q1 group (Scr ≤ 68.00 μmol/l, n = 2414)	Q2 group (Scr68.01-78.00 μmol/l, n = 2470)	Q3 group (Scr78.01-89.99μmol/l, n = 2540)	Q4 group (Scr≥90.00μmol/l, n = 2554)	
Demographics characteristics						
Age, years	58.58 ± 7.30	57.89 ± 7.30	58.68 ± 7.24	58.46 ± 7.41	59.26 ± 7.17	<0.001
Age, %						
<60	4935(49.46)	1311(54.31)	1223(49.51)	1270(50.00)	1131(44.28)	<0.001
≥60	5043(50.54)	1103(45.45.69)	1247(50.49)	1270(50.00)	1423(55.72)	
Male, %	4173(41.82)	512(21.21)	825(33.40)	1098(43.23)	1738(68.05)	<0.001
Rural, %	8678(86.97)	1984(82.19)	2213(89.60)	2294(90.31)	2187(85.63)	<0.001
Clinical characteristics						
SBP, mm Hg	150.79 ± 11.95	149.45 ± 10.82	150.73 ± 11.25	151.33 ± 12.27	151.57 ± 13.13	<0.001
DBP, mm Hg	94.16 ± 7.37	92.71 ± 6.59	93.80 ± 7.22	94.75 ± 7.36	95.30 ± 7.93	<0.001
WC, cm	89.40 ± 10.14	87.53 ± 10.05	89.08 ± 10.39	90.02 ± 10.13	90.87 ± 9.70	<0.001
BMI, %						
Underweight <18.5 kg/m^2	107(1.07)	37(1.53)	36(1.46)	21(0.83)	13(0.51)	<0.001
Normal 18.5–23.9 kg/m^2	2407(24.12)	659(27.30)	654(26.48)	572(22.52)	522(20.44)	
Overweight 24.0–27.9 kg/m^2	4287(42.96)	1009(41.80)	1042(42.19)	1099(43.27)	1137(44.52)	
Obesity ≥28.0 kg/m^2	3177(31.84)	709(29.37)	738(29.88)	848(33.39)	882(34.53)	
Heart rate, bpm	73.52 ± 8.41	74.12 ± 6.90	73.37 ± 7.97	73.37 ± 9.21	73.26 ± 9.24	0.001
Diabetes, %	614(6.15)	138(5.72)	150(6.07)	162(6.38)	164(6.42)	0.714
Dyslipidemia, %	3511(35.18)	787(32.60)	821(33.24)	910(35.83)	993(38.88)	<0.001
TC, mmol/L	4.86 ± 1.92	4.66 ± 1.98	4.75 ± 0.93	4.89 ± 1.05	5.10 ± 2.94	<0.001
TG, mmol/L	1.83 ± 1.33	1.80 ± 1.35	1.81 ± 1.32	1.83 ± 1.25	1.88 ± 1.42	0.239
HDL-C, mmol/L	1.64 ± 0.54	1.70 ± 0.54	1.63 ± 0.46	1.63 ± 0.59	1.61 ± 0.54	<0.001
LDL-C, mmol/L	2.70 ± 0.89	2.71 ± 0.92	2.69 ± 0.87	2.69 ± 0.88	2.71 ± 0.89	0.794
Course of hypertension, %						
< 5 years	6040(60.53)	1593 (65.99)	1563(63.28)	1498(59.98)	1386(54.27)	<0.001
≥5 years	3938(39.47)	821(34.01)	907(36.72)	1042(40.02)	1168(45.73)	
Hypertension treatment, %	8156(81.74)	1953(80.90)	1953(78.07)	2063(81.22)	2187(85.63)	<0.001
Lifestyle characteristics						
Smoking, %	1899(19.03)	237(9.73)	395(15.99)	506(19.92)	761(29.80)	<0.001
Drinking, %	1632(16.36)	179(7.42)	314(12.71)	433(17.05)	706(27.64)	<0.001
Intake of vegetables and fruits, %						
≤400g/d	3320(33.27)	769(31.86)	794(32.15)	826(32.52)	931(36.45)	0.001
>400g/d	6658(66.73)	1645(68.14)	1676(67.85)	1714(67.48)	1623(63.55)	
Limiting intake of high fat cholesterol foods, %	5198(52.09)	1243(51.49)	1291(52.27)	1302(51.26)	1362(53.33)	0.449

(Continued)

TABLE 1 Continued

Variables	All the participants (n=9978)	Quartiles of Serum creatinine (Scr)				*P* value
		Q1 group (Scr ≤ 68.00 μmol/l, n = 2414)	Q2 group (Scr68.01-78.00 μmol/l, n = 2470)	Q3 group (Scr78.01-89.99μmol/l, n = 2540)	Q4 group (Scr≥90.00μmol/l, n = 2554)	
Physical exercise, %						
<3 times/week	3950(39.59)	473(20.42)	954(39.62)	1198(47.17)	1325(51.88)	<0.001
≥3 times/week	6028(60.41)	1941(80.41)	1516(61.38)	1342(52.83)	1229(48.12)	

Normal continuous variables were expressed using the mean ± SD. Categorical variables were reported as the counts and percentages. SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; BMI, body mass index; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol.

showed that serum creatinine was positively associated with age, while negatively associated with physical activity in both genders.

3.4 10-year cardiovascular risk according to quartiles of serum creatinine

The 10-year predicted cardiovascular risk according to quartiles of serum creatinine is shown in Figure 3. In the total participants, the average risk of CVD in Q1 and Q4 groups were 10.57% and 14.10%, respectively, and the difference was statistically significant ($P < 0.001$). The mean risk of CVD in Q1 and Q4 groups were 13.56% and 15.53% in men, and 9.76% and 11.07% in women, respectively (all $P < 0.001$).

3.5 Distribution of 10-year cardiovascular risk classes according to quartiles of serum creatinine

The distribution of cardiovascular risk classes according to quartiles of serum creatinine is shown in Figure 4. In the total participants, the proportions of participants with high predicted risk in Q1 and Q4 groups were 54.18% and 77.56%, respectively, and the difference was statistically significant ($P < 0.001$). After grouping by gender, the proportions of individuals at high risk in Q1 and Q4 groups were 80.07% and 86.42% in males, and 47.21% and 58.70% in females, respectively (all $P < 0.05$).

TABLE 2 Association between serum creatinine and cardiovascular risk factors.

Variables		OR (95%CI)	*P* value
Age	<60	1(Reference)	
	≥60	1.403(1.237,1.592)	<0.001
Male		9.775(8.316,11.490)	<0.001
Rural		1.517(1.265,1.819)	<0.001
SBP		0.997(0.991,1.003)	0.280
DBP		1.035(1.025,1.046)	<0.001
BMI	<24	1(Reference)	
	≥24	1.432(1.237,1.658)	<0.001
Heart rate		0.991(0.983,0.998)	0.013
Dyslipidemia		1.311(1.150,1.494)	<0.001
Course of hypertension≥5 years		1.530(1.341,1.746)	<0.001
Hypertension treatment		1.320(1.115,1.564)	0.001
Smoking		1.053(0.863,1.284)	0.610
Drinking		1.336(1.080,1.653)	0.008
Intake of vegetables and fruits>400g/d		0.727(0.637,0.829)	<0.001
Physical exercise≥3 times/week		0.189(0.165,0.217)	<0.001

OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; TC, total cholesterol; HDL-C, high density lipoprotein-cholesterol.

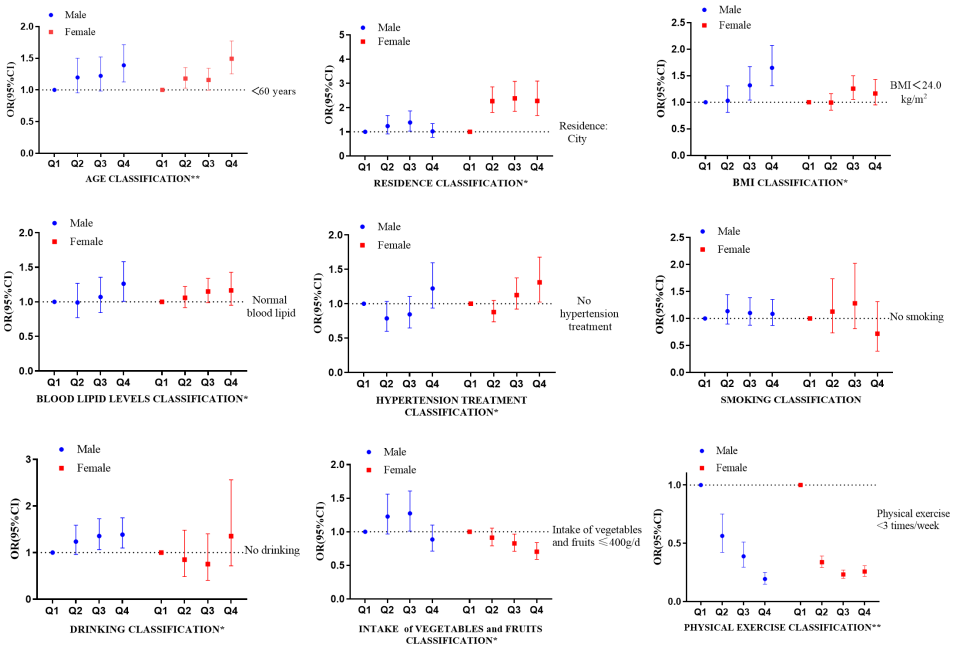

FIGURE 2
Association between serum creatinine and cardiovascular risk factors according to gender stratification. CI, confidence interval. *The difference in males or females was statistically significant (the Q4 group vs. the Q1 group, $P < 0.05$). **The difference both in males and females were statistically significant (the Q4 group vs. the Q1 group, $P<0.05$).

3.6 Association between serum creatinine level and 10-year cardiovascular risk

The results of the multiple linear regression are shown in Table 3. In the total participants, 10-year cardiovascular risk derived from the China-PAR model is positively associated with serum creatinine levels after adjusting for multiple risk factors in Model 3 ($\beta = 0.432$, $P<0.001$). Comparing by gender, cardiovascular risk was positively correlated with serum creatinine level in men ($\beta = 0.504$, $P=0.001$), although no statistical significance has been found in women.

3.7 Sensitivity analysis

In order to exclude the confounding effects of hypertension treatment and diabetes on serum creatinine, we conducted sensitivity analysis and excluded hypertension patients with hypertension treatment or diabetes, as shown in Table 4. After adjusting various factors, the serum creatinine level was positively correlated with 10-year cardiovascular risk in participants without receive antihypertensive drugs ($\beta=1.337$, $P< 0.001$), especially in men ($\beta=0.602$, $P< 0.001$). In addition, serum creatinine is positively correlated with cardiovascular risk in hypertensive patients without

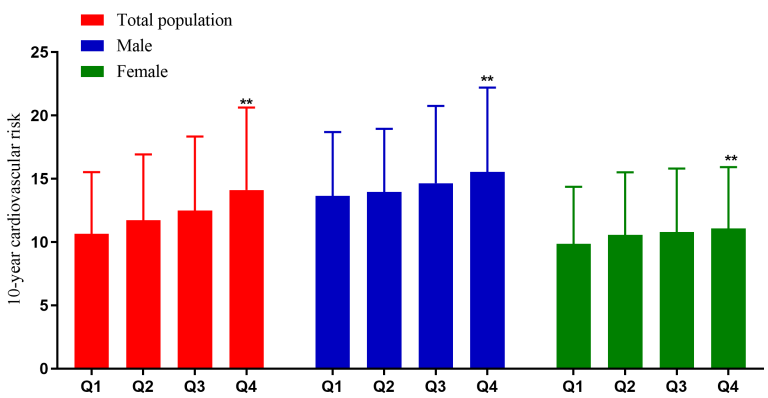

FIGURE 3
Cardiovascular risk according to quartiles of serum creatinine. **$P < 0.001$ (the Q4 group vs. the Q1 group).

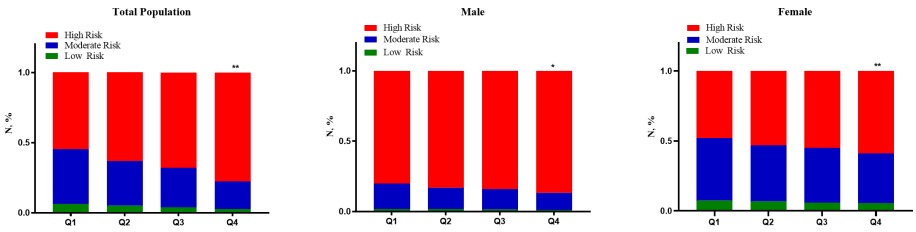

FIGURE 4
Distribution of cardiovascular risk classes according to quartiles of serum creatinine. *P < 0.05 (the Q4 group vs. the Q1 group). **P < 0.001 (the Q4 group vs. the Q1 group).

TABLE 3 Association between serum creatinine level and cardiovascular risk.

	Model 1		Model 2		Model 3	
	Beta coefficients	*P* value	Beta coefficients	*P* value	Beta coefficients	*P* value
Total participants	2.502	<0.001	0.920	<0.001	0.432	<0.001
Male	1.337	<0.001	1.268	<0.001	0.504	0.001
Female	0.733	<0.001	0.409	<0.001	0.165	0.131

Model 1: uncorrected covariates; Model 2 was adjusted for age and sex; Model 3 was adjusted for Model 2 plus heart rate, dyslipidemia, smoking, drinking, intake of vegetables and fruits, physical exercise and residence, diabetes and hypertension treatment.

diabetes (β=0.490, P< 0.001) in Model 3, comparing by gender, serum creatinine and 10-year cardiovascular risk are positively correlated in both men (β=0.569, P< 0.001) and women (β=0.209, P=0.046), respectively.

4 Discussion

The morbidity and mortality of CVD have been increasing gradually in China, partly attributed to the increased exposure and aggregation of multiple cardiovascular risk factors (20). Previous studies have shown that prevention and control measures based on risk factors can effectively reduce cardiovascular risk (21). Elevated creatinine levels have been reported to play a role in the increased risk of a variety of CVD, in addition, some clinical studies have found that increased serum creatinine levels, which often indicate a decrease in glomerular filtration rate, may be used as a predictive marker for CVD (22, 23), similarly, our study showed that the average risk in serum creatinine levels Q1 and Q4 groups were 10.57% and 14.10%, and the proportions of participants with high predicted risk of CVD were 54.18% and 77.56% in the total population. Hypertension is an important risk factor in the development of CVD. The relationship between creatinine and multiple cardiovascular risk factors and cardiovascular risk in patients with hypertension needs to be fully elucidated. In our study, serum creatinine levels were found to be strongly associated with cardiovascular risk factors in hypertensive patients.

The results have important clinical significance. Firstly, we used a relatively novel risk prediction model to evaluate individual cardiovascular risk and provided reference for the control of hypertensive patients with high creatinine level to reduce cardiovascular risk. Secondly, serum creatinine is a relatively convenient biochemical index, and serum creatinine in addition to traditional CVD risk factors should be taken into account when

TABLE 4 Association between serum creatinine level and cardiovascular risk (sensitivity analysis).

Sensitivity analysis	Model 1		Model 2		Model 3	
	Beta coefficients	*P* value	Beta coefficients	*P* value	Beta coefficients	*P* value
Participants without hypertension treatment	2.522	<0.001	0.810	<0.001	1.337	<0.001
Male	1.243	<0.001	1.194	<0.001	0.602	<0.001
Female	0.560	0.004	0.269	0.084	0.114	0.352
Participants without diabetes	2.574	<0.001	0.933	<0.001	0.490	<0.001
Male	1.360	<0.001	0.346	<0.001	0.569	<0.001
Female	0.696	<0.001	0.421	<0.001	0.209	0.046

Model 1: uncorrected covariates; Model 2 was adjusted for age and sex; Model 3 was adjusted for Model 2 plus heart rate, dyslipidemia, smoking, drinking, intake of vegetables and fruits, physical exercise and residence, diabetes and hypertension treatment.

evaluating risk for development of CVD in hypertensive patients, especially in male.

Based on the China-PAR project, the China-PAR risk score has good internal consistency and has been proved to be a suitable method for predicting 10-year cardiovascular risk in Chinese population (10). The 10-year cardiovascular risk for each individual was calculated using the China-PAR risk calculation equation. Hypertension patients are at high risk of CVD, at the same time, the pathogenesis of hypertension is closely related to the kidney, which is not only an important organ for blood pressure regulation, but also one of the target organs of hypertension, studies have shown that hypertensive patients with renal impairment have an increased risk of overall CVD, and even mild renal dysfunction can lead to increased mortality and morbidity of CVD (24). In our study, it was also shown that hypertensive individuals with higher creatinine levels had a higher cardiovascular risk.

The rationale for the positive association between serum creatinine and cardiovascular risk remains to be fully clarified. Serum creatinine refers to endogenous serum creatinine, which is the product of human muscle metabolism and the surrogate of renal function (23). Its level is relatively constant in normal people, when the majority of the human kidney is suffering from pathological damage and the proportion of glomerular filtration rate is decreased (more than 50%), the situation of increased serum creatinine may be clinically apparent, and its concentration depends on many factors such as creatinine production rate, distribution volume, extrarenal metabolism and renal injury (23, 25, 26). Serum creatinine behaves as a marker of pro-inflammatory state, and inflammation-mediated endothelial dysfunction has been shown to be associated with the occurrence of cardiovascular events in women with reduced renal function, in addition, high serum creatinine is often accompanied by a decrease in glomerular filtration rate, which is prone to water-sodium retention and increases the burden on the heart as well as cardiovascular risk (9, 27).

Although this study highlights the association between serum creatinine levels and cardiovascular risk factors and 10-year risk of CVD in patients with hypertension in Jiangsu province of China, there are several limitations. The participants with hypertension were recruited from a single province in China, so extrapolation to other populations should be cautious. In addition, our study is a cross-sectional study, and prospective studies are needed for further verification. Finally, other factors that may affect creatinine levels and cardiovascular risk factors such as urea nitrogen and uric acid were missing in this study, and the number and type of antihypertensive drugs were not considered in the study, but we conducted a sensitivity analysis to reduce part of the confounding effect.

5 Conclusions

In conclusion, serum creatinine was associated with several cardiovascular risk factors in a hypertensive population in Jiangsu province. The 10-year cardiovascular risk was higher in hypertensive patients with higher serum creatinine levels, especially in men. Creatinine-reduction and kidney-sparing therapy is essential for patients with hypertension to optimize control of cardiovascular risk factors and reduce cardiovascular risk.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Review Board of Jiangsu Center for Disease Control and Prevention (SL2015-B004-01). The patients/participants provided their written informed consent to participate in this study.

Author contributions

Study concept and design: QX, YuZ, YoZ, YQ, XC; Acquisition of data: XC, DW, HJ, JL, YQ, QX; Analysis and interpretation of data: XC, DW, HJ, JL, YQ, YoZ, QX; Drafting of the manuscript: XC, DW, JL, YQ, QX; Critical revision of the manuscript for important intellectual content: QX, YQ, YuZ; Statistical analysis: XC, DW, JL, YQ, QX; Obtained funding: QX; Technical, or material support: YQ, YoZ, YuZ, QX; Study supervision: QX. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by the Projects in the Chinese National Science and Technology Pillar Program during the 12th Five-year Plan Period (2011BAI11B01), and Jiangsu Province Health Research Project (H201224).

Acknowledgments

We thank Wang Zenwu and Wang Xin (Division of Prevention and Community Health, National Center for Cardiovascular Disease, Fuwai Hospital) for their constructive suggestions and the technical support. We thank all the colleagues involving in this survey from Pizhou, Haian, Peixian, Sihong County and Jiangye District Center for Disease Control and Prevention.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 27 March 2023
DOI 10.3389/fendo.2023.1124565

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Endocrinology of Aging, a section of the journal Frontiers in Endocrinology

RECEIVED 15 December 2022
ACCEPTED 14 March 2023
PUBLISHED 27 March 2023

CITATION
Hu Y, Liu J and Jin H (2023) Association between serum uric acid and phase angle in patients with type 2 diabetes mellitus: A cross-sectional study.
Front. Endocrinol. 14:1124565.
doi: 10.3389/fendo.2023.1124565

Association between serum uric acid and phase angle in patients with type 2 diabetes mellitus: A cross-sectional study

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Background: The purpose of this analysis was to investigate the associations between serum uric acid and phase angle in patients with type 2 diabetes mellitus.

Methods: In this retrospective cross-sectional study, we included 200 type 2 diabetes mellitus (T2DM) patients treated during 2018–2019 at Zhongda Hospital Southeast University. Phase angle (PhA) and other body composition indicators were measured by bioelectrical impedance analysis (BIA). All patients underwent routine clinical examinations on the day of hospitalization, and the basic information and clinical symptoms of these patients were recorded.

Results: Serum uric acid (UA) was significantly associated with PhA ($p < 0.001$). Overall, in the crude model and minor, all adjusted models (crude model, Models I–II), the phase angle increased as the tertiles of serum uric acid increased. In the minor adjusted model (Model I, adjustment for age and duration) fully adjusted model (Model II, adjustment for age, duration, Lpa, BMI, and WHR), the adjusted β for participants in tertiles of serum uric acid were 0.26 (95% CI: 0.05–0.46) and 0.32 (95% CI: 0.11–0.54), respectively, compared with those in the lowest tertile 1.

Conclusion: There was a nonlinear relationship between serum uric acid and PhA in T2DM patients, and the phase angle increased as uric acid increased within a certain range, and this effect disappeared when uric acid exceeded a certain value.

KEYWORDS

serum uric acid, phase angle, type 2 diabetes mellitus, nutritional status, body composition

1 Introduction

Phase angle (PhA) is a useful instrument to identify dysfunction in cell membrane integrity; therefore, it is seen as an important prognostic marker in many clinical contexts (1), such as malnutrition (2). PhA is also used as an important nutritional indicator. In general, the lower the PhA, the worse the nutrition outcome. According to several studies, people with diabetes show decreased PhA compared with healthy people (3, 4). In addition, PhA is also directly associated with other nutritional markers such as BMI and grip strength (5). Measuring PhA is relatively cheap and is considered a non-invasive procedure based on bioelectrical impedance (BIA) (6). Many recent studies have shown that bioimpedance measurements such as visceral fat area can be correlated with nutritional indicators (7).

Uric acid is the end product of purine metabolism and is considered abnormally high in the human body when its serum concentration exceeds 360 or 420 mmol/L (8). Uric acid may have both proinflammatory and antioxidant properties, and therefore its exact role in disease risk is not clear (9). Studies have shown that SUA may be a nutritional marker in hemodialysis patients (10). In recent years, there have been many studies on UA in the kidney diseases field. However, in reviewing the literature, we did not find any information regarding the association between UA and nutritional status in diabetes mellitus patients. As far as we know, there is no information in the literature to explore the association between serum uric acid and phase angle in patients with diabetes mellitus. The relationship between phase angle and metabolism in diabetic patients has been worked out in many laboratories, and it is well reported. However, reports on direct work related to uric acid and phase angle in relation to diabetes are few (3, 11, 12).

We therefore aimed to investigate the associations between serum uric acid and phase angle in patients with diabetes mellitus. Paying attention to the relationship between serum uric acid and nutritional status in diabetes mellitus patients has predictive value for early intervention in malnutrition.

2 Methods

2.1 Study design and participants

A total of 200 patients with T2DM who were admitted to the Department of Endocrinology and Metabolism at Zhongda Hospital Southeast University between January 2018 and December 2019 were recruited in this cross-sectional study. The flow chart displaying patient selection is presented in Figure 1. Inclusion criteria for the T2DM group include having been previously diagnosed with T2DM according to American Diabetes Association (ADA) criteria. Children were diagnosed when their fasting plasma glucose was ≥ 126 mg/dl (7.0 mmol/L). Exclusion criteria were: 1) age <18 years; 2) severe liver and kidney functional abnormalities; 3) malignant tumor; 4) the use of drugs that affect uric acid metabolism; and 5) an incomplete laboratory examination or BIA data.

The study adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Review Board of Zhongda Hospital Southeast University. Given the retrospective nature of the study and the use of anonymized patient data, the requirements for informed consent were waived.

2.2 Measurement body composition and UA

Body composition was measured using multi-frequency BIA (InBody 770; InBody Co., Ltd., Korea) in the morning on the patient's first day in hospital. Before the BIA test, patients were required to abstain from food and water, empty their bladders, remove their shoes and socks, wear clothing of known weight, and remove other items. The participants were instructed to stand barefoot on the metal footplate of the analyzer, holding the handgrip with arms straight and pointing downwards in a neutral standing position. The surface of the hand electrode was placed in contact with each of the participant's five fingers, whereas the participant's heels and forefoot were placed on the circular-shaped foot electrode. All parameters, including PhA, waist–hip ratio (WHR), skeletal muscle mass (SMM), and body mass index (BMI), were directly measured and recorded by the devices. After 8–10 h of fasting, blood samples were collected for measurement of uric acid, fasting plasma lipids, glucose, and HbA1c.

2.3 Statistical analysis

Patient characteristics were analyzed according to serum uric acid tertiles. Categorical variables are expressed in numbers and percentages. Continuous variables are expressed as mean and standard deviation (SD) for normal distributions or median and interquartile range (IQR) for skewed distributions. We used the chi-square test and Kruskal–Wallis test for the comparison of categorical, normally distributed, and nonnormally distributed continuous variables, respectively.

Univariate linear regression analyses and multivariable linear regression analyses were performed to evaluate the associations between serum uric acid and PhA. According to the recommendation of the Strengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement (13), analyses were first performed without adjustment. Further analyses cumulatively included adjustment for age, duration (a minimally adjusted model), Lpa, BMI, and WHR (a fully adjusted model). Linear regression models were used for the subgroup analyses and included terms for sex group, BMI group, age group, and the interaction of each subgroup.

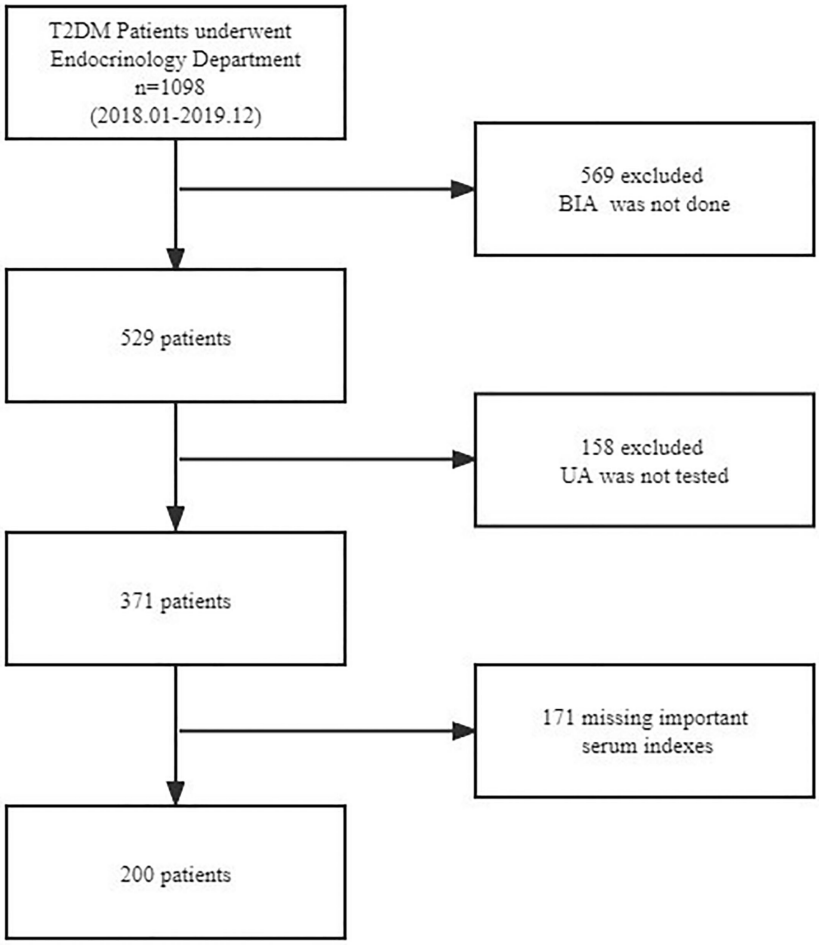

FIGURE 1
Flowchart of participant selection. T2DM, type 2 diabetes mellitus; BIA, bioelectrical impedance analysis; UA, uric acid.

All the analyses were performed with the statistical software packages R (http://www.R-project.org, The R Foundation) and Free Statistics software version 1.7.1. A two-sided *P*-value of <0.05 was statistically significant.

3 Results

3.1 Participants selection

Baseline characteristics of the 200 enrolled participants (122 men and 78 women) stratified by serum uric acid level are shown in Table 1. Patients enrolled were grouped by the tertiles of serum uric acid levels as follows: UA T1group, ≥196.5 to ≤279 ummol/L; UA T2group, ≥281 to ≤350 ummol/L; and UA T3group, ≥352 to ≤626 ummol/L. Some differences existed between the serum uric acid level groups with respect to various covariates (TC, FPG, FCP, SMM, BMI, WHR, PhA, and TG). The number of patients in thethree groups was 66, 67, and 67, respectively.

3.2 Associations between serum uric acid and PhA

In univariate analysis, age, duration, Lpa, skeletal muscle mass (SMM), BMI, PBF, visceral fat area (VFA), TG, and UA were significantly associated with the phase angle ($p < 0.001$) (Table 2).The b and corresponding 95% CIs for the phase angle according to serum uric acid tertiles are summarized in Table 3. Overall, in the crude model and all adjusted models (Models I–II), the phase angle increased as the tertiles of serum uric acid increased. In the fully adjusted model (Model II, adjustment for age, duration, Lpa, BMI,and WHR), the adjusted b for participants in the two tertiles of serum uric acid were 0.29 (95% CI: 0.08–0.5) and 0.41 (95% CI:0.19–0.62), respectively, compared with those in tertile 1.

3.3 Nonlinear relationship between serum uric acid and PhA

We observed a nonlinear dose-response relationship between serum uric acid and PhA after adjusting for some covariates

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TABLE 1 Clinical characteristics of the study population by serum uric acid levels.

Characteristic	Serum uric acid			*p*-Value
	UA T1 (196.5–279) (n = 66)	UA T2 (281–350) (n = 67)	UA T3 (352–626) (n = 67)	
Age (years)	57.8 ± 12.7	56.7 ± 14.0	52.9 ± 14.9	0.102
Duration (years)	8.9 ± 6.5	8.5 ± 6.4	8.8 ± 8.0	0.922
TC (mmol/L)	4.6 ± 1.1	4.5 ± 1.2	5.1 ± 1.3	0.006
HbA1c (%)	9.4 ± 1.8	9.1 ± 2.0	8.9 ± 1.7	0.279
FPG (mmol/L)	7.1 ± 1.6	7.2 ± 1.6	7.8 ± 1.6	0.045
FCP (nmol/L	0.5 ± 0.3	0.6 ± 0.4	0.8 ± 0.4	< 0.001
SMM (kg)	25.4 ± 5.3	28.3 ± 5.5	30.1 ± 5.6	< 0.001
BMI (kg/m2)	24.0 ± 3.1	25.4 ± 3.2	26.5 ± 3.6	< 0.001
PBF (%)	28.9 ± 7.6	28.6 ± 6.3	28.9 ± 7.6	0.970
WHR	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.1	0.009
VFA (cm2)	92.5 ± 36.5	98.0 ± 32.2	106.1 ± 42.3	0.109
Phase Angle (°)	4.9 ± 0.7	5.2 ± 0.7	5.4 ± 0.7	< 0.001
TG (mmol/L)	1.3 (0.9, 2.0)	1.7 (1.0, 2.6)	2.1 (1.4, 4.2)	< 0.001
Lpa (g/L)	112.5 (44.5, 368.5)	160.0 (32.0, 270.5)	60.0 (32.0, 172.5)	0.062

T, tertile; TC, total cholesterol; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; FCP, fasting C-peptide; SMM, skeletal muscle mass; BMI, body mass index; PBF, percent body fat; WHR, waist-to-hip ratio; VFA, visceral fat area; TG, triglyceride; LPa, lipoprotein.

TABLE 2 Association of phase angle and measured indicators.

Variables	β (95% CI)	*p*-Value
Age (years)	−0.027 (−0.033, −0.021)	<0.001
Duration (years)	−0.029 (−0.043, −0.014)	<0.001
TC (mmol/L)	0.079 (−0.004, 0.162)	0.0617
HbA1c (%)	−0.038 (-0.094, 0.018)	0.1862
Lpa (g/L)	−0.001 (−0.001, 0)	<0.001
FPG (mmol/L)	0.018 (-0.047, 0.084)	0.5774
FCP (nmol/L)	0.258 (−0.016, 0.533)	0.0651
SMM (kg)	0.08 (0.066, 0.094)	<0.001
BMI (kg/m^2)	0.059 (0.03, 0.088)	<0.001
PBF (%)	−0.034 (−0.048, −0.021)	<0.001
WHR	1.266 (−0.495, 3.028)	0.1578
VFA (cm^2)	−0.003 (−0.006, 0)	0.0324
TG (mmol/L)	0.106 (0.061, 0.151)	<0.001
UA (mmol/L)	0.002 (0.001, 0.003)	<0.001
sex: female vs male	−0.782 (−0.964, −0.599)	<0.001

CI, confidence interval; TC, total cholesterol; HbA1c, glycosylated hemoglobin; FPG, fasting plasma glucose; FCP, fasting C-peptide; SMM, skeletal muscle mass; BMI, body mass index; PBF, percent body fat; WHR, waist-to-hip ratio; VFA, visceral fat area; TG, triglyceride; LPa, lipoprotein; UA, uric acid.

(Figure 2). Within a certain range, PhA progressively increased with serum uric acid levels, and the effect stopped beyond a certain threshold.

3.4 Sensitive analysis

The stratified analyses were performed to examine whether the association between serum uric acid and phase angle was stable among different subgroups. None of the variables, including gender (female and male), age (<65 years and ≥65 years), and BMI (<24 kg/m2, 24–28 kg/m2, ≥28 kg/m2), significantly affected the association between phase angle and serum uric acid (all P for interaction >0.05) (Table 4; Figure 3).

4 Discussion

In this retrospective cross-sectional study, serum uric acid was independently associated with PhA. We observed a positive association between serum uric acid and PhA in patients with T2DM. The association was reliable and independent of essential covariates and confounders. To the best of our knowledge, this is the first report of an association between serum uric acid and PhA. Furthermore, the changing trend of the effective value at different serum uric acid levels was non-equidistant, which suggested that the association between serum uric acid and PhA was likely to be

TABLE 3 Association between serum uric acid and phase angle.

Variable	N	Crude model β (95% CI)	*p*-Value	Model I β (95% CI)	*p*-Value	Model II β (95% CI)	*p*-Value
UA	200	0.002 (0.001–0.003)	0.001	0.001 (0–0.002)	0.003	0.001 (0–0.002)	0.036
UA. T1	66	0 (Ref)		0 (Ref)		0 (Ref)	
UA. T2	67	0.32 (0.08–0.56)	0.011	0.29 (0.08–0.5)	0.008	0.26 (0.05–0.46)	0.016
UA. T3	67	0.53 (0.29–0.77)	<0.001	0.41 (0.19–0.62)	<0.001	0.32 (0.11–0.54)	0.004
P for trend			<0.001		<0.001		0.004

Crude Model: unadjusted.
Model I: adjust for age + duration.
Model II: adjust for age + duration+ Lpa + BMI + WHR.
N, number; UA, uric acid; CI, confidence interval.

nonlinear. However, the effect of serum uric acid on PhA is significantly different in patients with T2DM when serum uric acid is below or above the threshold. According to the data in Figure 1, there is a threshold effect. Considering the clinical implications, the threshold could be inferred to be 420 ummol/L, which is also the threshold for hyperuricemia.

In numerous aspects, serum UA appears to be a two-faced marker of health and disease (14). The main cause of gout is hyperuricemia, which results in an elevated level of uric acid in the blood, whereas during peritoneal dialysis treatment, high uric acid is a positive prognostic factor (15). Other authors have previously concluded that BIA-derived phase angles can be associated with frailty and that phase angle values can be interpreted as a global marker of nutrition in aging (16). The phase angle is suggested to be an index of nutritional status (17), even better than anthropometric measurements or serum markers (18), which decrease with worsening of the nutritional status. On the one hand, phase angle increases as uric acid increases within a certain range, which may suggest uric acid could reflect nutrition. On the other hand, after exceeding a certain threshold of its concentrations, the metabolite can have a negative effect. Some studies have separately measured some variables of nutritional status and concluded that high UA levels are an indicator of better nutritional status, as evidenced by the positive association between UA levels and nutritional status variables. Furthermore, low concentrations of UA are considered a consequence of poor protein intake and the presence of malnutrition (19). Indeed, protein-rich diets tend to contain large quantities of purines (20), and higher uric acid concentrations may represent better nutritional status in the ESRD population. Some studies found a U- or J-shaped trend relationship between various outcomes and UA in different settings (21, 22). This could play a part in the observed different uric acid levels in the UA and PhA relationship because higher urate concentrations are associated with an inflammation status, which in turn might offset the potential beneficial effects of urate. From our experiment, we may be able to explain the relationship between uric acid and phase angle in a clinically meaningful way: before a certain threshold, uric acid can exist as a nutritional indicator and an antioxidant, and above a certain threshold, uric acid is harmful as an oxidant that accelerates damage.

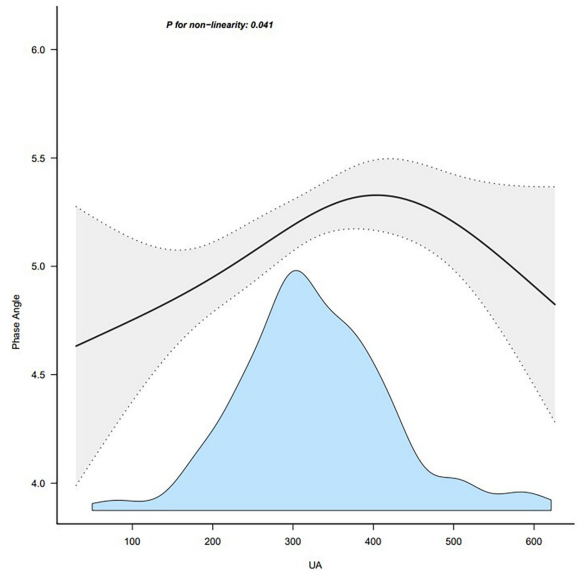

FIGURE 2
Association between UA and phase angle. Note: adjust for age + duration + body mass index. UA, uric acid.

To our best knowledge, this is the first study that explores the association between serum uric acid and PhA in T2DM patients. Phase angle will also be more likely elevated when serum uric acid is elevated, due to the ability of urate to indicate nutrition status. The results were, however, stable across the stratified subgroup analysis that was performed. As the UA increased, the PhA first increased and then decreased. It is interesting to consider the clinical implications of these results. Taking the clinical application and Figure 1 information into consideration, we could set the threshold at 420 mmol/L.

Several shortcomings of the present study should be acknowledged. The study is limited by its cross-sectional design, which does not enable it to draw definite causal relationships. The number of participants was not very large. Insulin estimation was done in these subjects, and the effect of insulin on the kidney urate transporter 1 (URAT1) may be a confounder. In addition, bioelectrical impedance analysis was used to measure body composition; however, it has limitations. Finally, the present study included only the Chinese population with T2DM, so the results might not be representative of all patients with diabetes mellitus. However, it is worth mentioning that the interplay between serum uric

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TABLE 4 Subgroup analysis between serum uric acid and phase angle.

Subgroups	N	UA T1 β (95%CI)/N	UA T2 β (95%CI)/N	UA T3 β (95%CI)/N	P for interaction
Sex					0.544
Male	122	0 (Ref)/28	0.22 (−0.06–0.49)/43	0.27 (0–0.54)/51	
Female	78	0(Ref)/38	0.13 (−0.14–0.39)/24	0.17 (−0.16–0.5)/16	
Age (years)					0.354
<65	146	0 (Ref)/43	0.13 (−0.12–0.39)/48	0.23(−0.03–0.48)/55	
≥65	54	0 (Ref)/23	0.4 (0.04–0.76)/19	0.42(−0.02–0.86)/12	
BMI (kg/m^2)					0.812
<24	73	0 (Ref)/36	0.22 (−0.11–0.56)/21	0.35(−0.03–0.74)/16	
24–28	87	0 (Ref)/24	0.31 (−0.01–0.64)/31	0.33 (−0.05–0.7)/32	
≥28	40	0 (Ref)/6	0.14 (−0.45–0.73)/15	0.32(−0.23–0.88)/19	

adjust for age + duration + Lpa + BMI + WHR.
UA, uric acid; N, number; T, tertile; BMI, body mass index; CI, confidence interval.

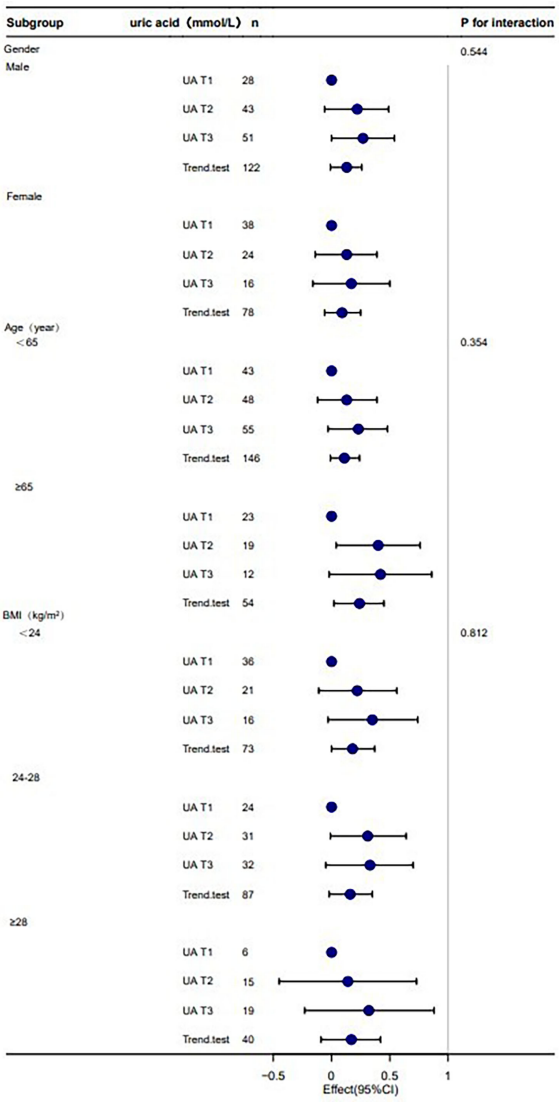

FIGURE 3
Stratification analysis on the association between UA and phase angle. Note: adjust for age + duration + BMI + Lpa + WHR. UA, uric acid; T, tertile; n number; BMI, body mass index.

acid and other factors has not yet been explored. Rethinking UA as a laboratory marker of nutritional status would require changing the dietary guidelines for subjects with T2DM.

5 Conclusion

There was a nonlinear relationship between serum uric acid and PhA in T2DM patients, and within a certain range, PhA progressively increased with serum uric acid raising, and the effect stopped beyond a certain threshold.

Data availability statement

The datasets presented in this article are not readily available because the research is still ongoing. Requests to access the datasets should be directed to YH, hyz1932sun@163.com.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Review Board of the Zhongda Hospital Southeast University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

HJ and JL designed this study. YH collected the clinical data and wrote the report. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 05 April 2023
DOI 10.3389/fendo.2023.1131566

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Cardiovascular Endocrinology, a section of the journal Frontiers in Endocrinology

RECEIVED 25 December 2022
ACCEPTED 24 March 2023
PUBLISHED 05 April 2023

CITATION
Wang C, Che H, Zhou Y, Wang R, Zhu D, Cheng L, Rao C, Zhong Q, Li Z, Duan Y, Xu J, Dong W, Bai Y and He K (2023) Joint association of hyperuricemia and chronic kidney disease with mortality in patients with chronic heart failure. *Front. Endocrinol.* 14:1131566. doi: 10.3389/fendo.2023.1131566

Joint association of hyperuricemia and chronic kidney disease with mortality in patients with chronic heart failure

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Background: The joint association of hyperuricemia and chronic kidney disease (CKD) with mortality in patients with chronic heart failure (CHF) is not conclusive.

Methods: This retrospective cohort study was conducted in Chinese People's Liberation Army General Hospital, Beijing, China. We included 9,367 patients with CHF, who were hospitalized between January 2011 and June 2019. The definitions of hyperuricemia and CKD were based on laboratory test, medication use, and medical record. We categorized patients with CHF into 4 groups according to the absence (-) or presence (+) of hyperuricemia and CKD. The primary outcomes included in-hospital mortality and long-term mortality. We used multivariate logistic regression and Cox proportional hazards regression to estimate the mortality risk according to the hyperuricemia/CKD groups.

Results: We identified 275 cases of in-hospital mortality and 2,883 cases of long-term mortality in a mean follow-up of 4.81 years. After adjusting for potential confounders, we found that compared with the hyperuricemia-/CKD- group, the risks of in-hospital mortality were higher in the hyperuricemia+/CKD- group (odds ratio [OR], 95% confidence interval [CI]: 1.58 [1.01-2.46]), hyperuricemia-/CKD+ group (OR, 95% CI: 1.67 [1.10-2.55]), and hyperuricemia+/CKD+ group (OR, 95% CI: 2.12 [1.46-3.08]). Similar results were also found in long-term mortality analysis. Compared with the hyperuricemia-/CKD- group, the adjusted hazard ratios and 95% CI for long-term mortality were 1.25 (1.11-1.41) for hyperuricemia+/CKD- group, 1.37 (1.22-1.53) for hyperuricemia-/CKD+ group,

and 1.59 (1.43-1.76) for hyperuricemia+/CKD+ group. The results remained robust in the sensitivity analysis.

Conclusions: Hyperuricemia and CKD, both individually and cumulatively, are associated with increased mortality risk in patients with CHF. These results highlighted the importance of the combined control of hyperuricemia and CKD in the management of heart failure.

KEYWORDS

uric acid, chronic kidney disease, heart failure, mortality risk, cohort study

Introduction

Chronic heart failure (CHF) is one of the major causes of mortality and affects 1%-2% adults worldwide (1, 2). Approximately 74% of CHF patients have at least one non-cardiac comorbidity (3), which increase the medical complexity and mortality rates. Chronic kidney disease (CKD) is a progressive condition characterized by decreased estimated glomerular filtration rate (eGFR) and/or presence of proteinuria. More than 50% of deaths in patients with CKD are resulted from cardiovascular disease (4). CKD is highly prevalent in CHF with the comorbidity rate ranging from 33% to 48% (3, 5, 6). A meta-analysis including 57 studies concluded that patients with the cooccurrence of CKD and CHF experienced nearly 2-fold higher risk of mortality (7). Hyperuricemia is one of the major metabolic diseases that caused by both an increased production and a decreased excretion of uric acid (UA). Various studies have shown that hyperuricemia was associated with higher risk of mortality in general population and patients with cardiovascular disease (8–10). Hyperuricemia affects about half of patients with CHF (11), and accounts for increased risk of hospitalization, cardiovascular mortality, and all-cause mortality regardless of the ejection fraction (EF) phenotype of CHF (12, 13).

Hyperuricemia is a common finding in CKD due to reduced excretion of UA (14), and also an independent risk factor for the development of CKD (15). The comorbidity of hyperuricemia and CKD poses worse outcomes in general population (16–18). Although, similar findings were not generated in several studies based on patients with CHF (19, 20). In the Beta-Blocker Evaluation of Survival Trial, hyperuricemia is associated with hospitalization and mortality in CHF patients without CKD, but not those with CKD (19). In addition, CHART-2 study and EVEREST study demonstrated that elevated serum uric acid is not associated with mortality in CHF patients with eGFR <60ml/min/1.73m^2 and CHF patients with eGFR <30ml/min/1.73m^2 (20, 21). However, these previous studies did not account for proteinuria in the definition of CKD, which have limited information on the association between hyperuricemia, CKD, and adverse outcomes. Moreover, their findings should be validated in other populations because the characteristics of heart failure vary greatly across different regions and ethnicities (22, 23). Therefore, the aim of our study was to comprehensively examine the joint association of hyperuricemia and CKD with in-hospital mortality and long-term mortality in a population of hospitalized CHF patients in China.

Abbreviations: ACR, albumin-to-creatinine ratio; BMI, body mass index; CHF, chronic heart failure; CI, confidence interval; CKD, chronic kidney disease; CRP, C-reactive protein; CV, cardiovascular; DBP, diastolic blood pressure; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; RAASi, renin-angiotensin-aldosterone system inhibitors; SBP, systolic blood pressure; SGLT2i, sodium-glucose cotransporter 2 inhibitors; UA, uric acid.

Materials and methods

Study design and patients

This retrospective cohort study was conducted in the Chinese People's Liberation Army General Hospital, a large-scale tertiary hospital in Beijing, China. We used the *International Classification of Diseases* (I110, I130, I132, I42, I43, I50), *Tenth Revision*, for the identification of potential heart failure patients. A panel of 3 physicians reviewed patient medical records to confirm the diagnosis of CHF. CHF was diagnosed according to the criteria of *2021 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure* (1), and further subclassified into heart failure with reduced ejection fraction (HFrEF), heart failure with mildly reduced ejection fraction (HFmrEF), and heart failure with preserved ejection fraction (HFpEF) according to the EF value reported on echocardiography. The study protocol complied with the Declaration of Helsinki and was approved by the ethics committee of the Chinese People's Liberation Army General Hospital (Number: S2018-269-02).

Data collection and definitions

Data on demographic characteristics, anthropometric measurements, laboratory tests, medication use during hospitalization, and medication use after discharge were abstracted from the hospital

electronic medical record database. Demographic characteristics included age and sex. Anthropometric measurements included height, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate. Body mass index was calculated as weight (kg) divided by the square of height (m). Laboratory tests included measurements of hemoglobin, blood glucose, serum creatinine, UA, N-terminal pro-B-type natriuretic peptide (NT-proBNP), C-reactive protein (CRP), glycated hemoglobin (HbA1c), urinary albumin-to-creatinine ratio (ACR), and dipstick proteinuria. eGFR was calculated using the *Chronic Kidney Disease Epidemiology Collaboration creatinine equation* (24). For patients who underwent repeated laboratory tests, we only included the result of the first test in our analyses. Anti-CHF medications included renin-angiotensin-aldosterone system inhibitors (RAASi), spironolactone, diuretics (including loop diuretics, thiazide diuretics, and tolvaptan), beta-blockers, digitalis, and nitrates.

Hyperuricemia was defined as serum UA >420 μmol/L, use of UA-lowering medication, or physician-diagnosed hyperuricemia (25–27). CKD was defined as eGFR <60 mL/min/1.73m^2, ACR ≥30 mg/g, proteinuria ≥2+ on dipstick, or physician-diagnosed CKD (28, 29). Other comorbidities, including myocardial infarction, hypertension, atrial fibrillation, valvular heart disease, thrombotic complication, diabetes, stroke, anemia, chronic pulmonary disease, liver disease, connective tissue disease, and cancer were identified based on the medical record. Diabetes was further identified by fasting blood glucose ≥7 mmol/L, random blood glucose ≥11.1 mmol/L, HbA1c ≥6.5%, or use of hypoglycemic medication (30). Anemia was further identified by hemoglobin <130 g/L in men, hemoglobin <120 g/L in women, or use of iron or erythropoietin therapy (6).

Assessment of outcomes

The outcome of the current study were in-hospital mortality and long-term mortality. Information on in-hospital mortality was checked by reviewing medical records. For those patients without in-hospital mortality, information on long-term mortality was obtained by checking subsequent medical records and telephonic interview. The cause of mortality (cardiovascular [CV] mortality or not) was asked during the telephonic interview.

Statistical analysis

We divided the study patients into 4 groups according to the absence (-) or presence (+) of hyperuricemia and CKD: hyperuricemia-/CKD-, hyperuricemia+/CKD-, hyperuricemia-/CKD+, and hyperuricemia+/CKD+. Continuous variables with a normal distribution are presented as mean ± standard deviation; those with a non-normal distribution are presented as median (interquartile range). Continuous variables were compared using one-way analysis of variance or the Kruskal-Wallis test as appropriate. Categorical variables are presented as numbers with percentage and were compared using the chi square test. Risk of in-hospital mortality was estimated using multivariate logistic regression to calculate odds ratios (ORs) with 95% confidence intervals (CIs). Cox proportional hazards regression was used to investigate the association between exposures (hyperuricemia/CKD groups) and long-term mortality by calculating hazard ratios (HRs) with 95% CIs. The proportional hazard assumption was checked using Schoenfeld residuals. The fully adjusted model included age, sex, BMI, SBP, DBP, heart rate, EF phenotype, NT-proBNP concentration, CRP concentration, myocardial infarction, hypertension, atrial fibrillation, valvular heart disease, thrombotic complication, diabetes, stroke, anemia, chronic pulmonary disease, liver disease, connective tissue disease, cancer, and medication use of RAASi, spironolactone, diuretics, beta-blockers, digitalis, and nitrates. Missing values were handled by multiple imputation.

A recent study suggested that hyperuricemia with crystalluria, but not asymptomatic hyperuricemia, was associated with progression of CKD (31). Therefore, we performed analyses examining the combined effect of CKD with asymptomatic hyperuricemia and gout, respectively. Given that the pathophysiology of reduced eGFR is different from that of proteinuria, we performed analyses defining CKD as only eGFR <60ml/min/1.73m^2 and only proteinuria, respectively. To test the robustness and consistency of our findings, we performed a sensitivity analysis using serum UA >420 μmol/L in men and >360 μmol/L in women as the cutoff points for hyperuricemia (32). To reduce the possibility of reverse causation in the long-term mortality analysis, we excluded patients who died within the 6 months of follow-up in a sensitivity analysis. To investigate the joint impact of hyperuricemia and CKD on CV mortality, we performed analyses using CV mortality as the outcome event.

To better understand the interaction between serum UA and renal dysfunction, we further performed subanalyses with patients grouped by serum UA level (≤420 μmol/L, 421-600 μmol/L, >600 μmol/L) (25, 27, 33, 34) and stratified by CKD and CKD subgroups (eGFR ≥90, 60-89, 30-59, <30ml/min/1.73m^2; with and without proteinuria) (35), and subanalyses with patients grouped by risk classification of CKD progression (low, moderate, high, and very high risk) (35) and stratified by hyperuricemia. To explore whether the association between hyperuricemia/CKD groups and mortality in CHF patients could be modified by age (≥65 and <65 years), sex, myocardial infarction, hypertension, EF phenotype (HFrEF, HFmrEF and HFpEF), and New York Heart Association (NYHA) classification (I-II, III, and IV), subgroup analyses by these factors were performed.

Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA). Two-sided P <0.05 was considered significant.

Results

In the current study, we identified 9,429 CHF patients who were hospitalized between 1 January 2011 and 30 June 2019. 18 patients were excluded due to the age of <18 years, 1 patient was excluded due to pregnancy, and 43 patients were excluded due to the diagnosis of acute kidney injury. A total of 9,367 CHF patients were included in the in-hospital mortality analysis (Figure 1). Of these, the mean age was 62.64 ± 14.61 years, 6,244 (66.66%) were men, 275 (2.94%) had in-hospital mortality (182 were CV mortality), and 1,323 (14.12%) lost to follow-up. Finally, a total of

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7,769 CHF patients were included in the long-term mortality analysis (Figure 1). The patients lost to follow-up were younger, and had a lower proportion of hyperuricemia but similar proportion of CKD (Supplementary Table 1). Patients in the hyperuricemia+/CKD- group were younger and more likely to be men. They also had higher BMI, heart rate, and higher prevalence of HFrEF, atrial fibrillation, and valvular heart disease, while patients in the hyperuricemia-/CKD+ group had higher blood pressure, and higher prevalence of diabetes, stroke, anemia, chronic pulmonary disease, and connective tissue disease. Those in the hyperuricemia+/CKD+ group had higher serum concentration of NT-proBNP and higher prevalence of NYHA class IV heart failure (Table 1). Patients included in the long-term mortality analysis exhibited similar characteristics (Supplementary Table 2).

Hyperuricemia+/CKD+ group had the highest incidence rate of in-hospital mortality (5.80%), followed by hyperuricemia-/CKD+ group (4.28%), hyperuricemia+/CKD- group (2.10%), and hyperuricemia-/CKD- group (1.41%) (Table 2). After adjusting for potential confounders, the risk of in-hospital mortality was

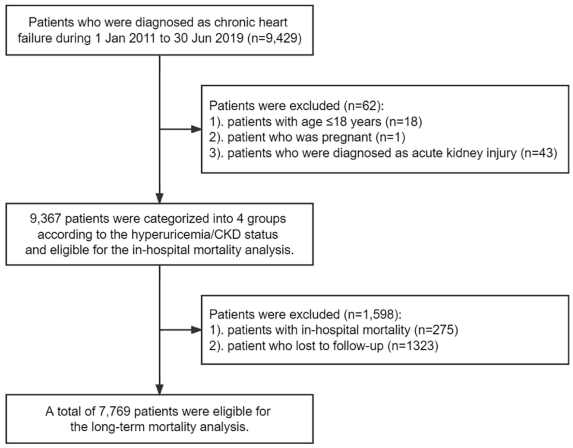

FIGURE 1
Eligibility of the study patients. The flowchart of the eligibility of 9,367 patients included in the in-hospital mortality analysis, and 7,769 patients included in the long-term mortality analysis.

TABLE 1 Characteristics of 9,367 patients with CHF according to hyperuricemia/CKD groups.

Variables	Hyperuricemia-/CKD-	Hyperuricemia+/CKD-	Hyperuricemia-/CKD+	Hyperuricemia+/CKD+	*P* value
No. of patients	4,198	1,712	1,355	2,102	
Age, mean ± SD, y	62.82 ± 13.15	55.92 ± 13.79	67.67 ± 15.10	64.50 ± 15.75	<0.01
Men, No. (%)	2,621 (62.43)	1,383 (80.78)	783 (57.79)	1,457 (69.31)	<0.01
BMI, mean ± SD, kg/m^2	24.80 ± 3.86	25.76 ± 4.56	24.55 ± 4.07	25.18 ± 4.47	<0.01
SBP, mean ± SD, mmHg	128.12 ± 20.07	123.38 ± 20.39	139.95 ± 25.10	134.35 ± 24.77	<0.01
DBP, mean ± SD, mmHg	74.40 ± 12.56	75.97 ± 14.12	77.14 ± 14.76	76.77 ± 16.13	<0.01
Heart Rate, mean ± SD, bpm	81.74 ± 17.62	84.68 ± 18.46	83.68 ± 18.22	84.05 ± 19.32	<0.01
EF phenotypes, No. (%)					<0.01
HFrEF	1,515 (36.08)	904 (52.80)	388 (28.63)	828 (39.39)	
HFmrEF	964 (22.96)	292 (17.06)	301 (22.21)	404 (19.22)	
HFpEF	1,719 (40.94)	516 (30.14)	666 (49.15)	870 (41.39)	
NYHA class, No. (%)					<0.01
I-II	2,139 (50.95)	610 (35.63)	436 (32.18)	519 (24.69)	
III	1,651 (39.32)	824 (48.13)	679 (50.11)	1,057 (50.29)	
IV	408 (9.72)	278 (16.24)	240 (17.71)	526 (25.02)	
Laboratory test					
UA, mean ± SD, μmol/L	313.26 ± 65.59	511.72 ± 92.53	329.24 ± 66.94	552.72 ± 126.67	<0.01
eGFR, median (IQR), ml/min/1.73m^2	87.71 (76.54, 97.22)	82.99 (71.75, 95.26)	49.01 (23.83, 59.71)	39.23 (20.04, 53.65)	<0.01
NT-proBNP, median (IQR), pg/mL	1224.0 (553.0, 2776.0)	1905.0 (805.0, 4350.0)	4570.0 (1719.0, 14702.0)	6106.5 (2318.0, 17351.0)	<0.01
CRP, No. (%)					<0.01
<10 mg/L	2,752 (78.05)	1,155 (78.09)	833 (66.43)	1,262 (65.59)	
10-30 mg/L	380 (10.77)	205 (13.86)	219 (17.46)	376 (19.54)	

(Continued)

TABLE 1 Continued

Variables	Hyperuricemia-/CKD-	Hyperuricemia+/CKD-	Hyperuricemia-/CKD+	Hyperuricemia+/CKD+	*P* value
≥30 mg/L	394 (11.17)	119 (8.05)	202 (16.11)	286 (14.86)	
Proteinuria, No. (%)	0 (0)	0 (0)	579 (46.47)	786 (39.92)	<0.01
Comorbidities					
Myocardial infarction, No. (%)	1,560 (37.16)	478 (27.92)	493 (36.38)	663 (31.54)	<0.01
Hypertension, No. (%)	2,212 (52.69)	817 (47.72)	1,053 (77.71)	1,586 (75.45)	<0.01
Atrial fibrillation, No. (%)	1,275 (30.37)	574 (33.53)	367 (27.08)	654 (31.11)	<0.01
Valvular heart disease, No. (%)	1,083 (25.80)	446 (26.05)	190 (14.02)	395 (18.79)	<0.01
Thrombotic complications, No. (%)	215 (5.12)	101 (5.90)	89 (6.57)	123 (5.85)	0.19
Gout, No. (%)	0 (0)	68 (3.97)	0 (0)	138 (6.57)	<0.01
Diabetes, No. (%)	1,458 (34.73)	532 (31.07)	743 (54.83)	1,042 (49.57)	<0.01
Stroke, No. (%)	783 (18.65)	230 (13.43)	386 (28.49)	463 (22.03)	<0.01
Anemia, No. (%)	1,152 (27.44)	358 (20.91)	839 (61.92)	1,217 (57.90)	<0.01
Chronic pulmonary diseases, No. (%)	501 (11.93)	184 (10.75)	227 (16.75)	316 (15.03)	<0.01
Liver diseases, No. (%)	529 (12.60)	240 (14.02)	203 (14.98)	340 (16.18)	<0.01
Connective tissue diseases, No. (%)	58 (1.38)	23 (1.34)	37 (2.73)	49 (2.33)	<0.01
Cancer, No. (%)	165 (3.93)	46 (2.69)	51 (3.76)	62 (2.95)	0.05
Medication during hospitalization					
UA-lowering agents, No. (%)	0 (0)	108 (6.31)	0 (0)	311 (14.80)	<0.01
RAASi, No. (%)	2,368 (56.41)	1,070 (62.50)	749 (55.28)	1,141 (54.28)	<0.01
Spironolactone, No. (%)	2,916 (69.46)	1,434 (83.76)	845 (62.36)	1,471 (69.98)	<0.01
Diuretics, No. (%)	3,071 (73.15)	1,464 (85.51)	1,092 (80.59)	1,921 (91.39)	<0.01
Beta-blockers, No. (%)	3,256 (77.56)	1,426 (83.29)	1,072 (79.11)	1,689 (80.35)	<0.01
Digitalis, No. (%)	1,918 (45.69)	1,032 (60.28)	465 (34.32)	961 (45.72)	<0.01
Nitrates, No. (%)	2,553 (60.81)	959 (56.02)	965 (71.22)	1,450 (68.98)	<0.01

BMI, body mass index; bpm, beats per minute; CHF, chronic heart failure; CKD, chronic kidney disease; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RAASi, renin–angiotensin–aldosterone system inhibitors; SBP, systolic blood pressure; SD, standard deviation; UA, uric acid.

twice as high in the hyperuricemia+/CKD+ group compared with the hyperuricemia-/CKD- group (OR [95% CI], 2.12 [1.46-3.08]). Those with hyperuricemia alone and CKD alone also exhibited a significantly higher risk of in-hospital mortality compared with the hyperuricemia-/CKD- group (OR [95% CI], 1.58 [1.01-2.46] and 1.67 [1.10-2.55], respectively) (Table 2). Analyses of asymptomatic hyperuricemia and gout, defining CKD as only proteinuria, using serum UA >420 μmol/L in men and >360 μmol/L in women as the cutoff point to define hyperuricemia all generated similar results (Table 2). Similar findings were also observed in the CV mortality analyses (Supplementary Table 3).

During the mean follow-up of 4.81 years, a total of 2,883 deaths were identified. Among them, 1,433 were CV death, 1,059 were non-CV death, and 391 deaths could not be classified due to lack of information. The hyperuricemia+/CKD+ group had the highest incidence rate of long-term mortality among all 4 groups (Table 2). Compared with the hyperuricemia-/CKD- group, the adjusted HRs and 95% CI for long-term mortality were 1.25 (1.11-1.41) for the hyperuricemia+/CKD- group, 1.37 (1.22-1.53) for the hyperuricemia-/CKD+ group, and 1.59 (1.43-1.76) for the hyperuricemia+/CKD+ group (Table 2). The results did not materially change in analyses of asymptomatic hyperuricemia and gout, analyses defining CKD as only reduced eGFR and only proteinuria, sensitivity analyses, and CV mortality analyses (Table 2 and Supplementary Table 3).

The long-term mortality risk was proportional to serum UA level, regardless of the CKD status or CKD subtypes (Table 3). Although, further analyses showed that the association of serum UA with in-hospital mortality was more evident in patients with eGFR ≥60 ml/min/1.73m^2 (*P*-interaction =0.02), it was not significant in patients with eGFR <60ml/min/1.73m^2 (Table 3). The association with long-term mortality was more evident in patients without proteinuria compared with those with proteinuria (*P*-interaction =0.02)

TABLE 2 Risk of in-hospital mortality and long-term mortality according to hyperuricemia/CKD groups.

	Hyperuricemia/CKD Groups			
	Hyperuricemia-/CKD-	Hyperuricemia+/CKD-	Hyperuricemia-/CKD+	Hyperuricemia+/CKD+
In-hospital mortality, OR (95% CI)				
Cases, No.	59	36	58	122
Incidence rate, %	1.41	2.10	4.28	5.80
Model 1	1 (Reference)	1.51 (0.99-2.29)	3.14 (2.17-4.53)	4.32 (3.15-5.93)
Model 2	1 (Reference)	1.91 (1.25-2.92)	2.61 (1.80-3.78)	4.00 (2.91-5.50)
Model 3	1 (Reference)	1.58 (1.01-2.46)	1.67 (1.10-2.55)	2.12 (1.46-3.08)
Model 4	1 (Reference)	1.57 (1.00-2.45)	1.65 (1.08-2.51)	2.05 (1.41-3.00)
Model 5	1 (Reference)	1.64 (0.22-12.48)	1.68 (1.05-2.68)	2.82 (1.22-6.53)
Model 6	1 (Reference)	2.12 (1.44-3.11)	1.29 (0.83-2.02)	1.49 (1.03-2.17)
Model 7	1 (Reference)	1.51 (1.08-2.10)	1.77 (1.04-3.03)	2.51 (1.58-3.99)
Model 8	1 (Reference)	1.40 (0.91-2.16)	1.62 (1.04-2.53)	2.05 (1.40-2.98)
Long-term mortality, HR (95% CI)				
Cases, No.	1,020	420	571	872
Incidence rate, per 1000-person-year	54.15	58.50	121.06	131.26
Model 1	1 (Reference)	1.08 (0.96-1.21)	2.20 (1.98-2.44)	2.37 (2.16-2.59)
Model 2	1 (Reference)	1.32 (1.18-1.48)	1.84 (1.66-2.04)	2.23 (2.03-2.44)
Model 3	1 (Reference)	1.25 (1.11-1.41)	1.37 (1.22-1.53)	1.59 (1.43-1.76)
Model 4	1 (Reference)	1.28 (1.14-1.44)	1.37 (1.22-1.53)	1.59 (1.43-1.77)
Model 5	1 (Reference)	0.70 (0.39-1.24)	1.31 (1.16-1.48)	1.44 (1.09-1.90)
Model 6	1 (Reference)	1.26 (1.13-1.41)	1.38 (1.23-1.56)	1.56 (1.41-1.73)
Model 7	1 (Reference)	1.39 (1.27-1.52)	1.53 (1.31-1.78)	1.55 (1.34-1.80)
Model 8	1 (Reference)	1.16 (1.04-1.30)	1.32 (1.17-1.48)	1.57 (1.42-1.74)
Model 9	1 (Reference)	1.28 (1.13-1.45)	1.41 (1.25-1.59)	1.61 (1.44-1.80)

CKD, chronic kidney disease; CI, confidence interval; HR, hazard ratio; OR, odds ratio.
Model 1 was crude model. Model 2 was adjusted for age and sex. Model 3 was further adjusted for BMI, SBP, DBP, heart rate, EF phenotype, NT-proBNP, CRP, myocardial infarction, hypertension, atrial fibrillation, valvular heart disease, thrombotic complication, diabetes, stroke, anemia, chronic pulmonary disease, liver disease, connective tissue disease, cancer, and medication use of RAASi, spironolactone, diuretics, beta-blockers, digitalis, and nitrates. Model 4 was the analysis examining the combined effect of asymptomatic hyperuricemia and CKD. Model 5 was the analysis examining the combined effect of gout and CKD. Model 6 defined CKD as eGFR <60ml/min/1.73m^2. Model 7 defined CKD as proteinuria. Model 8 was sensitivity analysis using serum uric acid ≥420 μmol/L in men and ≥360 μmol/L in women as another cutoff value for the definition of hyperuricemia. Model 9 was sensitivity analysis excluding those who died within the 6 months of follow-up.

(Table 3). Furthermore, the in-hospital and long-term mortality risk increased with the upgrade of risk classification of CKD progression, and did not vary between patients with and without hyperuricemia (*P*-interaction =0.29 for in-hospital mortality and 0.55 for long-term mortality) (Table 4).

In the subgroup analyses, we did not find significant interactions between hyperuricemia/CKD groups and age, sex, hypertension, EF phenotype, and NYHA classification in relation to both in-hospital mortality and long-term mortality (*P*-interaction >0.10 for all). However, the association between hyperuricemia/CKD groups and in-hospital mortality appeared to be more pronounced in CHF patients without myocardial infarction (*P*-interaction =0.05) (Figures 2, 3).

Discussion

In this retrospective cohort study, we found that hyperuricemia and CKD were individually and cumulatively associated with increased risk of in-hospital mortality and long-term mortality in patients with CHF. These findings persisted after adjusting for a wide spectrum of confounding factors and in sensitivity analyses. Moreover, the risks of both in-hospital mortality and long-term mortality were proportional to the serum UA level and risk classification of CKD progression. However, serum UA had a weaker association with in-hospital mortality in patients with eGFR <60 ml/min/1.73m^2, and a weaker association with long-term mortality in patients with proteinuria.

TABLE 3 Mortality risk grouped by serum UA level and stratified by CKD and CKD subtypes.

	Serum UA level			*P*-trend	*P*-interaction
	≤420μmol/L	420-600μmol/L	>600μmol/L		
In-hospital mortality, OR (95% CI)					
CHF without CKD	1 (Reference)	1.19 (0.70-2.01)	2.51 (1.19-5.30)	0.04	0.20
CHF with CKD	1 (Reference)	1.22 (0.82-1.80)	1.75 (1.11-2.78)	0.02	
CHF with eGFR ≥90ml/min/1.73m^2	1 (Reference)	0.79 (0.34-1.86)	4.97 (1.57-15.74)	0.13	0.02
CHF with eGFR 60-89ml/min/1.73m^2	1 (Reference)	2.19 (1.26-3.84)	4.54 (2.08-9.90)	<0.01	
CHF with eGFR 30-59ml/min/1.73m^2	1 (Reference)	1.16 (0.63-2.14)	1.67 (0.78-3.61)	0.21	
CHF with eGFR <30ml/min/1.73m^2	1 (Reference)	1.25 (0.62-2.51)	1.81 (0.84-3.92)	0.14	
CHF without proteinuria	1 (Reference)	1.36 (0.94-1.96)	1.65 (1.02-2.68)	0.03	0.35
CHF with proteinuria	1 (Reference)	1.30 (0.68-2.49)	2.79 (1.26-6.15)	0.02	
Long-term mortality, HR (95% CI)					
CHF without CKD	1 (Reference)	1.15 (1.01-1.31)	1.53 (1.20-1.96)	<0.01	0.29
CHF with CKD	1 (Reference)	1.15 (1.02-1.29)	1.41 (1.21-1.66)	<0.01	
CHF with eGFR ≥90ml/min/1.73m^2	1 (Reference)	1.04 (0.83-1.30)	1.74 (1.11-2.72)	0.10	0.42
CHF with eGFR 60-89ml/min/1.73m^2	1 (Reference)	1.25 (1.07-1.45)	1.66 (1.27-2.19)	<0.01	
CHF with eGFR 30-59ml/min/1.73m^2	1 (Reference)	1.14 (0.97-1.33)	1.37 (1.09-1.73)	<0.01	
CHF with eGFR <30ml/min/1.73m^2	1 (Reference)	1.17 (0.95-1.44)	1.38 (1.07-1.78)	0.01	
CHF without proteinuria	1 (Reference)	1.29 (1.17-1.43)	1.59 (1.36-1.85)	<0.01	0.02
CHF with proteinuria	1 (Reference)	1.06 (0.87-1.28)	1.40 (1.04-1.89)	0.06	

CHF, chronic heart failure; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio; OR, odds ratio; UA, uric acid.
Models were adjusted for age, sex, BMI, SBP, DBP, heart rate, EF phenotype, NT-proBNP, CRP, myocardial infarction, hypertension, atrial fibrillation, valvular heart disease, thrombotic complication, diabetes, stroke, anemia, chronic pulmonary disease, liver disease, connective tissue disease, cancer, and medication use of RAASi, spironolactone, diuretics, beta-blockers, digitalis, and nitrates.

TABLE 4 Mortality risk grouped by risk classification of CKD progression and stratified by hyperuricemia.

	Risk classification of CKD progression				*P*-trend	*P*-interaction
	Low risk	Moderate risk	High risk	Very high risk		
In-hospital mortality, OR (95% CI)						
CHF without hyperuricemia	1 (Reference)	1.48 (0.86-2.53)	2.03 (1.00-4.12)	2.76 (1.35-5.66)	<0.01	0.29
CHF with hyperuricemia	1 (Reference)	1.16 (0.65-2.05)	1.36 (0.72-2.55)	1.06 (0.57-1.98)	0.84	
Long-term mortality, HR (95% CI)						
CHF without hyperuricemia	1 (Reference)	1.22 (1.07-1.39)	1.40 (1.16-1.71)	1.80 (1.48-2.19)	<0.01	0.55
CHF with hyperuricemia	1 (Reference)	1.28 (1.08-1.52)	1.38 (1.14-1.68)	1.78 (1.46-2.16)	<0.01	

CHF, chronic heart failure; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; OR, odds ratio.
Models were adjusted for age, sex, BMI, SBP, DBP, heart rate, EF phenotype, NT-proBNP, CRP, myocardial infarction, hypertension, atrial fibrillation, valvular heart disease, thrombotic complication, diabetes, stroke, anemia, chronic pulmonary disease, liver disease, connective tissue disease, cancer, and medication use of RAASi, spironolactone, diuretics, beta-blockers, digitalis, and nitrates.

In recent years, the prognostic role of hyperuricemia in patients with heart failure has garnered particular interest. Findings from Metabolic Exercise Cardiac Kidney Index score database showed that each 60 μmol/L increase in UA was associated with 12% increased risk of mortality in patients with HFrEF (36), whereas Mantovani et al. found that hyperuricemia increased the mortality risk by 37% in general patients with CHF (12). CKD has a bidirectional relationship with hyperuricemia (37, 38), and may mediate the association between hyperuricemia and health outcomes (16). However, to the best of our knowledge, only a few studies examined the combined effect of hyperuricemia and CKD on mortality risk in patients with CHF, but generated inconsistent

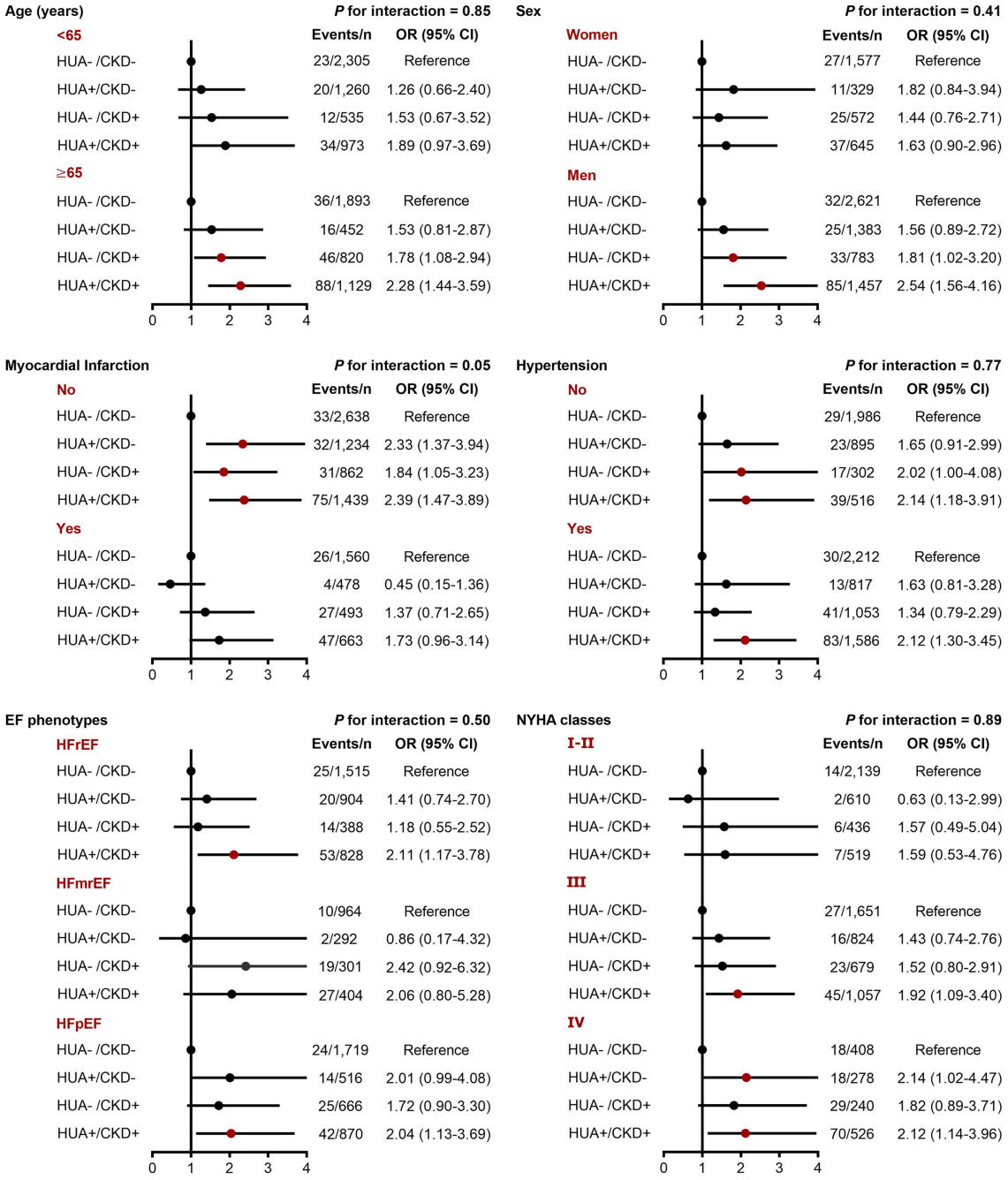

FIGURE 2
Subgroup analyses for the adjusted OR (95% CI) of hyperuricemia/CKD groups for in-hospital mortality by age, sex, myocardial infarction, hypertension, EF phenotype, and NYHA classification. CI, confidence interval; CKD, chronic kidney disease; EF, ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HUA, hyperuricemia; NYHA, New York Heart Association; OR, odds ratio.

results with our study (19–21). For example, a study of 1,260 systolic heart failure patients from the Beta-Blocker Evaluation of Survival Trial found that hyperuricemia was associated with a 1.4-fold higher risk of mortality in patients without CKD, but not in those with CKD (19). However, this previous study only included patients with NYHA class III and IV systolic heart failure who were screened for participation in a clinical trial, while our study was performed in a real-world setting and included patients with all phenotypes of CHF. Thus, the study patients in our study might be more representative. In another cohort study including 4,652 patients with CHF, the association between serum UA and all-cause mortality was significantly modified by eGFR, and hyperuricemia was not associated with outcome in patients with CKD (20). Vaduganathan et al. also found that serum UA (per 300 μmol/L increase) was not associated with increased hazard of all-cause mortality in CHF patients with eGFR <30 ml/min/1.73m^2

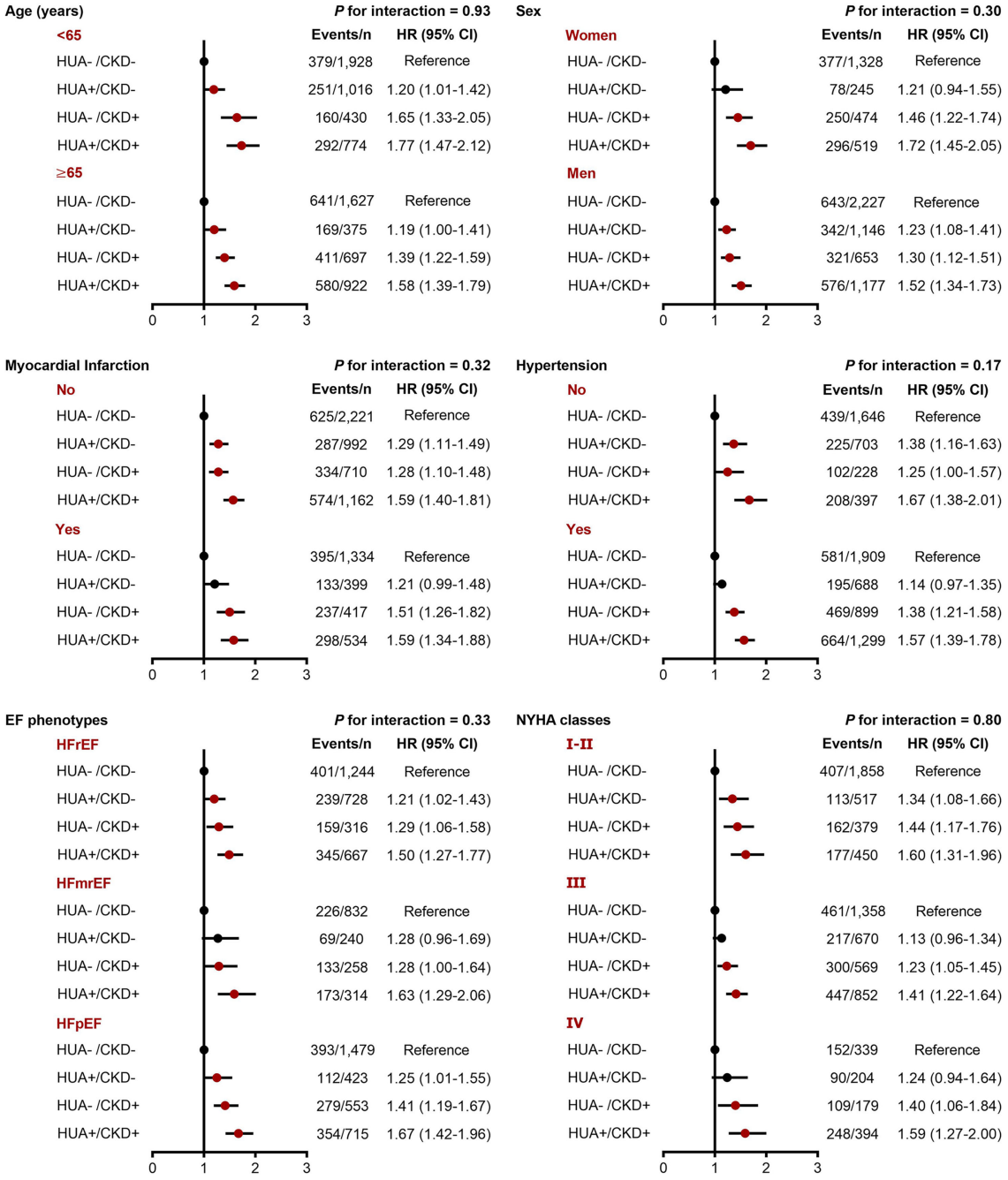

FIGURE 3
Subgroup analyses for the adjusted HR (95% CI) of hyperuricemia/CKD groups for long-term mortality by age, sex, myocardial infarction, hypertension, EF phenotype, and NYHA classification. CI, confidence interval; CKD, chronic kidney disease; EF, ejection fraction; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; HUA, hyperuricemia; NYHA, New York Heart Association.

(21). Notably, the definition of CKD in these studies did not account for proteinuria, which could not provide complete information on renal dysfunction. In the current study, we used a more complete definition of CKD, and observed that elevated serum UA was associated with increased risk of mortality in CHF patients with and without CKD, low eGFR, and proteinuria. Taken together, our study provided a more comprehensive understanding regarding the association between hyperuricemia, CKD, and mortality in patients with CHF by using well-characterized information and larger sample size.

It is well-known that CKD contributes to worse outcomes in patients with CHF by uremic toxins, fluid overload, enhancing systemic inflammation and oxidative stress, and activating the sympathetic nervous system and renin-angiotensin-aldosterone

system (39–41). Several mechanisms may explain why the presence of both CKD and hyperuricemia cause a cumulative increase in risk of mortality. First, hyperuricemia may cause renal tubular injury, and accelerate the progression of CKD (42, 43), hence increases mortality risk. Second, increased xanthine oxidase activity, a major cause of hyperuricemia, can promote oxidative stress and upregulation of inflammatory cytokines, which further result in cardiac fibrosis and left ventricular dysfunction (44). It is still conflicting that whether UA is a direct risk factor of cardiovascular outcomes or just a passive marker of xanthine oxidase activity. However, in the current study, the risk of long-term mortality related to hyperuricemia was similar between patients with eGFR ≥60 ml/min/1.73m^2 (hyperuricemia mainly caused by reduced UA excretion) and patients with eGFR <60 ml/min/1.73m^2 (hyperuricemia mainly caused by increased xanthine oxidase activity). Recent studies of sodium-glucose cotransporter 2 inhibitors (SGLT2i) have suggested that the beneficial effect of SGLT2i on heart failure outcomes is mediated by their enhancement of renal UA excretion (45). Thus, elevated serum UA may directly contribute to the adverse outcomes in patients with CHF. Potential mechanisms include UA-induced vascular fibrosis, vascular inflammation, endothelial dysfunction, and nitric oxide reduction (46).

The findings of our study provide important clinical implications. Hyperuricemia is commonly recognized as a bystander in patients with CHF and CKD. However, our study showed that hyperuricemia and CKD cumulatively increased the risk of mortality in patients with CHF. This suggests that measurement of serum UA concentration might provide useful information on the assessment of outcome risk, regardless of kidney function. Moreover, these findings support the importance of including UA management in the treatment strategies of CHF regardless of the cause of hyperuricemia (increased production or decreased excretion). There is also a need to strengthen the patient education regarding limiting their intake of purine-rich food. Several novel medications for heart failure (e.g., angiotensin receptor neprilysin inhibitors, SGLT2i) have been demonstrated to lower serum UA concentration, which may be associated with improved outcomes (45, 47). Further clinical trials are warranted to assess the effect of UA-lowering treatment on adverse health outcomes in patients with CHF, CKD, and hyperuricemia.

The strengths of our study included the cohort design, large sample size, and well-characterized data on a broad spectrum of biological and demographic fields. However, several limitations should be noted. First, our study was conducted in a single center, although, over 70% of the study patients were from other 30 provinces of China. Therefore, the patients included in our study were still nationally representative, but may not be completely generalizable to other countries. Second, 14.12% of the patients were lost to follow-up, which may have introduced bias into the long-term mortality analysis. However, the proportion of CKD and many other basic characteristics were comparable between patients who lost to follow-up and those included in the long-term mortality analysis (Supplementary Table 1). Therefore, the bias could be small. Third, due to the limitation of telephonic interview, we did not collect information on specific causes of death in all study patients. Fourth, data on serum UA, eGFR, and proteinuria were only obtained at baseline and were not assessed over time. Since these are all modifiable factors, the longitudinal trajectories of these parameters and their association with mortality in patients with CHF warrant investigation in the future.

In conclusion, hyperuricemia and CKD individually and cumulatively increase the risk of in-hospital mortality and long-term mortality in patients with CHF. These findings provided further evidence demonstrating the combined effect of hyperuricemia and CKD on heart failure outcomes, and highlighted the importance of the management of serum UA in CHF patients, with or without CKD.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the ethics committee of the Chinese People's Liberation Army General Hospital. The ethics committee waived the requirement of written informed consent for participation.

Author contributions

Conceptualization: CW, WD, YB, and KH; Data curation: CW, HC, YZ, RW, DZ, LC, CR, QZ, ZL, YD, and JX; Formal analysis: CW and HC; Funding acquisition: KH; Investigation: CW, HC, and YZ; Methodology: CW and HC; Project administration: KH; Writing-original draft: CW and HC; Writing-review and editing: All authors. All authors contributed to the article and approved the submitted version.

Funding

The study was supported by the grants from the Technology Innovation 2030 Major Project of China (No. 2021ZD0140406).

Acknowledgments

We thank the staff of the Medical Big Data Research Center, Medical Innovation Research Department of PLA General Hospital for their contributions.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1131566/full#supplementary-material

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frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 08 May 2023
DOI 10.3389/fendo.2023.1153462

OPEN ACCESS

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RECEIVED 29 January 2023
ACCEPTED 03 April 2023
PUBLISHED 08 May 2023

CITATION
Shen X, Yang L, Liu Y-Y, Zhang X-H, Cai P, Huang J-F and Jiang L (2023) Associations between urinary iodine concentration and the prevalence of metabolic disorders: a cross-sectional study.
Front. Endocrinol. 14:1153462.
doi: 10.3389/fendo.2023.1153462

Associations between urinary iodine concentration and the prevalence of metabolic disorders: a cross-sectional study

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Background: Few studies have examined the role of iodine in extrathyroidal function. Recent research has shown an association between iodine and metabolic syndromes (MetS) in Chinese and Korean populations, but the link in the American participants remains unknown.

Purpose: This study aimed to examine the relationship between iodine status and metabolic disorders, including components associated with metabolic syndrome, hypertension, hyperglycemia, central obesity, triglyceride abnormalities, and low HDL.

Methods: The study included 11,545 adults aged ≥ 18 years from the US National Health and Nutrition Examination Survey (2007–2018). Participants were divided into four groups based on their iodine nutritional status(ug/L), as recommended by the World Health Organization: low UIC, < 100; normal UIC, 100-299; high UIC, 300-399; and very high, ≥ 400. The Odds ratio (OR) for MetS basing the UIC group was estimated using logistic regression models for our overall population and subgroups.

Results: Iodine status was positively associated with the prevalence of MetS in US adults. The risk of MetS was significantly higher in those with high UIC than in those with normal UIC [OR: 1.25; 95% confidence intervals (CI),1.016-1.539; p = 0.035). The risk of MetS was lower in the low UIC group (OR,0.82; 95% CI: 0.708-0.946; p = 0.007). There was a significant nonlinear trend between UIC and the risk of MetS, diabetes, and obesity in overall participants. Participants with high UIC had significantly increased TG elevation (OR, 1.24; 95% CI: 1.002-1.533; P = 0.048) and participants with very high UIC had significantly decreased risk of diabetes (OR, 0.83; 95% CI: 0.731-0.945, p = 0.005). Moreover, subgroup analysis revealed an interaction between UIC and MetS in participants aged < 60 years and ≥ 60 years, and no association between UIC and MetS in older participants aged ≥ 60 years.

Conclusion: Our study validated the relationship between UIC and MetS and their components in US adults. This association may provide further dietary control strategies for the management of patients with metabolic disorders.

KEYWORDS

iodine, metabolism, metabolic disorders, epidemiology, NHANES

1 Introduction

The metabolic syndrome (MetS) (1) is a collection of metabolic abnormalities that include central obesity (Waist Circumference), triglycerides (TG), high-density lipoprotein cholesterol levels(HDL-C), hypertension, and glucose abnormalities. Its prevalence is increasing as society's economic development and lifestyle change (2, 3). There is also a growing concern about the metabolic disease because it may increase the risk of not only all-cause mortality (4) but also increase cardiovascular disease, type 2 diabetes, and specific cancers (5, 6). Multiple interactions between environmental, metabolic, and genetic factors play a role in the pathogenesis of metabolic syndrome (7). Dietary changes are also thought to be a factor in the rising prevalence of metabolic disorders (8). Therefore, identifying relevant factors can help to prevent or reduce the occurrence of metabolic syndrome.

Iodine is an indispensable micronutrient for the human body. It regulates the growth and development of the body and tissue forms largely through the synthesis of thyroid hormones (9). Iodine is almost completely absorbed by the tiny intestine, while it is excreted mainly through the kidneys (10). The main sources of iodine in the diet are seafood (such as fish, crustaceans, and shellfish), eggs, milk, and products rich in iodine (11). The consumption of appropriate dietary iodine is essential for the maintenance of normal thyroid function. Iodine abnormalities (including iodine deficiency and iodine excess) are associated with goiters and abnormal thyroid function, which can increase the incidence of autoimmune thyroiditis and the risk of thyroid cancer (12, 13). Furthermore, iodine abnormalities can lead to developmental disorders, mental disorders, hearing loss, lower intelligence, and increased mortality in children (14, 15), as well as infertility, neurocognitive disorders, and narcolepsy in adults (16, 17).

Numerous studies have been conducted on iodine and thyroid-related diseases (18, 19). However, research on the effects of iodine on tissues and organs is limited. A few studies have shown that high or low levels of iodine in the body can directly or indirectly affect blood glucose, blood pressure, and lipid metabolism (20), but the results are not entirely consistent. Studies have confirmed that the prevalence of the metabolic syndrome is strongly related to regional economics and ethnicity, and varies by geographic location (21). The relationship between iodine and metabolic syndrome in American adults is currently unclear. The purpose of this study was to determine the impact of abnormal iodine consumption on metabolic syndrome in American adults. It will provide some reference to the effects of abnormal iodine on organs other than the thyroid gland.

2 Materials and methods

2.1 Study population

Data from six contiguous cycles of the National Health and Nutrition Examination Survey (NHANES) from 2007-2018. The data is publicly released on a two-year cycle and all of it used in the manuscript can be available on the website: https://wwwn.cdc.gov/nchs/nhanes/search/default.aspx. The NHANES is based on a stratified, multistage, and probability cluster designed and is mobilized by the National Center of Health Statistics of the Centers for Disease Control and Prevention to ensure sample representativeness (22). Participants were invited to stay at home or at a mobile examination center (MEC), where they were questioned about relevant demographic information, lifestyle, and diet and performed blood tests by professionally trained staff. The total sample size from 2007 to 2018 was 21,546 participants, of which 15,808 were 18 years and older. We excluded people with missing information on urinary iodine and metabolic syndrome as well as those with extreme values of iodine (> 99th percentile). Furthermore, we excluded data for missing demographics (1,211), relevant diet (376), lifestyle (1852), and related disease history (376), yielding a final sample of 11,545. Additional details about the study's sampling and exclusion criteria are shown in Figure 1. The data was analyzed between November 2022 and January 2023. The study design strictly adheres to the guidelines of STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) (23). Furthermore, the National Center for Health Statistics Research Ethics Review Board approved this study, and participants provided written informed consent. And Continuation of Protocol #2005-06, Protocol #2011-17, Continuation of Protocol #2011-17, and Protocol #2018-01 are the ethics approval numbers.

2.2 Diagnosis of metabolic syndrome

Metabolic syndrome (MetS) was defined according to the National Cholesterol Education Program/Adult Treatment Panel

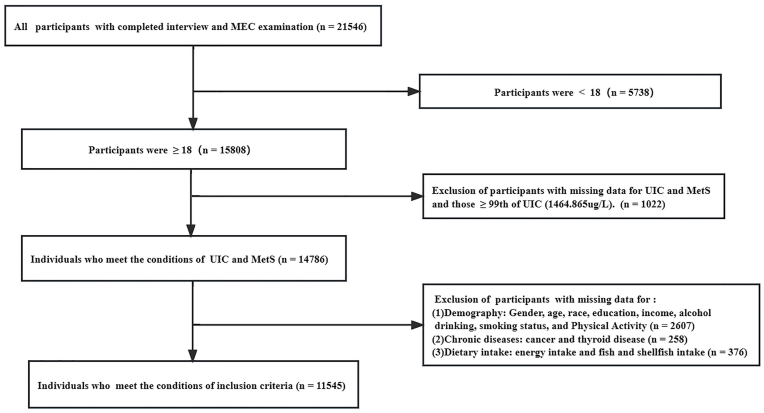

FIGURE 1
The Flow Chart of Inclusion and Exclusion in the study.

III criteria (NCEP-ATP III) (24), an update of the criteria proposed by the International Diabetes Federation and the World Health Organization, and was determined by meeting three to five of the following components (1): Central obesity: Waist Circumference (WC) ≥ 102 cm in men or ≥ 88 cm in women (2); hypertension: blood pressure ≥ 130/85 mmHg or hypertension history or treatment with antihypertensive medication (3); Diabetes: history of diabetes, glycosylated hemoglobin (HbA1c) > 6.5%, fasting glucose (mmol/L) ≥ 7.0, or medication used to treat diabetes (4); high TG: TG ≥ 150 mg/dL or pharmacological treatment of TG (5); low HDL-C: HDL-C < 40 mg/dL for men and < 50 mg/dL for women or using anti-lipid abnormalities. In NHANES, blood pressure was measured by a trained technician according to a standard protocol, using a manual mercury sphygmomanometer to measure the blood pressure of the participants, with every individual being measured three times (25). Since the first reading record was continuously higher than the second and third, while the latter two were closer. Therefore, if there are three measurements recorded, we would discard the first blood pressure reading and select the average of the second and third blood pressure readings for analysis. The average blood pressure was calculated by the following protocol (1): The diastolic reading with zero is not used to calculate the diastolic average (2); If all diastolic readings were zero, then the average would be zero (3); If only one blood pressure reading was obtained, that reading is average (4); If there is more than one blood pressure reading, the first reading is always excluded from the average.

2.3 Urinary iodine concentrations

Because almost all iodine ingested in the body is excreted in the urine (26), iodine is mostly present in the body as urine iodine. The World Health Organization (WHOs) also recommends that urine assessments be used to measure iodine levels in people (27). And Several studies have shown that urine iodine can be used as a proxy measure of dietary iodine content (28, 29). To sum up, urinary iodine concentration (UIC) was used indirectly as an indicator to estimate iodine consumption in the study, as there was a good correlation between iodine content in urine and intake. UIC as the most appropriate biochemical marker, which was determined by inductively coupled plasma dynamic reaction cell mass spectrometry (ICP-DRC-MS) (30). In NHANES, on-site urine samples were used to assess the nutritional status of iodine, while laboratory methods for the determination of UIC are publicly available (31). Urine iodine (μg/L) was divided into five groups from low to high according to the WHO guidelines: low UIC, < 100; normal UIC, 100-299; high UIC, 300-399; and very high, ≥ 400 (32).

2.4 Covariate assessments

Selecting covariates based on clinical experience, previous literature, and the statistical significance of reason. The questionnaire collected information on age, gender, race/ethnicity, education, income, alcohol consumption, smoking, physical activity, disease history, and medication history. Race/ethnicity was categorized as Mexican American, non-Hispanic white, non-Hispanic black, or other. Education levels were classified as below high school; high school grad/GED (General education development diploma) or Equivalent (33); above high school. Two categories of the annual family income were considered: “above $20000”, and “below $20000”. Participants were categorized as “mild”, “moderate”, “heavy”, and “no” based on the number of drinks per day he/she had drunk in 1 year. Participants who are “mild” were considered to be drinking alcohol ≤ 1 drink in women in 1 year or ≤ 2 drinks in men in 1 year; Participants who are “moderate” were considered to be drinking alcohol ≤ 2 drinks in women in 1 year or ≤ 3drinks in men in 1 year; Participants who are “heavy” were considered to be drinking alcohol ≥ 3 drinks of women in 1 year or ≥ 4drinks of man in 1 year; Participants who drank before last year but don’t drink now and those who never drank before are defined as “no” (34). Smoking status was defined as the numbers and timeline of cigarettes in life: “never” (smoked less than 100 cigarettes); “former” (smoked more than 100 cigarettes in life and smoke not

at all now); "now" (smoked more than 100 cigarettes in life and smoke some days or every day now). Physical activity was measured based on the scores of the Metabolic Equivalent Task (MET) (35). Weekly as well as monthly exercise was converted to daily activity. The MET scores for vigorous-intensity work and vigorous recreational activities were calculated by multiplying by eight. You can get their MET score by multiplying cycling or walking, moderate-intensity activity, and moderate recreational activity by four. Cancer disease history was defined by a doctor's diagnosis of cancer. The diagnosis of thyroid disease includes the use of thyroid medications and patients who have been diagnosed with thyroid disease by a physician. Other corresponding biochemical data such as Uric acid (umol/L), Triglyceride (mmol/L), HbA1c (%), HDL-C (mmol/L), LDL-C (mmol/L), Total cholesterol (mmol/L), and fasting glucose (mmol/L) were obtained from the blood Hemal Biochemistry file. Glomerular filtration rate (eGFR) (36) was calculated using the Chronic Kidney Disease Epidemiology Collaborative (CKD-EPI) formula,1:eGFR (mL/minute/1.73 m2) = 141*min(SCr/κ, 1) α*max(SCr/κ, 1)-1.209*0.993 age *1. 018 if female*1.159 If non-Hispanic black, where SCr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum value of SCr/κ or 1, and max indicates the maximum value of SCr/κ or 1. Fasting glucose (37) tests were performed in the morning after a 9-hour fast, and after the initial venipuncture, participants were asked to drink a calibrated dose of TrutolTM (usually containing 75 g of glucose) and to perform a second venipuncture for 2 hours (plus or minus 15 minutes) after drinking TrutolTM for the OGTT. FT4 and TSH comes from the thyroid Profile, and the detailed instructions for specimen collection and handling are well documented in the NHANES Laboratory/Medical Technician Procedure Manual (38). For example, the TSH was obtained by Access HYPERsensitive human thyroid-stimulating hormone (hTSH) assay, which is a 3rd generation, two-site immunoenzymatic ("sandwich") assay.

2.5 Statistical analysis

We considered complex sampling designs and sample sizes during data analysis according to NHANES analysis guidelines (39). And the present data can represent a sample population of 67,771,194. Continuous variables were expressed as weighted means with standard deviation, whereas categorical variables are presented as cases (n) and percentage (%) categorical variables compared using Rao Scott's $\chi 2$ test. One-way ANOVA was used to compare differences between groups. A multivariate logistic regression model was used to calculate the Odds ratio (OR) and 95% CI for the relationship between UIC and the prevalence of MetS, and the categorical normal group of UIC (≥ 100μg/L and < 300μg/L) was used as a reference. The crude model was not adjusted. Model 1 was adjusted for age and gender. Model 2 was adjusted for age, gender, education levels, race/ethnicity, smoking status, alcohol consumption, and physical activity. Model 3 was adjusted for Uric acid, eGFR, salt intake, energy intake, fish and shellfish intake, cancer, thyroid disorders, and the covariates of Model 2 besides. We investigated the continuous relationship between UIC (log10) and MetS by fitting a restricted cubic spline model at the 5th, 35th, 65th, and 95th percentiles of UIC (log10) (22). In addition, we further analyzed the relationship between UIC and the components of MetS. All analyzes were performed using the statistical software package R (http://www.r-project.org; version 4.2.2, The R Foundation) and Free Statistics software versions Statistics 1.7. And a two-sided *p*-value of less than 0.05 indicates a denoted statistically significant difference.

3 Results

3.1 Participant characteristics according to UIC

In this study, we selected nine continuous NHANES cycles (2007–2018) and focused on 11,545 adults with the completed interview, MEC examination, and laboratory examination in the US (≥18 years). Among the all participants in the study 5,740 (49.7%) females and 5,805 (50.3%) males were recruited, and a total of 3,200 participants had MetS. Based on the weighted analyzes, the mean UIC of total participants was 187.86 μg/L (IQR,184.58-191.14), which includes the recommended range by the WHO (IQR: 100-299μg/L), and those with education above high school accounted for 51.1%, and most of the participants were non-Hispanic white (44.5%). Participants with very high UIC whose value of glucose, triglyceride, and glucose of OGTT was higher and participants with low UIC were more likely to be female, non-Hispanic white, with higher annual household income, obesity, non-hypertensive, mild drinkers, nonsmokers, individuals who consume more fish or shellfish and with lower HbA1c (%). Hypertension, physical activity, systolic pressure, Sodium intake, and total cholesterol had no significant differences between the groups by UIC ($p > 0.05$). The baseline characteristics of the participants are summarized **in** Table 1.

3.2 Prevalence of MetS and its components in different UIC groups

Table 2 showed the prevalence of MetS was associated with UIC, and this relationship was found in both females and males. The overall prevalence of MetS was 27.7%. High waist circumference is the most common component of MetS, followed by hypertension, high TG levels, low HDL-C levels, and elevated glucose levels. When stratified by UIC, the prevalence of metabolic syndrome was 22.2%, 27.0%, 32.6 and 29.4% in the low-iodine, normal-iodine, and high-iodine, and very high-iodine groups, respectively. The prevalence of metabolic syndrome was significantly different among different UIC groups ($p < 0.001$). When analyzing the prevalence of each component of MetS in different UIC subgroups, we found that only hypertension was not statistically different from the UIC group ($p = 0.99$), while all other components were statistically different from the UIC subgroup (all *p* values < 0.05). In the gender subgroup, glucose abnormalities were

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TABLE 1 Baseline characteristics of participants with respect to urinary iodine.

Characteristics	Total	Low UIC (<100ug/L)	Normal UIC (100-299ug/L)	High UIC (300-399ug/L)	Very high UIC (≥400ug/L)	*P*-value
	11545	4064	5507	835	1139	
UIC, (ug/L)	187.86±3.28	60.14±0.51	175.96±1.03	343.55±1.51	627.15±7.87	< 0.001
Age, (Years)	47.12±0.30	45.26±0.37	47.67±0.40	49.88±0.74	49.58±0.67	< 0.001
Gender, (%)						< 0.001
Female	5740(49.7)	2218(55.5)	2631(48.4)	375(45.3)	516(45.2)	
Male	5805(50.3)	1846(44.5)	2876(51.6)	460(54.7)	623(54.8)	
Ethnic, (%)						0.004
Mexican American	1813(15.7)	586(7.7)	936(9.2)	129(7.8)	162(7.6)	
Non-Hispanic Black	2368(20.5)	889(10.9)	1137(11.1)	138 (8.0)	204 (9.3)	
Non-Hispanic White	5138(44.5)	1726(68.5)	2413(68.2)	422(74.9)	577(71.5)	
Other Race	2226(19.3)	863(12.9)	1021(11.4)	146 (9.3)	196(11.6)	
Education levels, (%)						0.02
Above high school	5940(51.5)	2182(62.3)	2794(58.4)	425(60.0)	539(57.4)	
Below high school	2875(24.9)	899(13.9)	1441(17.1)	213(16.3)	322(18.2)	
High School Grad/GED or Equivalent	2730(23.6)	983(23.8)	1272(24.5)	197(23.6)	278(24.4)	
Income, (%)						< 0.001
Above 20000$	9116(79)	3268(87.5)	4363(86.2)	651(86.5)	834(81.4)	
Below 20000$	2429(21)	796(12.5)	1144(13.8)	184(13.5)	305(18.6)	
Alcohol drinking, (%)						< 0.001
Heavy	2386(20.7)	883(22.6)	1114(22.0)	165(19.2)	224(22.7)	
Mild	3798(32.9)	1339(35.8)	1858(37.2)	266(36.6)	335(32.6)	
Moderate	1820(15.8)	735(20.9)	815(16.7)	123(16.1)	147(12.3)	
No	3541(30.7)	1107(20.7)	1720(24.1)	281(28.1)	433(32.5)	
Smoking, (%)						0.08
Former	2922(25.3)	961(24.9)	1420(25.3)	220(24.3)	321(28.6)	
Never	6221(53.9)	2194(53.3)	2982(55.1)	457(57.5)	588(53.4)	
Now	2402(20.8)	909(21.8)	1105(19.6)	158(18.3)	230(18.0)	
Physical activity, (Met)	567.6±14.3	532.6±20.8	596.2±22.5	612.0±49.3	529.7±29.8	0.11
Energy, (kcal)	2189.0±12.0	2157.4±21.6	2196.5±16.8	2305.3±36.4	2184.1±38.2	0.01
Sodium intake, (mg/d)	3579.0±22.8	3547.2±35.4	3603.0±32.3	3695.5±78.5	3492.5±66.1	0.22
Fish and shellfish intake, (%)						0.03
No	2290(19.8)	814(18.7)	1052(18.3)	158(18.7)	266(23.3)	
Yes	9255(80.2)	3250(81.3)	4455(81.7)	677(81.3)	873(76.7)	
Waist, (cm)	99.19±0.28	96.67±0.33	100.36±0.38	101.98±0.72	101.12±0.61	< 0.001
OGTT glucose, (mmol/L)	7.29±0.06	7.06±0.09	7.36±0.08	7.57±0.17	7.64±0.19	0.003
Fasting glucose, (mmol/L)	5.93±0.02	5.84±0.04	5.96±0.03	6.04±0.09	6.04±0.09	0.01
HbA1c, (%)	5.62±0.01	5.56±0.02	5.64±0.02	5.70±0.05	5.70±0.04	< 0.001
eGFR	94.89±0.45	97.19±0.61	94.06±0.47	91.54±0.95	92.65±0.85	< 0.001

(Continued)

TABLE 1 Continued

Characteristics	Total	Low UIC (<100ug/L)	Normal UIC (100-299ug/L)	High UIC (300-399ug/L)	Very high UIC (≥400ug/L)	*P*-value
	11545	4064	5507	835	1139	
Uric acid, (umol/L)	324.43±1.24	318.82±2.05	328.97±1.72	327.93±3.19	321.39±3.42	< 0.001
TG, (mmol/L)	2.73±0.03	2.64±0.05	2.73±0.05	2.89±0.12	2.96±0.10	0.03
Total cholesterol, (mmol/L)	5.02±0.02	5.04±0.02	5.02±0.02	4.96±0.05	4.95±0.05	0.23
HDL, (mmol/L)	1.38±0.01	1.43±0.01	1.36±0.01	1.32±0.02	1.31±0.02	< 0.001
LDL, (mmol/L)	2.42±0.01	2.43±0.03	2.44±0.02	2.34±0.04	2.32±0.04	0.02
TSH, (mIU/L)	1.95±0.04	1.98±0.10	1.91±0.06	1.98±0.04	1.91±0.06	0.661
FT4, (ug/dL)	7.98±0.03	8.00±0.09	8.00±0.04	7.96±0.04	7.99±0.07	0.824
SBP, (mmHg)	121.8±0.3	121.3±0.4	121.9±0.4	122.6±0.6	122.4±0.7	0.42
DBP, (mmHg)	70.98±0.22	71.56±0.32	70.62±0.24	70.26±0.60	71.01±0.45	0.02
Cancer, (%)						0.001
No	10401(90.1)	3754(91.6)	4928(89.5)	723(85.5)	996(89.2)	
Yes	1144(9.9)	310 (8.4)	579(10.5)	112(14.5)	143(10.8)	
Thyroid disease, (%)						0.002
No	10329(89.5)	3711(90.0)	4915(88.9)	729(86.5)	974(85.2)	
Yes	1216(10.5)	353(10.0)	592(11.1)	106(13.5)	165(14.8)	

UIC, urinary iodine concentration. MetS, metabolic syndrome; HbA1c, eGFR, Glomerular filtration rate; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, Systolic blood pressure; DBP, Diastolic blood pressure;
Data are presented as means (standard error), or weighted percentages as appropriate for the variable. Demographic and biochemical characteristics of the study population for Continuous normal variables were expressed as weighted mean ± standard deviation, One-way ANOVA was used to compare differences between groups. Categorical variables were expressed as frequencies and percentages and compared using Rao Scott's $\chi 2$ test.

statistically significant in different UIC groups in men (p = 0.006), however, this association was not seen in women (p = 0.125). Meanwhile, all other four groups were statistically different in the gender subgroup from the different UIC subgroups (p < 0.05).

3.3 The relationship between UIC and the risk of MetS and components

The OR and corresponding 95% CI of the risk for MetS according to UIC (log10) and four UIC groups are summarized in Table 3. When UIC was a continuous value, a multivariate regression model was used to adjust for other possible confounding factors, including demographic factors, chronic illness, lifestyle habits, dietary factors, and thyroid hormones. We found that with each log-unit increase in UIC level, there was a corresponding 50% increase in the probability of developing MetS (OR, 1.50; 95% CI, 1.275-1.756; p < 0.001). The same trend was observed in the category of low UIC group (< 100μg/L) has a protective effect on MetS (OR, 0.82; 95%CI, 0.708-0.946; p = 0.007) and high UIC group (300-399μg/L) has an adverse effect on MetS (OR, 1.25; 95%CI, 1.016-1.539; p = 0.035) compared to the normal group of UIC, adjusting for all relevant covariates in Table 3. The relationship between the risk of other MetS components and UIC was similarly validated. Furthermore, restricted cubic splines showed the relationship between UIC and MetS and components of MetS **in** Figure 2. And a *p-value* less than 0.05 shows non-linearity, while a *p-value* greater than 0.05 represents a linear relationship.

The association between blood glucose abnormalities and UIC (log10) showed an inverted u-shaped curve with a maximum point of 2.14 μg/L and a non-linear p < 0.001 (Figure 2). Figure 2 demonstrated an approximately inverted U-shaped relationship between obesity and UIC (log10) (non-linear p < 0.001). Table 3 showed that the very high UIC group (≥ 400 μg/L) was associated with a lower occurrence of glucose abnormalities compared to the normal group UIC (OR, 0.68; 95%CI, 0.542-0.855; p = 0.001), but the incidence of reducing obesity was associated with lower UIC (OR, 0.83; 95%CI, 0.731-0.945; p = 0.005). In addition, we further analyzed the relationship between BMI and UIC in Table S1. We found a positive correlation between urinary iodine and BMI (Coefficient,1.97; 95% CI: 1.591 2.355; p < 0.001). And BMI was lower in participants with low UIC compared to those with the normal UIC group (Coefficient, -1.29; 95% CI: -1.644 to -0.936; p < 0.001). Because there is co-linearity between BMI and waist circumference (40), we did not adjust BMI in the process of data analysis. The results in Table S1 once again verify the accuracy of the relationship between obesity and UIC, which is the component of MetS in Table 3. At the same time, Lower UIC favored lower HDL-C (OR, 0.81; 95%CI, 0.732-0.894; p < 0.001), whereas higher UIC (300-399ug/L) increased the incidence of HDL-C (OR, 1.30; 95%CI, 1.043-1.630; p = 0.020), although the 95% CI in the very high UIC group spanned 1. Furthermore, Low UIC (< 100μg/L) was

TABLE 2 Prevalence of metabolic syndrome and its components in US adults with different urinary iodine concentration.

Variable		Prevalence (%) of Metabolic Syndrome and Its Components				
	Total	Normal UIC (100-299ug/L)	Low UIC (<100ug/L)	High UIC (300-399ug/L)	Very high UIC (≥400ug/L)	*P*-value
All participants						
MetS	3200 (27.7)	1627 (27.0)	962 (22.2)	262 (32.6)	349 (29.4)	< 0.001
MetS.Diabetes	3550 (30.7)	1831 (29.7)	1129 (25.3)	285 (32.8)	305 (24.7)	< 0.001
MetS.low-HDL-C	3571 (30.9)	1741 (30.3)	1151 (26.6)	293 (35.5)	386 (34.0)	< 0.001
MetS.TG	4248 (36.8)	2103 (37.1)	1298 (31.6)	350 (43.5)	497 (44.0)	< 0.001
MetS.obesity	6668 (57.8)	3284 (58.2)	2192 (53.6)	506 (61.1)	686 (59.5)	< 0.001
MetS.hypertension	2023 (17.5)	964 (15.9)	707 (16.1)	149 (16.2)	203 (15.6)	0.99
Female						
MetS	1724 (30.0)	857 (28.8)	566 (22.3)	118 (28.9)	183 (31.1)	< 0.001
MetS.Diabetes	1555 (27.1)	795 (26.7)	533 (20.8)	104 (27.4)	123 (19.8)	0.006
MetS.low-HDL-C	2102 (36.6)	982 (34.7)	751 (30.2)	147 (35.6)	222 (41.5)	0.001
MetS.TG	1856 (32.3)	908 (31.5)	598 (25.9)	141 (38.1)	209 (38.9)	< 0.001
MetS.obesity	3994 (69.6)	1896 (68.8)	1438 (61.2)	275 (71.6)	385 (71.7)	< 0.001
MetS.hypertension	939 (16.4)	447 (16.1)	351 (14.5)	65 (16.1)	76 (12.3)	0.322
Male						
MetS	1476 (25.4)	770 (25.4)	396 (21.9)	144 (35.6)	166 (28.0)	< 0.001
MetS.Diabetes	1995 (34.4)	1036 (32.5)	596 (30.8)	181 (37.2)	182 (28.7)	0.125
MetS.low-HDL-C	1469 (25.3)	759 (26.1)	400 (22.3)	146 (35.4)	164 (27.7)	< 0.001
MetS.TG	2392 (41.2)	1195 (42.3)	700 (38.7)	209 (48.0)	288 (48.2)	0.004
MetS.obesity	2676 (46.1)	1388 (48.0)	754 (44.0)	231 (52.4)	301 (49.5)	0.05
MetS.hypertension	1084 (18.7)	517 (15.9)	356 (18.0)	84 (16.3)	127 (18.3)	0.484

UIC, urinary iodine concentration. MetS, metabolic syndrome,
MetS.Diabetes, History of diabetes, Glycosylated hemoglobin (HbA1c) > 6.5%, fasting glucose (mmol/L) ≥ 7.0, or medication used to treat diabetes;
MetS.obesity, Waist Circumference (WC) ≥ 102 cm in men or ≥ 88 cm in women;
MetS.hypertension, blood pressure ≥ 130/85 mmHg or hypertension history or treatment with antihypertensive medication;
MetS.low-HDL-C, HDL-C < 40 mg/dL for men and < 50 mg/dL for women or use of anti-lipid abnormalities;
MetS.TG, TG ≥ 150 mg/dL, or pharmacological treatment of TG. The prevalence of metabolic syndrome components according to the urinary iodine concentration was compared using Rao Scott's $\chi 2$ test.

associated with lower TG levels but the incidence of TG levels was higher when UIC was ≥ 300μg/L. However, the occurrence of hypertension was not associated with UIC both higher and lower UIC compared to normal UIC. There was a linear relationship between hypertension, HDL, TG, and UIC (log10) with their p of non-linear were 0.112,0.869, and 0.663 in Figure 2, respectively.

We performed further sensitivity analysis. After excluding 10.5% of patients with thyroid disease, we also analyzed the relationship between different UIC levels and the metabolic syndrome and its components, as shown in Table S2. We found that low UIC (<100ug/L) was associated with a higher incidence of hypertension, and there was no statistical difference between UIC (<100ug/L) and metabolic syndrome. Additional results were consistent with those already analyzed in patients without thyroid exclusion in Table 3. In addition, the results of the subgroup analysis of age, sex, race, and thyroid disease are presented in Figure 3. After adjusting for education, annual family income, smoking status, alcohol intake, physical activity, cancer, energy intake, fish or shellfish intake, sodium intake, eGFR, TSH, and FT4, we found an interaction in the age stratification (p = 0.003), with a positive association between UIC (log10) (continuous variable) and MetS when the age was less than 60, while there was no statistically significant association in the participants with age ≥ 60. However, there was no interaction between UIC and MetS in the other subgroups as shown in Table S3.

4 Discussion

This study evaluated a nationally representative sample of American adults and discovered a positive correlation between UIC and the risk of MetS, though after controlling for potentially significant confounders. We also discovered a non-linear relationship between UIC and MetS in the fully adjusted model

(non-linear $p = 0.017$). We investigated the prevalence of MetS and its components in participants aged ≥ 18 years in this cross-sectional study based on US NHANES data, as well as the relationship between iodine status and MetS and their components. We not only demonstrated the relationship between UIC (log10) and MetS and their components, but we also looked into it in different UIC strata. We found that UIC of < 100μg/L was significantly associated with obesity and, low HDL-C, MetS, and

TABLE 3 Multiple logistic regression between UIC and MetS and its components.

Variables	N (%)	Crude model		Model 1		Model 2		Model 3	
		OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*
MetS									
UIC (log10)		1.69(1.441,1.982)	<0.001*	1.54(1.301,1.816)	<0.001*	1.50(1.272,1.757)	<0.001*	1.50(1.275,1.756)	<0.001*
Classified UIC									
normal UIC	1627(48.23)	ref		ref		ref		ref	
low UIC	962(31.68)	0.77(0.665,0.891)	<0.001*	0.81(0.699,0.941)	0.006*	0.82(0.706,0.949)	0.009*	0.82(0.708,0.946)	0.007*
high UIC	262(9.48)	1.31(1.069,1.600)	0.01*	1.26(1.018,1.547)	0.033*	1.26(1.020,1.555)	0.033*	1.25(1.016,1.539)	0.035*
very high UIC	349(10.61)	1.13(0.933,1.358)	0.213	1.08(0.888,1.314)	0.435	1.04(0.858,1.263)	0.681	1.05(0.862,1.270)	0.644
p for trend			0.222		0.39		0.531		0.515
MetS.Diabetes									
normal UIC	1831(49.24)	ref		ref		ref		ref	
low UIC	1129(33.61)	0.80(0.704,0.916)	0.001*	0.90(0.791,1.026)	0.114	0.91(0.798,1.032)	0.138	0.90(0.791,1.022)	0.103
high UIC	285(8.86)	1.16(0.909,1.470)	0.234	1.06(0.814,1.382)	0.659	1.08(0.828,1.407)	0.57	1.08(0.830,1.407)	0.560
very high UIC	305(8.28)	0.78(0.622,0.972)	0.027*	0.70(0.555,0.869)	0.002*	0.69(0.549,0.860)	0.001*	0.68(0.542,0.855)	0.001*
p for trend			0.063		0.009*		0.01*		0.008*
MetS.obesity									
normal UIC	3265(47.12)	ref		ref		ref		ref	
low UIC	2189(34.93)	0.84(0.749,0.946)	0.004*	0.84(0.742,0.947)	0.005*	0.85(0.749,0.954)	0.007*	0.83(0.731,0.945)	0.005*
high UIC	502(8.03)	1.12(0.919,1.357)	0.262	1.08(0.881,1.329)	0.448	1.09(0.879,1.356)	0.422	1.11(0.885,1.390)	0.364
very high UIC	691(9.92)	1.11(0.933,1.309)	0.246	1.08(0.910,1.281)	0.376	1.05(0.879,1.252)	0.592	1.01(0.837,1.204)	0.970
p for trend			0.454		0.693		0.852		0.856
MetS.hypertension									
normal UIC	964(46.18)	ref		ref		ref		ref	
low UIC	707(37.13)	1.01(0.857,1.180)	0.947	1.12(0.952,1.319)	0.169	1.12(0.948,1.322)	0.181	1.13(0.953,1.329)	0.162
high UIC	149(7.61)	1.01(0.782,1.315)	0.915	0.94(0.718,1.224)	0.631	0.96(0.731,1.252)	0.746	0.95(0.726,1.237)	0.688
very high UIC	203(9.08)	0.97(0.775,1.211)	0.775	0.90(0.706,1.135)	0.357	0.91(0.719,1.154)	0.435	0.92(0.725,1.166)	0.481
p for trend			0.876		0.532		0.654		0.683
MetS.low-HDL-C									
normal UIC	1741(47.09)	ref		ref		ref		ref	
low UIC	1151(33.23)	0.84(0.758,0.928)	<0.001*	0.80(0.723,0.887)	<0.001*	0.81(0.729,0.895)	<0.001*	0.81(0.732,0.894)	<0.001*
high UIC	293(9.00)	1.27(1.020,1.578)	0.033*	1.31(1.041,1.636)	0.021*	1.31(1.046,1.634)	0.019*	1.30(1.043,1.630)	0.020*
very high UIC	386(10.68)	1.19(1.002,1.401)	0.047*	1.22(1.030,1.436)	0.021*	1.17(0.990,1.392)	0.065	1.18(0.985,1.410)	0.072
p for trend			0.049*		0.033*		0.061		0.064

(Continued)

TABLE 3 Continued

Variables	N (%)	Crude model		Model 1		Model 2		Model 3	
		OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*
MetS.TG									
normal UIC	2103(47.30)	ref		ref		ref		ref	
low UIC	1298(32.31)	0.79(0.691,0.893)	<0.001*	0.84(0.739,0.960)	0.011*	0.84(0.738,0.959)	0.011*	0.85(0.746,0.965)	0.013*
high UIC	350(9.05)	1.31(1.069,1.604)	0.01*	1.25(1.016,1.547)	0.035*	1.25(1.013,1.537)	0.038*	1.24(1.002,1.533)	0.048*
very high UIC	497(11.35)	1.33(1.137,1.565)	<0.001*	1.28(1.083,1.522)	0.004*	1.26(1.068,1.492)	0.007*	1.26(1.082,1.503)	0.004*
p for trend			0.006*		0.018*		0.024*		0.018*

UIC, urinary iodine concentration; MetS, metabolic syndromes; HDL, high-density lipoprotein; TG, triglyceride.
MetS.Diabetes, History of diabetes, Glycosylated hemoglobin (HbA1c) > 6.5%, fasting glucose (mmol/L) ≥ 7.0, or medication used to treat diabetes;
MetS.obesity, Waist Circumference (WC) ≥ 102 cm in men or ≥ 88 cm in women;
MetS.hypertension, blood pressure ≥ 130/85 mmHg or hypertension history or treatment with antihypertensive medication;
MetS.low-HDL-C, HDL-C < 40 mg/dL for men and < 50 mg/dL for women or use of anti-lipid abnormalities;
MetS.TG, TG ≥ 150 mg/dL or pharmacological treatment of TG.
Data are expressed as weighted percentages. OR and 95% CI for risk of metabolic syndrome and its components were estimated using complex samples logistic regression. * represents p < 0.05.
Normal UIC: < 100ug/L; Low UIC: 100-299ug/L; High UIC: 300-399ug/L; Very high UIC: ≥ 400ug/L.
Crude Model: not adjusted;
Model 1: Adjusted for age, sex;
Model 2: Adjusted for age, sex, race/ethnicity, education, the annual family income, smoking status, alcohol intake, physical activity,
Model 3: Adjusted for age, sex, race/ethnicity, education, the annual family income, smoking status, alcohol intake, physical activity, thyroid problems, cancer, energy intake, fish or shellfish intake, sodium intake, eGFR, TSH, and FT4.

TG. There is also a significant correlation between UIC and MetS, low HDL-C, and TG when UIC is between 300 and 399 ug/L. And the UIC of ≥ 400μg/L was linked to fewer glucose abnormalities. However, after adjusting for confounders, there was no significant association between each UIC group and hypertension compared to the normal group.

In the sensitivity analysis, we found that low urinary iodine (UIC<100ug/L) was associated with a higher incidence of hypertension, and there was no statistical difference between urinary iodine (UIC<100ug/L) and metabolic syndrome. Other results were consistent with those already analyzed in patients without thyroid exclusion. According to the data presented above, high UIC may be potentially protective against the development of blood glucose abnormalities and have a positive correlation with low HDL-C levels, TG, and MetS. However, low iodine UIC is potentially protective against low HDL-C levels, TG, and obesity. As a result, the detection of iodine has a crucial role in metabolic disorders.

To our knowledge, studies have investigated the relationship between iodine and metabolism-related diseases and support our results. A study of the relationship between iodine and MetS in Central American children and parents confirmed that high iodine concentration increases the incidence of MetS in adults (41). In the study, we also found that lower UIC was associated with a lower incidence of metabolic syndrome, whereas this association was not found after excluding participants with thyroid disease. A cross-sectional study of epidemiology in China indicated that the association between UIC and MetS was not present in iodine deficiency (<100μg/L) in non-thyroid disease populations (42). Similarly, Kim et al. found no association between iodine intake and MetS risk in male Korean adults ≥ 19 years of participants with normal thyroid function (43). In the present study, UIC was negatively associated with the prevalence of diabetes, TG levels, and low HDL levels at ≥ 400 μg/L, ≥ 300μg/L, and < 100 μg/L, respectively. A nationwide cross-sectional epidemiological study from China discovered a link between UIC ≥ 300μg/L and dyslipidemia, which also supports our results (42). Following that, a randomized controlled trial of iodine supplementation in overweight women reported that iodine supplementation reduced the incidence of hypercholesterolemia (44). One study reported that mild iodine deficiency (100-150μg/L) was associated with an increased risk of gestational diabetes (45). Larsson et al. observed that adequate iodide levels improved insulin secretory function in isolated pancreatic islets during glucose-stimulated insulin secretion (46). we also found that low urinary iodine (UIC<100ug/L) was associated with a higher incidence of hypertension in participants without thyroid disorders exclusion, but there was no significant correlation between each UIC group and hypertension compared to the normal group in all participants without excluding those who were thyroid disease. Next, an Indian cross-sectional study (47) showed that iodine levels were negatively correlated with age and SBP (42). A study (31) of US adults from 2010 found that current hypertension or a history of hypertension was also not significantly associated with iodine deficiency or high iodine status in men and women compared to those who did not have hypertension. Furthermore, a cross-sectional study (42) from TIDE data showed that UIC <100 μg/L was associated with hypertension (OR, 1.097;95%CI:1.035-1.162) in participants without thyroid disorder. Moreover, our study shows that UIC is positively associated with obesity and BMI. Pablo and his colleague's study of 10 public elementary schools in 50 cities in the Mexican state of Queretaro showed the same positive relationship between the median UIC and the median body mass index (BMI) in each school (48). And Farebrother et al. recently studied the iodine nutritional status of multiracial obese pregnant women from inner-city areas in the United Kingdom and found that lower iodine status was associated with lower birth weight (49).

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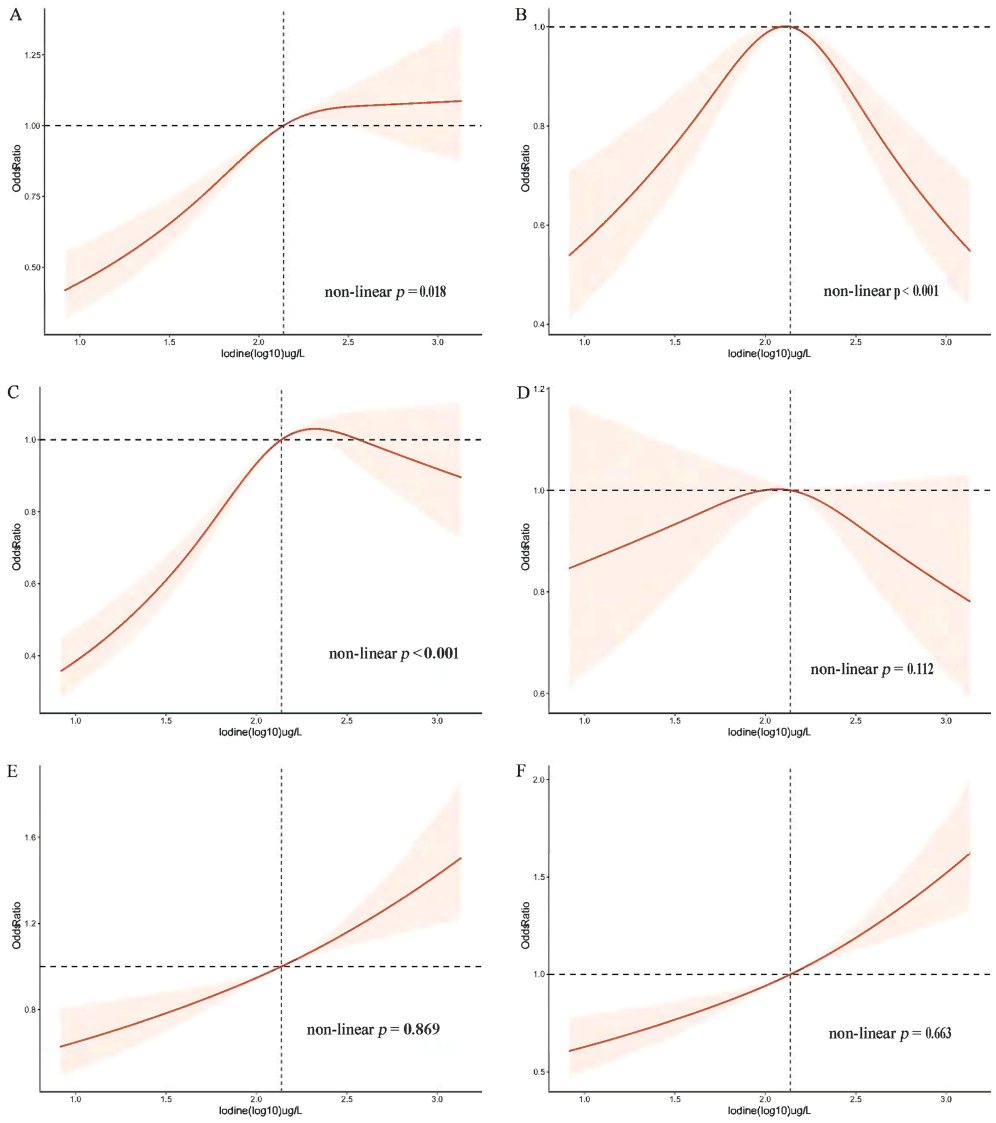

FIGURE 2
Restricted cubic spline plot of the association between UIC and MetS and components in participants of American adults (age ≥ 18). **(A)** Prevalence of metabolic syndrome (MetS); **(B)** Prevalence of diabetes mellitus (Diabetes); **(C)** Prevalence of obesity; **(D)** Prevalence of hypertension; **(E)** Prevalence of low High-density lipoprotein (low-HDL-C); **(F)** Prevalence of triglycerides (TG). Adjusted for age, sex, race/ethnicity, education, annual family income, smoking status, alcohol intake, physical activity, thyroid problems, cancer, energy intake, fish or shellfish intake, sodium intake, eGFR (Glomerular filtration rate), TSH, and FT4.

However, some studies contradict our findings. Several clinical trials have reported a negative association between high UIC and dyslipidemia and MetS. According to the Riyadh Cohort Study (50) found that UIC was significantly lower in type 2 diabetic patients than in healthy controls. The survey, which Lee and his colleagues completed in 2016, confirmed that individuals in the lowest UIC 10th percentile had a higher probability of dyslipidemia than adults above the 10th percentile and that UIC was protective against low HDL-C in the United States (51). In a Chinese study on iodine and dyslipidemia in drinking water, HDL-C was found to be negatively correlated with iodine in water in the excess iodine group (52). Subsequently, the TIDE study (42) confirmed that a slightly higher UIC (300-399μg/L) had a protective effect on reducing MetS, which is inconsistent with our results. In our nationally representative epidemiological cross-sectional survey, we discovered that slightly higher UIC (≥ 300μg/L and < 400μg/L) was associated with higher levels of TG and a higher prevalence of MetS when compared to normal UIC. An animal test discovered that TG levels in male mice and TG levels in female mice in the excess iodine group were much lower than in the normal iodine group (53). A study (20) from Shanxi verified that excessive iodine intake may result in elevated blood glucose and blood pressure. Moreover, a Korean multi-rural community cohort study (47) found no significant relationship between dietary iodine, seaweed consumption, and waist circumference in postmenopausal women. In contrast, a review (54) reported that low UIC increased the prevalence of obesity. These differences can be explained by a variety of reasons. First, it is possible that the iodine was collected in different ways, for example,

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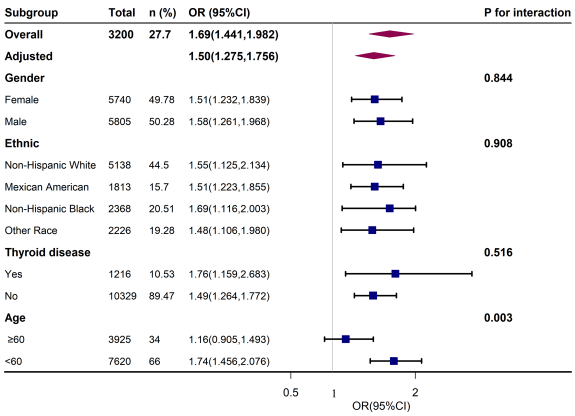

FIGURE 3
Association Between UIC (log10) and metabolic syndrome (MetS). Each stratification was adjusted for age, sex, race/ethnicity, education, annual family income, smoking status, alcohol intake, physical activity, thyroid problems, cancer, energy intake, fish or shellfish intake, sodium intake, eGFR (Glomerular filtration rate), TSH, and FT4.

some studies used on-site urine samples, others conducted 24-hour collections, and still, others used aqueous iodine concentrations; in addition, there were also subtle differences in the definitions of the studies' outcomes. Furthermore, differences in ethnicity, age, and national populations, as well as differences in salt intake, may also account for the disparities.

The physiopathological mechanisms and explanations of iodine and metabolic disorders are currently unclear and rare, but the following points may help to explain them. First, the potential effect of excess iodine on MetS and components may be due to the interaction of nutrients with thyroid hormones (55). Although iodine intake and status are not directly related to thyroid hormone levels, both severe iodine deficiency and severe iodine excess can lead to hypothyroidism (56). TSH has been found to be positively correlated with triglycerides (57) and the balance of insulin resistance (58). Second, chronic inflammatory states and oxidative stress appear to be central to the pathophysiology of MetS. Excess iodine puts cells in a state of high oxidative stress, which predisposes them to organ damage and is detrimental to disease recovery (59). Moreover, iodine functions as both a pro-oxidant and an antioxidant (60, 61), and it can balance oxidative homeostasis at the physiological and molecular levels of the cell (62). For example, iodine acts as a free radical and can prevent the reaction of iodinated tyrosine, histidine, and some polyunsaturated fatty acids from reacting with oxygen radical double bonds (63). As a result, thyroid function is limited when iodine is insufficient, thus reducing the rate of metabolism in order to reduce the risk of MetS and dyslipidemia. Similarly, when iodine is higher, thyroid hormones are produced more, leading to increased metabolism to further increase the risk of MetS and dyslipidemia. The association between excess UIC and reduced incidence of diabetes could be explained by the anti-inflammatory and antioxidant effects of iodine, as well as the decreased rate of liver glycogen synthesis due to excess iodine-induced hypothyroidism. Low urinary iodine may lead to decreased thyroid hormone levels, which in turn affect the function of the cardiovascular system and increase the incidence of hypertension. In addition, low urinary iodine may also affect kidney function, resulting in an imbalance of water and sodium balance in the body, which may also indirectly lead to the occurrence of high blood pressure. Thus, low UIC is associated with an increased risk of hypertension in participants with normal thyroid function. When iodine is deficient, insufficient thyroid hormone production reduces the body's demand for energy, which may influence participants' behavior, such as reducing energy intake, resulting in decreased fat synthesis, and thus reducing the incidence of obesity.

This study has several advantages. Firstly, this study includes data accumulated in the NHANES database, which covers states across the United States, visiting 15 of these counties each year. Therefore, the sample size was adequate. Secondly, we adjusted for diet, lifestyle habits, demographic information, thyroid medications, and thyroid disease in the full model. However, there are also some limitations in this study. Firstly, this is a cross-sectional survey, and the causal relationship between UIC and MetS and their components cannot be established. Secondly, we adjusted for as many potential confounders as possible, but it is still possible that some factors were not included. For example, seaweeds and sea vegetables are important sources of iodine. And iodine content is also reported to vary widely among seaweed species (64), which are rarely eaten in the United States, making estimates using NHANES data impractical. Therefore, we cannot exclude the effect of seaweed and seaweed on UIC. Thirdly, we excluded adolescents under the age of 18 and thus cannot represent the entire US population, but only US adults. We will further investigate this association in the future.

5 Conclusions

In conclusion, excess iodine is associated with lowered hyperglycemia. A slightly higher UIC is associated with increased MetS and TG. However, low iodine may be associated with a reduced prevalence of metabolic disorders and their associated diseases, including MetS, low HDL-C, TG, and central obesity. While

our study adds to the existing evidence on UIC and metabolic syndrome and its components, there has been little research on this relationship, which warrants further investigation by related studies.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://wwwn.cdc.gov/nchs/nhanes/search/default.aspx.

Ethics statement

This study was supported by the National Center for Health Statistics Research Ethics Review Board, and the ethics approval number is Continuation of Protocol #2005-06, Protocol #2011-17, Continuation of Protocol #2011-17, and Protocol #2018-01. You can find it at this website: https://www.cdc.gov/nchs/nhanes/irba98.htm. This study is an analysis of the publicly available NHANES data. Informed consent was obtained from NHANES participants by the National Center for Health Statistics Research Ethics Review Board.

Author contributions

XS and LY contributed to the conception and design, acquisition and drafting of the manuscript or critical revision for important intellectual content. Y-YL and X-HZ contributed to interpretation of the data and analysis. PC, J-FH and LJ contributed to the conception and design and reviewing of the manuscript or critical revision for important intellectual content. All authors approved the final version, and agree to be accountable for all aspects of the work.

Acknowledgments

We thank the researchers, staff, and participants of the National Health and Nutrition Examination Survey for their contributions to making this analysis possible.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1153462/full#supplementary-material

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frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 22 August 2023
DOI 10.3389/fendo.2023.1197628

OPEN ACCESS

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RECEIVED 31 March 2023
ACCEPTED 31 July 2023
PUBLISHED 22 August 2023

CITATION
Han F, Yu C, Hu F, Zhou W, Wang T, Zhu L, Huang X, Bao H and Cheng X (2023) Association between serum uric acid levels and peripheral artery disease in Chinese adults with hypertension.
Front. Endocrinol. 14:1197628.
doi: 10.3389/fendo.2023.1197628

Association between serum uric acid levels and peripheral artery disease in Chinese adults with hypertension

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Background: Higher serum uric acid (SUA) can cause gout, which is principally characterized by arthritis due to monosodium urate crystal deposition in the lower extremities. High levels of SUA have been linked to endothelial dysfunction, oxidative stress, and inflammation, all of which are involved in the pathogenesis of peripheral artery disease(PAD). To date, the relationship between SUA levels and PAD is still poorly understood.

Method: An analysis of 9,839 Chinese adults with essential hypertension from the ongoing China H-type Hypertension Registry Study was conducted in this cross-sectional study. Patients with an ABI ≤0.9 was diagnosed with PAD. Hyperuricemia was defined as SUA levels >420 mol/L in men and >360 mol/L in women. The association between SUA levels and PAD was evaluated using multivariable logistic regression models based on odds ratios (ORs) and their 95% confidence intervals (CIs).

Results: The enrolled subjects ranged in age from 27 to 93 years, with a mean age of 63.14 ± 8.99 years. The proportion of male patients was 46.22%, and the prevalence of hyperuricemia was 50.72%. In males, hyperuricemia was positively associated with the risk of PAD (adjusted OR per SD increase: 1.72, 95% CI 1.17 to 2.53, P =0.006). Males in the highest SUA tertile were significantly more likely to have PAD (adjusted OR: 2.63, 95% CI 1.42 to 4.86, P = 0.002; P for trend = 0.001). However, this positive relationship was not observed in females (adjusted OR: 1.29, 95% CI 0.77 to 2.17, P = 0.327; P for trend = 0.347).

Conclusion: According to this cross-sectional study, higher SUA levels were positively associated with PAD in male hypertensive patients, while this positive relationship disappeared in female participants.

KEYWORDS

serum uric acid, peripheral artery disease, hyperuricemia, hypertension, adult

Introduction

Peripheral artery disease (PAD) is a circulatory condition that affects the blood vessels outside of the heart and brain, most commonly in the legs. It occurs when the arteries that supply oxygen and nutrients to the muscles of the legs become narrowed or blocked by an accumulation of fatty deposits or plaque, a process called atherosclerosis. The reduced blood flow can cause symptoms such as claudication, ischemic rest pain, numbness, and cramping, which can interfere with mobility and reduce the quality of life. Besides, PAD can also cause sores or ulcers on the legs or even lead to tissue loss and amputation (1). The presence of PAD is usually diagnosed via ankle-brachial index (ABI), which is calculated by dividing the ankle systolic pressure by the brachial systolic pressure with a sphygmomanometer or ultrasound Doppler device. Previous studies showed that several cardiovascular events might be linked to PAD, including atrial fibrillation, acute myocardial infarction, stroke, and death (2–4). However, the perniciousness of PAD was underestimated on account of its asymptomatic manifestation in the early stage, and the biomarkers that may identify patients with new-onset PAD or individuals at higher risk of PAD are urgently needed (5).

The purine nucleotide cycle produces serum uric acid (SUA). Hyperuricemia (HUA), or elevated serum uric acid, is a metabolic disorder caused by purine metabolism disorders, excessive uric acid production, or reduced excretion (6).On this basis, HUA could further cause gout, which is principally characterized by arthritis due to monosodium urate crystal deposition in the lower extremities (7).

HUA has also been associated with subclinical atherosclerosis, markers of inflammation, oxidative stress, and endothelial dysfunction according to the current literature, all of which are involved in the pathogenesis of PAD (8). Numerous investigations have demonstrated that HUA is an independent risk factor for the occurrence and prevalence of several diseases, including diabetes, heart disease, hypertension, and chronic kidney disease (9–12). Therefore, HUA may contribute to the development or progression of PAD by promoting atherosclerosis, inflammation, and endothelial dysfunction, which are all key pathological mechanisms involved in the development of PAD. However, further research is needed to fully elucidate the possible association between HUA or elevated SUA and PAD.

To date, research on the relationship between PAD and SUA or community-based studies has been limited (13). Researchers found that HUA is an independent risk factor for carotid plaque in men without metabolic syndrome in a cross-sectional study (14). Yoko Sotoda et al. demonstrated that HUA was associated with leg ischemia in patients with PAD, independent of other atherosclerotic risk factors (15). However, most of this research aimed to investigate the relationship between PAD and SUA in a common population. To explore the relationship between SUA and PAD in hypertensive patients, we conducted this real-world, multi-center, observational study in South China in March 2018.

Methods

Study design and participants

This study utilized the baseline data from the China H-type Hypertension Registry Study (Registration number: ChiCTR1800017274), which was a prospective, real-world, and observational study. Data collection methods and exclusion criteria have been described previously (16). A protocol for the study was approved by the Ethics Committee of the Institute of Biomedicine, Anhui Medical University (No. CH1059), in accordance with the Declaration of Helsinki. Forms of informed consent were completed by all participants before enrollment.

A total of 10, 923 participants completed the ankle brachial index (ABI) measurement in this study. After excluding 17 individuals without hypertension, 6 cases without serum uric acid data, 1,056 cases with eGFR ≤ 60 ml/min/1.73m^2, and 5 individuals with ABI >1.4 (17, 18), finally 9, 839 participants were enrolled in our analysis (Figure 1).

Data collection and indexes determination

In this study, researchers utilized carefully compiled questionnaires to collect data on a variety of participant characteristics, including demographic information such as age and gender, lifestyle habits like smoking and drinking, medical history (atrial fibrillation, hypertension, diabetes mellitus, and dyslipidemia), as well as medication use including antihypertensive, hypoglycemic, lipid-lowering, and antiplatelet agents. Current smokers were defined as participants who smoked at least 20 packets of cigarettes in their lifetime and currently smoke cigarettes. Former smokers were participants who had smoked at least 20 packets of cigarettes in their lifetime, and quit smoking for at least 1 month. A drinker was defined as someone who has consumed at least one alcoholic beverage per week in the past month (19).

Additionally, we collected participants' anthropometric measurements, including weight, height, waist circumference, hip circumference, systolic blood pressure (SBP), diastolic blood (DBP), and heart rate (HR), as well as their height and waist circumference measurements. A validated upper arm medical electronic sphygmomanometer (HBP-1300; Omron; Kyoto, Japan) was utilized with the appropriate cuff size for the upper right arm to measure blood pressure. For each participant, four consecutive office blood pressure measurements were performed, and the mean of the last three readings was analyzed. A 1.5-m-long inelastic measuring tape with 0.1 cm resolution was used to measure waist circumference and hip circumference. Body weight without heavy clothing was measured using a body fat and weight measurement device (V-body HBF-371, Omron; Kyoto, Japan). BMI was calculated by multiplying weight (in kilograms) by height (in meters squared: kg/m2). The waist-hip ratio (WHR) was calculated by dividing the waist circumference by the hip circumference. The mean values of the last three readings were analyzed.

Participants were classified into three groups based on their BMI values: underweight (<24 kg/m2), overweight (24-28 kg/m2),

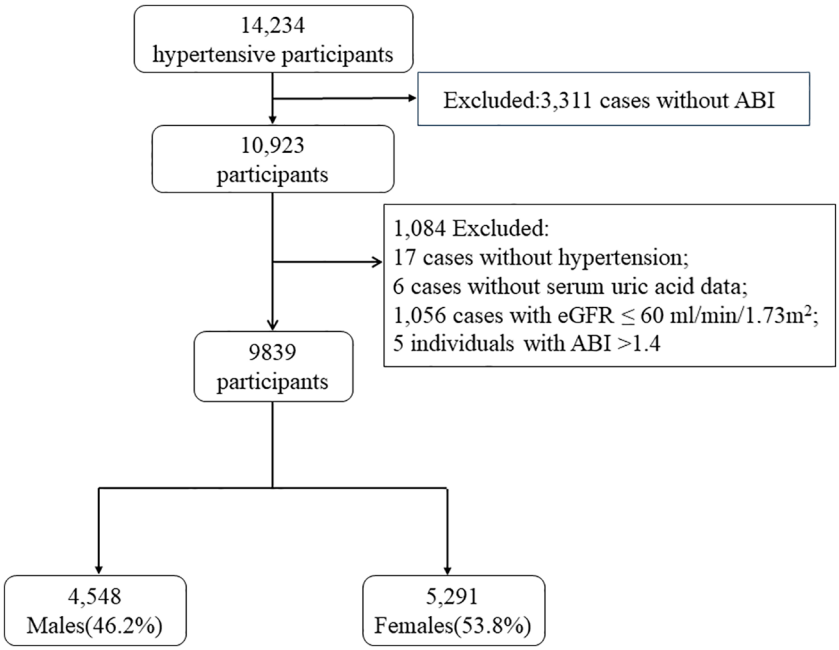

FIGURE 1
Flow chart of the study population. ABI, ankle brachial index; PAD, peripheral arterial disease; SUA, serum uric acid; eGFR, estimated glomerular filtration rate.

and obese (≥28 kg/m2), using published standards for the Chinese population. Central obesity was defined as male participants with a WHR of ≥0.9 or female participants with a WHR of ≥0.85 (20).

After an overnight fast of at least 12 hours, blood samples were collected by venipuncture. Blood biochemical tests for plasma total homocysteine (tHcy), fasting blood glucose (FBG), total cholesterol (TC), total triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), SUA, serum creatinine, blood urea nitrogen (BUN), total and direct bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were measured using automatic clinical analyzers (Beckman Coulter) at the core laboratory of the National Clinical Research Center for Kidney Disease, Guangzhou, China. In our study, DM was defined as FBG levels above 7.0 mmol/L or treatment for diagnosed DM (21). Dyslipidemia was defined as having TG >2.3 mmol/L, TC >6.2 mmol/L, LDL >4.1 mmol/L, HDL <1.0 mmol/L in men and <1.2mmol/L in women (22), or being treated with appropriate lipid-lowering agents. HUA was defined as SUA levels >420 mol/L in men and >360 mol/L in women by most studies among Chinese populations (23, 24). In some studies, HUA was designated with lower cutoff points (25, 26).CKD-EPI's (Chronic Kidney Disease Epidemiology Collaboration) equation was used to estimate glomerular filtration rate (eGFR) (27).

Measurement of ABI and definition of PAD

The ABI was performed using a BP-203 RPE III networked arteriosclerosis detection device (VP-2000, Omron Health Care, Kyoto, Japan) following the guidelines recommended by the American College of Cardiology/American Heart Association (28). Participants rested in a quiet room for at least five minutes in a supine position before undergoing ABI measurements. Consumption of coffee, tea, cigarettes, or alcohol was prohibited for 30 minutes prior to the test. Electrodes were attached to the participant's forearms to measure an electrocardiogram (ECG). Both arms (brachial artery) and ankles (posterior tibial artery) were fitted with a blood pressure cuff and a Doppler ultrasound device. The ABI was measured for a period of 10-30 seconds, and the lowest ABI value between right and left was used as a normality parameter. Patients with an ABI ≤0.9 was diagnosed as PAD (17, 18, 28–30). Patients with diabetes and/or advanced chronic kidney disease are more likely to have ABI values >1.40, indicating that the arteries cannot be compressed. Only five patients with ABI values higher than 1.4 were excluded at the entrance.

Statistical analysis

The clinical characteristics of participants were determined based on their baseline SUA levels. A continuous variable was expressed as its mean ± standard deviation (SD) or median (Q1-Q3). In both groups, variables with normal distributions and homoscedasticity were analyzed using a one-way analysis of variance. The Kruskal-Wallis test was performed on variables that showed skewed distribution. A chi-square or Fisher's exact probability test was used to compare groups based on categorical variables expressed as counts (percentages).

The association between SUA levels and PAD was evaluated using multivariable logistic regression models based on odds ratios (ORs) and their 95% confidence intervals (CIs). Covariates were not taken into account in the crude model. Age was the only adjustment

made to Model I. Model II was a covariate model. The covariate model screened for covariates including age, SBP, DBP, BMI, smoking and drinking status, homocysteine, TC, TG, HDL-C, LDL-C, AST, ALT, serum creatinine, DM, antihypertensive agents, lipid-lowering agents, and antiplatelet agents. Supplementary Table 1 showed the associations of each covariate with PAD. Covariates were the main model. Subjects were categorized into SUA tertiles, and SUA predictive capacity was explored for SUA, with either considered as a continuous or a categorical variable.

Finally, to ensure the robustness between SUA levels and PAD in different genders, the subgroup analysis was presented in tabular form with a forest plot using stratified multivariate regression and interaction analyses.

The statistical package R (The R Foundation; http://www.r-project.org; version 4.2.0) was used to perform all statistical analyses and EmpowerStats (R; www.empowerstats.com; X&Y Solutions, Inc, Boston, MA, USA; version 4.2). Statistical significance was denoted by a P value of <0.05, and each P value is two-tailed.

Results

Characteristics of the population studied

This study enrolled 9,839 Chinese adults with hypertension, with ages ranging from 27 to 93 years and a mean age of 63.14 ± 8.99. Table 1 presents the clinical characteristics of the study participants, grouped by HUAAs the schematics revealed, the proportion of male participants was 46.22%, and the prevalence of HUA was 50.72%.

Study participants were grouped by sex and their clinical characteristics are summarized in Supplementary Table 2. The overall prevalence of PAD was 2.67%, with male participants exhibiting a higher proportion (3.17%) than female participants (2.25%). The proportion of HUA was higher in male (56.82%) than in female participants (45.47%). Furthermore, as shown in Supplementary Table 2, we found significant differences between male and female participants with regard to current smoking (50.53% vs. 5.43%) and drinking habits (43.68% vs. 6.03%). No significant difference was observed in medication use, including antihypertensive agents and lipid-lowering agents, between the two genders. Supplementary Table 2 also illustrates that women had a higher use rate of hypoglycemic agents (5.44%) compared to men (4.27%), while men had a higher use rate of antiplatelet agents (4.20%) compared to women (3.35%), with statistical significance (P = 0.007 and P = 0.026, respectively). Specifically, male patients exhibited a higher likelihood of having elevated levels of DBP, WHR, Hcy, SUA, BUN, serum creatinine, eGFR, total and direct bilirubin, AST, ALT, and ABI. Conversely, female patients exhibited lower levels of SBP, BMI, FBG, TC, TG, HDL-C, and LDL-C.

Association between SUA levels and PAD in the hypertensive population

To assess the association between SUA levels and PAD, multivariable logistic regression was conducted after adjusting for covariates that could impact the outcome by more than 10%. Results showed no significant association between SUA levels and PAD risk when SUA was analyzed as a continuous variable in the whole sample (adjusted OR per SD increase: 1.00, 95% CI 1.00 to 1.00, P = 0.055; Supplementary Table 3).

Multivariable logistic regression analyses were then performed separately for male and female particiants. There was no significant association between SUA levels and PAD risk when SUA levels were viewed as continuous variables in both men (adjusted OR per SD increase: 1.19, 95% CI 0.98 to 1.45, P = 0.087; Table 2) and women (adjusted OR per SD increase: 1.15, 95% CI 0.91 to 1.46, P = 0.232; Table 2). Furthermore, multivariable logistic regression analyses were conducted to examine the relationship between PAD and hyperuricemia, which was defined as SUA > 420 μmol/L in men and > 360 μmol/L in women. A positive association was found between hyperuricemia and PAD risk in men (adjusted OR per SD increase: 1.72, 95% CI 1.17 to 2.53, P = 0.006; Table 2). However, when HUA was defined as SUA > 5.1 mg/dL for female and 5.6 mg/dL for male participants, we did not observe a significant relationship between HUA and PAD in the overall population (adjusted OR per SD increase:1.30, 95% CI: 0.91 to 1.87, p = 0.147, Supplementary Table 4). This lack of association was consistent when analyzing male participants separately (adjusted OR per SD increase: 1.78, 95% CI: 0.97 to 3.25, p = 0.062; Supplementary Table 5) and female participants separately (adjusted OR per SD increase: 1.00, 95% CI: 0.63 to 1.60, p = 0.991; Supplementary Table 5). The highest SUA tertile was associated with a significantly higher prevalence of PAD compared to the lowest tertile in men (adjusted OR: 2.63, 95% CI 1.42 to 4.86, P = 0.002; P for trend = 0.001). However, this relationship was not significant in women (adjusted OR: 1.29, 95% CI: 0.77 to 2.17, P = 0.327; P for trend = 0.347).

Subgroup analyses by potential effect modifiers

To explore whether the association between SUA levels and the prevalence of PAD was still stable in different subgroups, subgroup analysis was presented in tabular form with a forest plot using stratified multivariate regression and interaction analyses.

In any subgroup of male patients, there were no statistically significant interactions, including age (<60 vs. ≥60 years), SBP dichotomy (≤146.67 vs. ≥ 147.00 mmHg), DBP dichotomy (≤89.33 vs. ≥89.67 mmHg), different BMI group, smoking habit (no vs. yes), drinking habit (no vs. yes), antihypertensive agents (no vs. yes), homocysteine (<15 vs. ≥15 μmol/L), LDL dichotomy (< 2.93 vs. ≥2.94 mmol/L), and serum creatinine (≤62.0 vs. ≥63.0 mmol/L) (all P for interactions >0.05; Supplementary Figure 1).

Based on the subgroup analysis, none of the subgroups had statistically significant interactions for females, including age (<60 vs. ≥60 years), the SBP dichotomy (≤146.67 vs. ≥ 147.00 mmHg), the DBP dichotomy (≤89.33 vs. ≥89.67 mmHg), different BMI group, antihypertensive agents (no vs. yes), antiplatelet agents (no vs. yes), homocysteine (<15 vs. ≥15 μmol/L), LDL dichotomy (< 2.94 vs. ≥2.94 mmol/L), and AST dichotomy (≤23.00 vs. ≥24.00 U/L) (all P for interactions >0.05; Supplementary Figure 2).

10.3389/fendo.2023.1197628

TABLE 1 Clinical characteristics of the study population grouped by HUA.

Characteristics	Total subjects	HUA		*P-value*
		No	Yes	
Number of subjects (n)	9839	4849 (49.28%)	4990 (50.72%)	
Gender (n)				<0.001
Male	4548	1964 (40.50%)	2584 (51.78%)	
Female	5291	2885 (59.50%)	2406 (48.22%)	
Age (years)	63.14 ± 8.99	63.19 ± 8.85	63.09 ± 9.12	0.58
SBP (mmHg)	148.46 ± 17.56	149.31 ± 17.43	147.63 ± 17.64	<0.001
DBP (mmHg)	89.38 ± 10.55	89.06 ± 10.38	89.69 ± 10.72	0.003
HR (times/min)	76.31 ± 13.99	76.46 ± 14.28	76.16 ± 13.70	0.282
BMI (kg/m^2)	23.16 ± 4.02	23.16 ± 4.02	24.14 ± 3.60	<0.001
BMI group (kg/m^2)				<0.001
Control (<24)	5517 (56.07%)	3041 (62.71%)	2476 (49.62%)	
Overweight (≥24, <28)	3304 (33.58%)	1447 (29.84%)	1857 (37.21%)	
General obesity (≥28)	1018 (10.35%)	361 (7.44%)	657 (13.17%)	
WHR	0.91 ± 0.18	0.90 ± 0.25	0.92 ± 0.07	<0.001
Smoking status, n(%)				<0.001
Never	5743 (58.38%)	3019 (62.26%)	2724 (54.60%)	
Former	1510 (15.35%)	643 (13.26%)	867 (17.38%)	
Current	2585 (26.28%)	1187 (24.48%)	1398 (28.02%)	
Drinking status, n(%)				<0.001
Never	6135 (62.37%)	3203 (66.07%)	2932 (58.77%)	
Former	1397 (14.20%)	730 (15.06%)	667 (13.37%)	
Current	2305 (23.43%)	915 (18.87%)	1390 (27.86%)	
Hcy (μmol/L)	17.19 ± 10.17	16.20 ± 9.45	18.15 ± 10.74	<0.001
TC (mmol/L)	5.16 ± 1.10	5.06 ± 1.05	5.26 ± 1.13	<0.001
TG (mmol/L)	1.78 ± 1.25	1.57 ± 1.01	1.99 ± 1.42	<0.001
HDL-C (mmol/L)	1.60 ± 0.43	1.62 ± 0.44	1.57 ± 0.43	<0.001
LDL-C (mmol/L)	3.00 ± 0.80	2.92 ± 0.78	3.08 ± 0.82	<0.001
SUA (umol/L)	402.79 ± 113.72	316.48 ± 57.36	486.67 ± 89.59	<0.001
HUA, n(%)	4990 (50.72%)	2584 (56.82%)	2406 (45.47%)	<0.001
BUN (mmol/L)	5.25 ± 1.46	5.13 ± 1.41	5.36 ± 1.50	<0.001
Serum creatinine (mmol/L)	64.12 ± 17.23	58.30 ± 15.70	69.78 ± 16.76	<0.001
eGFR (ml/min/1.73m^2)	93.37 ± 14.59	97.62 ± 13.57	89.25 ± 14.37	<0.001
Total bilirubin (mmol/L)	14.82 ± 6.94	14.48 ± 7.18	15.14 ± 6.69	<0.001
Direct bilirubin (mmol/L)	5.66 ± 2.71	5.64 ± 3.16	5.69 ± 2.18	0.388
AST (U/L)	26.80 ± 16.91	25.26 ± 19.22	28.30 ± 14.14	<0.001
ALT (U/L)	20.62 ± 17.10	18.61 ± 18.56	22.58 ± 15.29	<0.001
DM, n(%)	1723 (17.51%)	764 (15.76%)	959 (19.22%)	<0.001
Dyslipidemia, n(%)	3598 (36.57%)	1456 (30.03%)	2142 (42.93%)	<0.001

(Continued)

TABLE 1 Continued

Characteristics	Total subjects	HUA		*P-value*
		No	Yes	
Atrial fibrillation, n(%)	252 (2.56%)	100 (2.06%)	152 (3.05%)	0.002
Antihypertensive agents, n(%)	6338 (64.42%)	3046 (62.82%)	3292 (65.99%)	0.001
Hypoglycemic agents, n(%)	482 (4.90%)	245 (5.05%)	237 (4.75%)	0.486
Lipid-lowering agents, n(%)	324 (3.29%)	167 (3.44%)	157 (3.15%)	0.408
Antiplatelet agents, n(%)	368 (3.74%)	181 (3.73%)	187 (3.75%)	0.969
Ankle brachial index	1.09 ± 0.09	1.09 ± 0.09	1.10 ± 0.10	0.032
PAD, n(%)	263 (2.67%)	109 (2.25%)	154 (3.09%)	0.01

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; BMI, body mass index; WHR, waist hip rate; Hcy, homocysteine; FBG, fasting blood glucose; TC, total cholesterol; TG, total triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SUA, serum uric acid; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; DM, diabetes mellitus; PAD, peripheral arterial disease.

TABLE 2 Hazard ratios of serum uric acid level categories for PAD by sex in different models.

Variables	Event, n(%)	Crude Model		Model I		Model II	
		HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value
Male							
SUA							
Per SD μmol/L increase	144 (3.17%)	1.06 (0.90, 1.25)	0.502	1.13 (0.95, 1.34)	0.171	1.19 (0.98, 1.45)	0.087[a]
HUA							
No	51 (2.60%)	*Ref*		*Ref*		*Ref*	
Yes	93 (3.60%)	1.40 (0.99, 1.98)	0.057	1.54 (1.09, 2.19)	0.016	1.72 (1.17, 2.53)	0.006[a]
Tertiles of SUA							
T1 [38.00, 344.00]	15 (2.07%)	*Ref*		Ref		Ref	
T2 [345.00, 439.00]	45 (2.87%)	1.40 (0.77, 2.52)	0.267	1.42 (0.78, 2.58)	0.245	1.65 (0.89, 3.05)	0.114[a]
T3 [440.00, 1056.00]	84 (3.73%)	1.83 (1.05, 3.19)	0.033	2.05 (1.17, 3.59)	0.012	2.63 (1.42, 4.86)	0.002[a]
P for trend		0.019		0.004		0.001	
Female							
SUA							
Per SD μmol/L increase	119 (2.25%)	1.26 (1.03, 1.53)	0.022	1.23 (1.01, 1.51)	0.041	1.15 (0.91, 1.46)	0.232[b]
HUA							
No	58 (2.01%)	*Ref*		*Ref*		*Ref*	
Yes	61 (2.54%)	1.27 (0.88, 1.82)	0.201	1.20 (0.83, 1.73)	0.323	1.03 (0.69, 1.55)	0.881[c]
Tertiles of SUA							
T1 [108.00, 344.00]	49 (1.93%)	*Ref*		*Ref*		*Ref*	
T2 [345.00, 439.00]	39 (2.26%)	1.17 (0.77, 1.79)	0.461	1.10 (0.72, 1.69)	0.653	0.97 (0.62, 1.52)	0.892[d]
T3 [440.00, 879.00]	31 (3.00%)	1.57 (0.99, 2.47)	0.054	1.49 (0.94, 2.35)	0.088	1.29 (0.77, 2.17)	0.327[d]
P for trend		0.056		0.096		0.347	

PAD, peripheral arterial disease; SUA, serum uric acid; HUA, hyperuricemia; Ref, reference; HR, hazard ratio; CI, confidence interval; SD, standard deviation.
Model I adjusted for age.
Model II: a.adjusted for age, SBP, DBP, BMI, smoking and drinking status, Hcy, TG, LDL-C, serum creatinine, ALT, AST, antihypertensive agents, and antiplatelet agents.
b.adjusted for age, SBP, DBP, BMI, Hcy, TG, LDL-C, serum creatinine, and antiplatelet agents.
c.adjusted for age, SBP, DBP, BMI, Hcy, TG, HDL-C, LDL-C, serum creatinine, ALT, AST, antihypertensive agents, lipid-lowering agents, and antiplatelet agents.
d.adjusted for age, SBP, DBP, BMI, Hcy, TG, HDL-C, LDL-C, serum creatinine, ALT, AST, and antihypertensive agents.

Discussion

This study investigated the association between PAD and SUA levels in hypertensive patients in South China. Higher levels of SUA might be positively associated with PAD after being adjusted for major cardiovascular risk factors in male patients with hypertension.

Numerous investigations have delved into the conceivable correlation between SUA levels and PAD. However, the outcomes have been inconsistent due to variations in the populations studied (31–34). The data regarding whether this connection is restricted to gender (male or female) or affects both remains inconclusive. Some research supported the results of our study. A cohort study scrutinized serum and 24-hour SUA levels and additional risk factors among two groups of hypertensive patients: 145 lacking PAD and 166 with PAD (35). This paper revealed that, in essential hypertensive patients, a higher level of SUA values was associated with worse peripheral circulatory function and was more pronounced in those with PAD. In 2008, Shankar Anoop and colleagues demonstrated a noteworthy correlation between SUA levels and PAD in both genders in a nationally representative sample of the US population (13). Furthermore, there was evidence suggesting that an association between SUA levels and atherosclerosis was plausible (36, 37). A cross-sectional study corroborated that higher SUA levels might be positively associated with leg ischemia in male patients with PAD (15). However, the small sample size of only 87 male participants at enrollment precludes definitive conclusions concerning any gender differences in the relationship between SUA and PAD. Dong Jing et al. discovered that elevated SUA was an independent risk factor for developing new onset hypertension in a cohort, single-center study (38). Combined with the conclusion of this analysis, it is hypothesized that the relationship between SUA and PAD is mediated by hypertension.

Several prior experimental studies have investigated the mechanisms by which elevated SUA levels are associated with hypertension, stroke, atrial fibrillation, and other cardiovascular diseases (7, 38–41). SUA is directly or circumstantially associated with inflammation, arterial stiffness, renal function decline, smooth muscle proliferation, and endothelial dysfunction. These inflammatory mediators also play a critical role in peripheral vasculature (42, 43). SUA has been reported to engulf smooth muscle proliferation through NLRP3 (Nod-like receptor family protein 3) (44, 45). Furthermore, SUA restrained the activity and phosphorylation of AMPK(AMP-activated protein kinase). A decrease in AMPK led to the activation of NLRP3 inflammasomes (36). Then the activation of NLRP3 further led to an increase of inflammatory markers such as interleukin-1 and interleukin-18. HUA activated the renin-angiotensin system, reduced endothelial nitric oxide bioavailability, simulated oxidative stress, and enhanced arterial stiffness (45, 46). A recent experiment declared that SUA might induce an increase in the Tissure Factor, which was the key initiator of the coagulation cascade (47). Nevertheless, the pathological mechanisms underlying the association between SUA levels and PAD remain incompletely elucidated to date. One potential explanation for this association is the influence of metabolic syndrome (48). Previous studies have discovered that higher SUA levels are strongly associated with metabolic syndrome, and HUA has been identified as a contributing risk factor within the context of multifactorial syndrome (49, 50). It is plausible that elevated uric acid levels represent a compensatory response to oxidative stress, as supported by previous research findings (51).

The main strength of our current study is that we collected a representative sample from southern China. This is the first study to elucidate the relationship between SUA and PAD in hypertensive patients in South China. To enhance the dependability of our study, subgroup analyses were conducted in addition to examining the overall relationship between SUA and PAD.

This study had some limitations that need to be further explained. First, given the cross-sectional nature of our study, we could not draw definitive conclusions about the causal relationship between SUA and PAD. Second, the limited scope of our study's population, which was confined to South China, may restrict the generalizability of our findings. Last but not least, the history of some therapies, such as revascularization (52), the treatment with diuretics (31), and uric acid-lowering drugs, was not captured at enrollment, which might be covariates in the multivariable logistic regression. Given the present limitations, caution should be exercised in interpreting the findings of this cross-sectional study.

Conclusion

In conclusion, higher SUA levels were positively associated with PAD in male hypertensive patients. We ascertained that elevated SUA levels were positively associated with an increased risk of PAD in the male hypertensives in this cross-sectional study. However, this positive correlation was not present in female patients with hypertension. Based on this cross-sectional study, further longitudinal, perspective, or multi-central studies are needed to determine the chronological or causal relationship between SUA and PAD in a hypertensive population.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material. Further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Institute of Biomedicine, Anhui Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

FYH designed and executed the experiments, performed data analysis, and wrote the initial draft of the manuscript. CY designed and conducted the experiments, analyzed the data, and wrote the majority of the Methods section, and provided critical feedback and revisions throughout the writing process. XH, WZ, TW, and LZ conducted literature review, contributed to the manuscript's organization, and provided editorial assistance. FH provided technical support for data analysis and critically reviewed the manuscript. HB and XC conceptualized the study, secured funding, and oversaw all aspects of the project. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the Cultivation of backup projects for the National Science and Technology Awards (20223AEI91007), Jiangxi Science and Technology Innovation Base Plan - Jiangxi Clinical Medical Research Center (20223BCG74012), and the Science and Technology Innovation Base Construction Project (20221ZDG02010). It was a Jiangxi Science and Technology Innovation Platform Project (20165BCD41005) and also supported by the Jiangxi Provincial Natural Science Foundation (20212ACB206019, 20224BAB206090), Key R&D Projects, Jiangxi (20203BBGL73173), Jiangxi Provincial Health Commission Science and Technology Project (202130440,202210495,202310528), Jiangxi Provincial Drug Administration Science and Technology Project (2022JS41), and was a Fund project of the Second Affiliated Hospital of Nanchang University (2016YNQN12034, 2019YNLZ12010, 2021efyA01, 2021YNFY2024).

Acknowledgments

The authors acknowledge the contribution of all the staff who participated in this study as well as the study participants who shared their time with us.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1197628/full#supplementary-material

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frontiers | Frontiers in Endocrinology

TYPE Original Research
PUBLISHED 23 August 2023
DOI 10.3389/fendo.2023.1195888

OPEN ACCESS

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RECEIVED 29 March 2023
ACCEPTED 13 July 2023
PUBLISHED 23 August 2023

CITATION
Kang HS, Lee N-E, Yoo DM, Han KM, Hong JY, Choi HG, Lim H, Kim J-H, Kim JH, Cho S-J, Nam ES, Park HY, Kim NY, Baek SU, Lee JY and Kwon MJ (2023) An elevated likelihood of stroke, ischemic heart disease, or heart failure in individuals with gout: a longitudinal follow-up study utilizing the National Health Information database in Korea. *Front. Endocrinol.* 14:1195888. doi: 10.3389/fendo.2023.1195888

An elevated likelihood of stroke, ischemic heart disease, or heart failure in individuals with gout: a longitudinal follow-up study utilizing the National Health Information database in Korea

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Objective: Accumulating evidence from other countries indicates potential associations between gout and cardiovascular diseases; however, the associations of gout with cardiovascular diseases, particularly stroke, ischemic heart disease, and heart failure, remain ambiguous in the Korean population. We hypothesized that individuals with gout are at a higher likelihood of stroke, ischemic heart disease, or heart failure. This study expands upon previous research by ensuring a comparable baseline between patient and control groups and analyzing 16 years of data derived from an extensive healthcare database.

Methods: We selected 22,480 patients with gout and 22,480 control individuals from the Korean National Health Insurance Service-Health Screening Cohort database (2002–2019), and matched them at a 1:1 ratio according to sex, age, income, and residence. A Cox proportional hazard model with weighted overlap was employed to examine the relationship between gout and the risk of stroke, ischemic heart disease, or heart failure after adjustment for several covariates.

Results: The incidences of stroke, ischemic heart disease, or heart failure in participants with gout were slightly higher than those in controls (stroke: 9.84 vs. 8.41 per 1000 person-years; ischemic heart disease: 9.77 vs. 7.15 per 1000 person-years; heart failure: 2.47 vs. 1.46 per 1000 person-years). After adjustment, the gout group had an 11% (95% confidence interval [CI] = 1.04–1.19), 28% (95% CI = 1.19–1.37), or 64% (95% CI = 1.41–1.91) higher likelihood of experiencing stroke, ischemic heart disease, or heart failure, respectively, than the control group.

Conclusion: The present findings suggest that individuals with gout in the Korean population, particularly those aged ≥ 60 years, were more likely to have stroke, ischemic heart disease, or heart failure.

KEYWORDS

gout, stroke, ischemic heart disease, heart failure, cardiovascular diseases, longitudinal follow-up study, nationwide health insurance research database

Introduction

Gout, a serious systemic and metabolic disorder causing joint inflammation, has been demonstrated to be associated with high uric acid levels (1). The accumulation of monosodium urate crystals in the joints could contribute to the development of comorbidities, such as obesity, insulin resistance, hypertension, kidney problems, and hyperlipidemia (1, 2). Gout is more prevalent in males than in females; the overall prevalence is 2.9–4.5 and peaks in individuals aged ≥ 80 years (3, 4). In recent years, the prevalence of gout has increased worldwide owing to an aging population, obesity, and metabolic diseases (5, 6). The prevalence rate of gout increased 5.15-fold from 0.39% in 2002 to 2.01% in 2015 in Korea, which resulted in a yearly average rise of 10.8% in health insurance costs related to gout (7). This is a larger increase compared with that in other countries; the prevalence of gout in the UK, USA, and Taiwan increased 1.64-times between 1997 and 2012 (5), 1.4-fold between 1988–1994 and 2007–2008 (3), and 1.12-fold between 2005 and 2010, respectively (4, 8). Owing to the increasing elderly population and lifestyle changes that have occurred in recent years, gout and its related problems have emerged as a noteworthy health concern in Korea (7).

Cardiovascular diseases (CVDs) are the principal source of mortality globally, representing approximately one-third of all fatalities (9). Particularly, CVDs are the main cause of death in East Asian countries, such as Taiwan, Singapore, Japan, and Korea, behind cancer (9). In Korea, a majority (70%), a large proportion (41%), and nearly a fifth (19%) of the adults have at least one, two or more, and three or more risk factors for CVDs, respectively, such as hypertension, diabetes, hypercholesterolemia, obesity, and smoking (10). Findings from recent experimental and epidemiologic studies suggest an elevated risk of CVDs associated with gout (11–13), which has drawn particular attention. The breakdown of purines yields serum uric acid, resulting in an inflammatory state and heightened risk of CVDs (14–16). Inflammation caused by monosodium urate crystals could potentially activate inflammasome pathways, cause gout attacks in joints, and result in deposits of coronary plaques, thereby contributing to the excessive cardiovascular risk in gout (17, 18), similar to the mechanism of action of cholesterol crystals (19). In addition, research has identified a correlation between gout and an increased probability of myocardial infarction (20, 21), stroke (22, 23), and atrial fibrillation (24), all of which are part of the broader category of cardiac conditions (25, 26). A cohort study revealed that gout was associated with a 1.49-fold greater risk of overall CVDs (95% confidence interval [CI]=1.44–1.53), without considering potential confounding factors, such as lifestyle, body mass index (BMI), alcohol intake, and smoking (11). Moreover, a meta-analysis has demonstrated an association of uric acid-lowering agents with decreased risk of myocardial infarction (27). Since the elderly have more comorbidities, such as CVDs and metabolic diseases, the effects of these systemic disorders on CVDs are anticipated to become more prominent (1). Indeed, these CVDs caused by gout have emerged as a major public health concern, which needs to be urgently addressed to reach the health goal of disease prevention.

The incidence and mortality rates of stroke have decreased, while the mortality and hospitalization rates of heart failure and ischemic heart disease have increased in Korea (9). The trends may vary depending on the type of CVDs and gout (9). Nevertheless, few studies have investigated the potential relationship between gout and stroke, ischemic heart disease, or heart failure in the Korean population. Moreover, merely one study has explored uric acid-lowering agent-associated abnormalities in different CVDs, and the findings are conflicting (28). Examining the effect of gout on each CVD is essential since CVDs are a varied group of diseases with diverse causes but similar vascular risks (25). Therefore, additional studies considering the potential mutual confounding factors are necessary.

We hypothesized that individuals with gout might be more likely to have stroke, ischemic heart disease, and heart failure. This study builds on earlier work (28) by carefully balancing the baseline

characteristics between the patient and control cohorts and examining 16 years of data compiled from a comprehensive healthcare database.

Materials and methods

Study population and participant selection

This study was approved by the ethics committee of Hallym University (2019-10-023), and the need for written informed consent was waived by the Institutional Review Board. All the analyses were performed in accordance with the rules and regulations of the ethics committee of Hallym University.

The Korean National Health Insurance Service-Health Screening Cohort (KNHIS-HSC) database provides Korean population-based and longitudinal information for research needs, which is selected in an arbitrary manner (29, 30). Since 1999, the KNHIS has been providing obligatory health insurance to nearly all Koreans. The KNHIS-HSC comprises anonymous and de-identified data and information. The diagnostic codes used in the KNHIS-HSC are based on the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM).

This longitudinal follow-up study retrospectively examined a gout group and a control group without a history of gout to determine the effect of gout on the probability of experiencing a stroke, ischemic heart disease, or heart failure. Participants with ICD-10 code M10 (gout) were identified from a total of 514,866 participants aged ≥ 40 years with 895,300,177 medical claim codes who had at least two clinic visits from 2002 to 2019 (n=27,313). To select participants who were diagnosed with gout for the first time, those who were diagnosed with osteoporosis in 2002 (1-year washout period, n=2470), did not have any documents of blood pressure level (n=1), or were diagnosed with stroke, ischemic heart disease, or heart failure before their gout diagnosis (n=2362) were all excluded.

Participants in the control group (n=487,553) did not match those in the gout group from 2002 to 2019, and 13,809 individuals with ICD-10 code M10 (gout) were excluded from the control group.

Matching was performed using a 1:1 ratio in terms of sex, age, economic status, and residence region to reduce variations in the basic demographic and medical characteristics between gout and comparison groups. To avoid selection bias, individuals without gout were randomly selected in numerical order. The index date for each participant with gout was the day when her/his gout diagnosis (M10) was initially logged in the medical insurance database. The index date for a control participant was the same as that for the matched participant with gout. All the participants in the comparison groups who died or had cardiovascular diseases before the index date were excluded. In total, 451,264 control participants were eliminated in the matching process. Finally, 22,480 participants with gout were paired with 22,480 control participants (Figure 1).

We examined the number of fresh diagnoses for stroke, ischemic heart disease, and heart failure based on ICD-10 labels in both gout and comparison groups from the index date to the end of 2019.

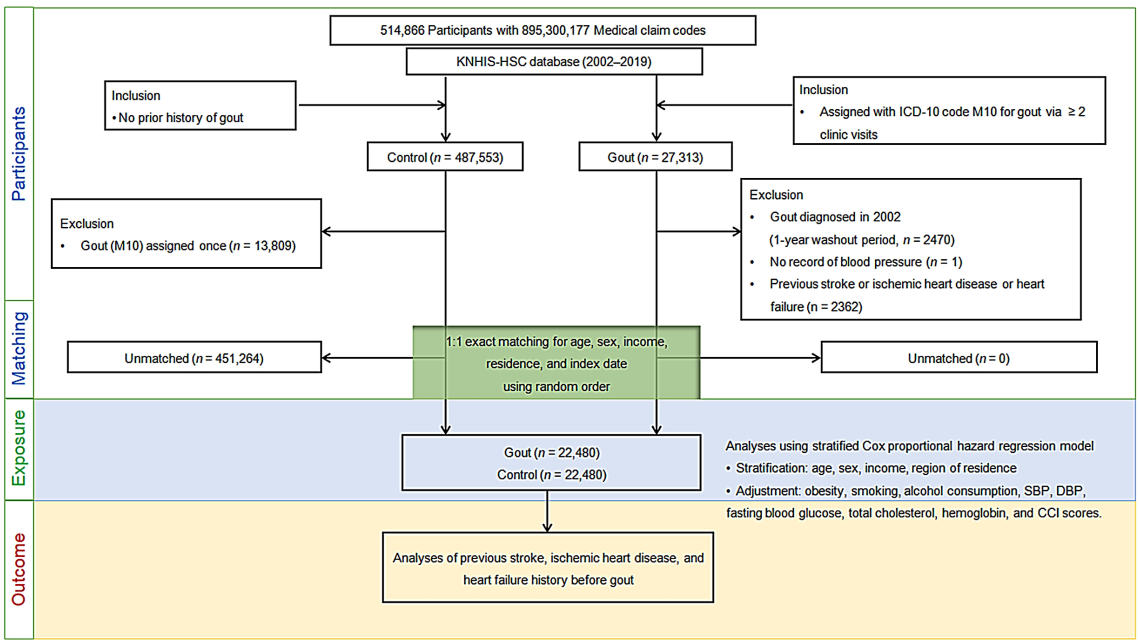

FIGURE 1
Flow of participant selection. Of the total 514,866 participants, 22,480 individuals with gout were paired with age, sex, financial status, and residential area-matched 22,480 controls. ICD-10, International classification of disease-10; CCI, Charlson comorbidity index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure.

Definition of gout

The study specified gout as a condition that had been either diagnosed or managed at least twice using ICD-10 codes (M10), as described previously (31, 32).

Definition of cardiovascular disease

We included only the participants who had been hospitalized for at least two days or who had died owing to any of the following diseases: stroke (ICD-10 codes I60–I69), ischemic heart disease (I20–I25), or heart failure (I50). This selection criterion has been reported previously (33).

Covariates

The 10 age groups ranged from 40–44 to ≥85 years in 5-year increments. Income classes were classified into 5 categories, with classes 1 and 5 having the lowest and highest salaries, respectively. The region of residence was classified as urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gangwon, Gyeongsangnam, Chungcheongbuk, Jeollabuk, Chungcheongnam, Jeollanam, Gyeongsangbuk, Gyeonggi, and Jeju) areas (34). In addition, participants were classified into current smokers, past smokers, or non-smokers based on smoking status. Alcohol consumption was divided into two categories based on consumption frequency (<1 time a week or ≥1 time a week). Obesity was classified into five categories as <18.5 (underweight), ≥ 18.5 to < 23 (normal), ≥ 23 to < 25 (overweight), ≥ 25 to < 30 (obese I), and ≥ 30 (obese II) using BMI (kg/m^2) based on the Asia-Pacific criteria and the Western Pacific Regional Office 2000 (35).

Hemoglobin (g/dL), systolic blood pressure (SBP, mmHg), fasting blood glucose (mg/dL), diastolic blood pressure (DBP, mmHg), and total cholesterol (mg/dL) were also measured. The Charlson Comorbidity Index (CCI) was used to quantify the burden of 17 comorbidities (acute myocardial infarction, congestive heart failure, peripheral vascular disease, cerebral vascular accident, dementia, pulmonary disease, connective tissue disorder, peptic ulcer, liver disease, diabetes, diabetes complications, paraplegia, renal disease, cancer, metastatic cancer, severe liver disease, and HIV) (36, 37). The CCI calculated for these comorbidities was summed as the continuous variable (0 [no comorbidities] to 29 [multiple comorbidities]) (36, 37). Cerebrovascular disease, acute myocardial infarction, and congestive heart failure were excluded when calculating the CCI score (36, 37).

Statistical analyses

Categorical data are expressed as percentages, and continuous data were summarized as means and standard deviations; the standardized difference was employed to compare the rate of general characteristics between the cohort sets. We employed propensity score overlap weighting to maintain the covariate balance and optimal sample size to diminish the probability of intergroup bias. We employed multivariable logistic regression to calculate the propensity score and subsequently used these scores to calculate the overlap weighting. The participants with gout were weighted using the probability of the propensity score, whereas the control participants were weighted with the probability of 1-propensity score, ranging from 0 to 1. The standardized differences before and after weighting were compared to examine the difference in general characteristics between gout and control groups. To assess the accuracy of matching, absolute standardized differences of the covariates before and after matching were compared, with ≤ 0.20 being considered an appropriate balance. The Cox proportional hazard model was used to adjust covariates with an absolute standardized difference of > 0.20 (38).

The Kaplan–Meier analysis and the log-rank test were employed to compare the collective risk of stroke, ischemic heart disease, and heart failure between gout and control groups. A Cox proportional hazard regression model with an overlap weight was used to determine the hazard ratios (HRs) and 95% CIs of gout in relation to stroke, ischemic heart disease, and heart failure. Both the crude (simple) and adjusted (for obesity, smoking, alcohol consumption, SBP, DBP, fasting blood glucose, total cholesterol, hemoglobin, and CCI scores) results were generated. The analyses were stratified based on factors, such as age, sex, income, and region of residence. Subgroup analyses were performed based on age (< 60 and ≥ 60 years) or sex (males and females). Statistical assessments were performed using two-tailed tests, and p-values of <0.05 were considered statistically significant. All the analyses were conducted using the SAS 9.4 software (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics

This study included 22,480 people diagnosed with gout between 2003 and 2019 and an equivalent number of age, sex, income, and region of residence-matched comparison participants. Table 1 summarizes the baseline characteristics of both groups before and after an overlap-weighting adjusted PS matching procedure. The two groups were exactly alike in terms of demographic characteristics (standardized difference=0), except for the proportion of obese participants; the gout group had a higher percentage of obese participants than the control group (69.16% vs. 60.15%). However, after the overlap weighting adjustment process, the standardized differences of all the covariates were minimized, and the two groups were balanced (standardized difference ≤0.2).

Incidence of stroke, ischemic heart disease, and heart failure in gout and control groups

In gout and control groups, stroke, ischemic heart disease, and heart failure occurred with incidence rates of 9.84 vs. 8.41, 9.77 vs.

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TABLE 1 General characteristics of participants.

Characteristics	Before Overlap weighting adjustment			After Overlap weighting adjustment		
	Gout	Control	Standardized Difference	Gout	Control	Standardized Difference
Age (years;mean, SD)	61.0 (9.7)	61.0 (9.8)	0.00	61.0 (6.8)	61.0 (6.8)	0.00
Age (years; n, %)			0.00			0.00
40–44	590 (2.62)	590 (2.62)		286 (2.62)	286 (2.62)	
45–49	2058 (9.15)	2058 (9.15)		988 (9.06)	988 (9.06)	
50–54	3553 (15.81)	3553 (15.81)		1717 (15.74)	1717 (15.74)	
55–59	4571 (20.33)	4571 (20.33)		2219 (20.35)	2219 (20.35)	
60–64	3899 (17.34)	3899 (17.34)		1898 (17.41)	1898 (17.41)	
65–69	3144 (13.99)	3144 (13.99)		1531 (14.03)	1531 (14.03)	
70–74	2392 (10.64)	2392 (10.64)		1160 (10.64)	1160 (10.64)	
75–79	1436 (6.39)	1436 (6.39)		701 (6.43)	701 (6.43)	
80–84	648 (2.88)	648 (2.88)		315 (2.89)	315 (2.89)	
85+	189 (0.84)	189 (0.84)		90 (0.83)	90 (0.83)	
Sex (n, %)			0.00			0.00
Male	17,800 (79.18)	17,800 (79.18)		8,600 (78.85)	8,600 (78.85)	
Female	4680 (20.82)	4680 (20.82)		2,307 (21.15)	2,307 (21.15)	
Income (n, %)			0.00			0.00
1 (lowest)	3231 (14.37)	3231 (14.37)		1575 (14.44)	1575 (14.44)	
2	2747 (12.22)	2747 (12.22)		1334 (12.23)	1334 (12.23)	
3	3455 (15.37)	3455 (15.37)		1678 (15.39)	1678 (15.39)	
4	4750 (21.13)	4750 (21.13)		2295 (21.05)	2295 (21.05)	
5 (highest)	8297 (36.91)	8297 (36.91)		4024 (36.90)	4024 (36.90)	
Region of residence (n, %)			0.00			0.00
Urban	9563 (42.54)	9563 (42.54)		4643 (42.57)	4643 (42.57)	
Rural	12,917 (57.46)	12,917 (57.46)		6263 (57.43)	6263 (57.43)	
BMI(kg/m^2, mean, SD)	24.8 (2.9)	23.9 (2.9)	0.29	24.4 (2.0)	24.3 (2.0)	0.06
Obesity† (n, %)			0.27			0.00
Underweight	302 (1.34)	567 (2.52)		194 (1.77)	194 (1.77)	
Normal	5663 (25.19)	7824 (34.80)		3246 (29.77)	3246 (29.77)	
Overweight	6221 (27.67)	6353 (28.26)		3106 (28.48)	3106 (28.48)	
Obese I	9328 (41.49)	7168 (31.89)		4006 (36.73)	4006 (36.73)	
Obese II						
Smoking status (n, %)			0.05			0.00
Non-smoker or Past smoker	17,390 (77.36)	17,862 (79.46)		8,559 (78.48)	8,559 (78.48)	
Current smoker	5090 (22.64)	4618 (20.54)		2,347 (21.52)	2,347 (21.52)	
Alcohol consumption (n, %)			0.10			0.00
<1 time a week	10,927 (48.61)	12,030 (53.51)		5571 (51.08)	5571 (51.08)	
≥1 time a week	11,553 (51.39)	10,450 (46.49)		5335 (48.92)	5335 (48.92)	

(Continued)

TABLE 1 Continued

Characteristics	Before Overlap weighting adjustment			After Overlap weighting adjustment		
	Gout	Control	Standardized Difference	Gout	Control	Standardized Difference
SBP (mmHg; Mean, SD)	129.42 (16.73)	126.94 (16.07)	0.15	128.15 (11.46)	128.15 (11.32)	0.00
DBP (mmHg; Mean, SD)	80.19 (10.97)	78.63 (10.41)	0.15	79.39 (7.50)	79.39 (7.33)	0.00
Fasting blood glucose (mg/dL; Mean, SD)	102.11 (27.52)	102.11 (29.65)	0.00	102.13 (19.97)	102.13 (19.93)	0.00
Total cholesterol (mg/dL; Mean, SD)	199.72 (39.83)	196.31 (37.48)	0.09	197.93 (27.24)	197.93 (26.45)	0.00
CCI score (score; Mean, SD)	0.84 (1.54)	0.72 (1.50)	0.07	0.78 (1.02)	0.78 (1.10)	0.00
Hemoglobin (g/dL; Mean, SD)	14.28 (1.51)	14.34 (1.43)	0.04	14.31 (1.05)	14.31 (1.01)	0.00
Stroke (n, %)	1666 (7.41)	1433 (6.37)	0.04	787 (7.22)	711 (6.52)	0.03
Ischemic heart disease (n, %)	1644 (7.31)	1219 (5.42)	0.08	773 (7.09)	608 (5.57)	0.06
Heart failure (n, %)	432 (1.92)	256 (1.14)	0.06	206 (1.89)	127 (1.17)	0.06

CCI, Charlson Comorbidity Index; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; SD, standard deviation.
†Obesity was categorized as <18.5 (underweight), ≥ 18.5 to < 23 (normal), ≥ 23 to < 25 (overweight), ≥ 25 to < 30 (obese I), and ≥ 30 (obese II) based on body mass index (kg/m^2).

7.15, and 2.47 vs. 1.46 per 1000 person-years, respectively; all the differences were statistically significant. The Cox proportional hazard analysis revealed that those with gout were 1.11, 1.28, and 1.64 times more likely to experience subsequent stroke, ischemic heart disease, and heart failure, respectively, than controls in the adjusted models (95% CI=1.04–1.19, p=0.003; 95% CI= 1.19–1.37, p<0.001; and 95% CI=1.41–1.91, p<0.001, respectively) over 16 years, after considering the demographic, lifestyle, and medical factors (Table 2).

The Kaplan–Meier analysis and the log-rank test indicated that individuals with gout had a greater likelihood of experiencing stroke, ischemic heart disease, and heart failure than those in the non-gout group (all p <0.0001; Figures 2A–C).

We further categorized the cohorts by sex and age to ascertain the potential relationship between gout and further incidence of stroke, ischemic heart disease, and heart failure. Stratification analyses showed that the threat of subsequent stroke was prominently augmented in participants with gout aged ≥ 60 years (HR=1.10, 95% CI=1.01–1.20, p=0.022), as well as in male (HR=1.09, 95% CI=1.01–1.18, p=0.036) and female (HR=1.22, 95% CI=1.03–1.44, p=0.018) patients (Figure 3A, Supplementary Table 1).

In the subgroup analyses by ischemic heart disease (Figure 3B, Supplementary Table 2), irrespective of age (< 60 years: HR=1.22, 95% CI=1.09–1.38, p<0.001; ≥ 60 years: HR=1.32, 95% CI=1.20–1.45, p<0.001) and sex (males: HR=1.27, 95% CI=1.17–1.37, p<0.001; males: HR=1.38, 95% CI=1.13–1.69, p=0.002), the correlation between gout and ischemic heart disease remained conspicuous.

In the subgroup analyses by heart failure (Figure 3C; Supplementary Table 3), the presence of gout was associated with an unremarkable but steady increase in the probability of heart failure in individuals aged ≥ 60 years (HR=1.69, 95% CI=1.43–2.01, p<0.001), as well as in men (HR=1.65, 95% CI=1.38–1.97, p<0.001) or women (HR=1.57, 95% CI=1.14–2.15, p=0.005).

Discussion

Based on a large sample of Korean adults, this longitudinal study, considering the demographic data and pre-existing medical conditions, demonstrated that individuals with gout were slightly more likely to experience stroke, ischemic heart disease, or heart failure over the 16 years of observation. We identified a small but

TABLE 2 Crude and adjusted hazard ratios of gout for cardiovascular disease.

Dependent variable	IR per 1000 person-year		IRD per 1000 person-years (95% CI)	Hazard ratios for cancers (95% confidence interval)			
	Gout (n=3070)	Control (n=12,280)		Crude†	*p*-value	Adjusted†‡	*p*-value
Stroke (n = 3099)	9.84	8.41	1.43 (0.79–2.08)	1.17 (1.09–1.26)	<0.001*	1.11 (1.04–1.19)	0.003*
Ischemic heart disease (n = 2863)	9.77	7.15	2.62 (2.00–3.24)	1.36 (1.27–1.47)	<0.001*	1.28 (1.19–1.37)	<0.001*
Heart failure (n = 688)	2.47	1.46	1.01 (0.72–1.30)	1.69 (1.45–1.97)	<0.001*	1.64 (1.41–1.91)	<0.001*

IR, incidence rate; IRD, incidence rate difference; CI, confidence interval.
*Stratified Cox proportional hazard regression model, Significance at p < 0.05.
†Models were stratified by age, sex, income, and region of residence.
‡The Model was adjusted for obesity, smoking, alcohol consumption, systolic blood pressure, diastolic blood pressure, fasting blood glucose, total cholesterol, hemoglobin, and CCI scores.

10.3389/fendo.2023.1195888

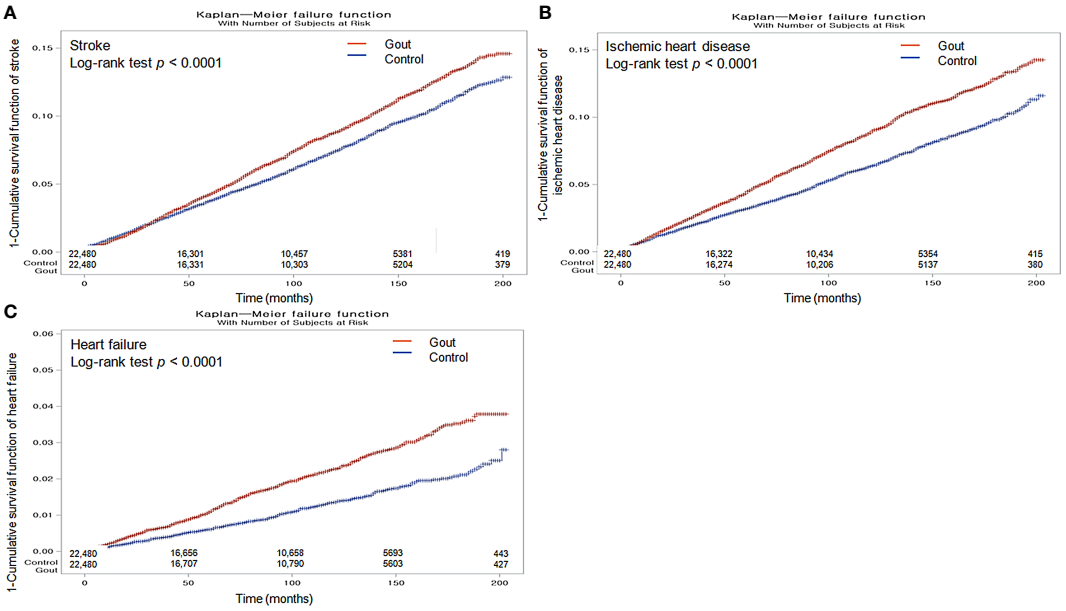

FIGURE 2
Kaplan-Meier probability of the incidence of stroke **(A)**, ischemic heart disease **(B)**, and heart failure **(C)** in gout and the control populations within 16 years of the index date.

statistically-significant increased incidence of stroke, ischemic heart disease, and heart failure among individuals with gout compared with those without (stroke: 9.84 vs. 8.41 per 1000 person-years; ischemic heart disease: 9.77 vs. 7.15 per 1000 person-years; and heart failure: 2.47 vs. 1.46 per 1000 person-years). The weighted Cox proportional hazard analysis, adjusted for factors including age, sex, economic status, anemia, hypertension, hyperlipidemia, hyperglycemia, obesity, smoking, alcohol consumption, and comorbidities, also confirmed that individuals with gout were 11% (95% CI=1.04–1.19), 28% (95% CI=1.19–1.37), and 64% (95% CI=1.41–1.91) more susceptible to stroke, ischemic heart disease, and heart failure, respectively, than those without gout. This study with a long-term follow-up period provides further evidence that gout is an independent risk factor

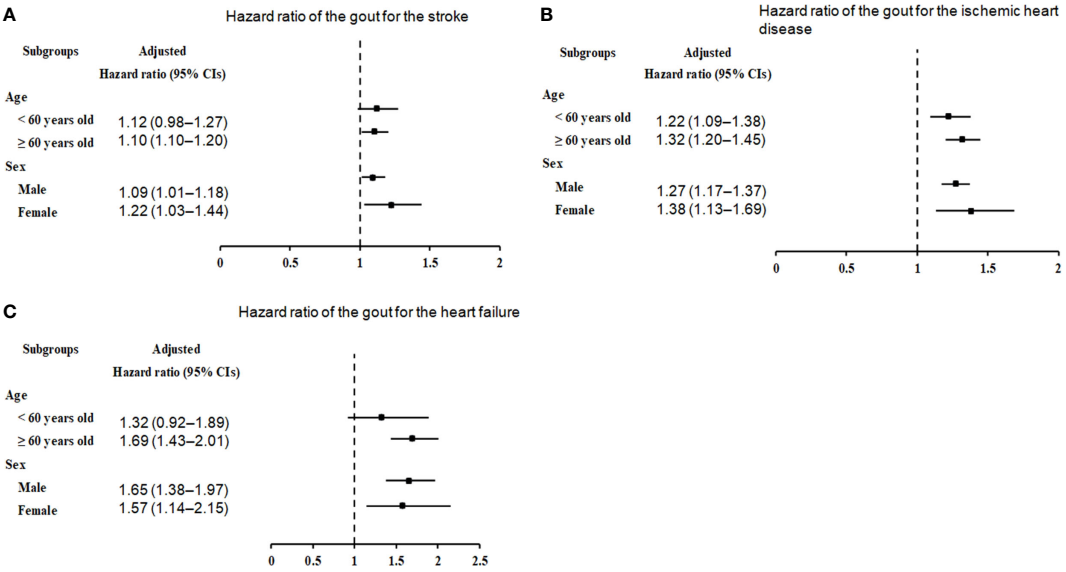

FIGURE 3
Forest plots for hazard ratios (95% confidence intervals [CI]) for the probability of stroke **(A)**, ischemic heart disease **(B)**, and heart failure **(C)** based on age and sex.

for CVDs, as demonstrated in a previous study (39). Thus, individuals with gout should be provided with extra information and training to ensure that they are aware of the potential risks of CVDs.

Our findings are consistent with those of a long-term survey that employed the National Health Insurance Research Database of Taiwan, which has a health insurance plan similar to that of Korea; 15,690 patients with gout and 246,210 controls were included in that survey, and the overall risk of heart diseases, including ischemic heart disease and heart failure, and the risk of stroke in the gout group were respectively 1.57 (95% CI=1.52–1.63) and 1.32 (95% CI=1.27–1.38) times higher than those in the control group (11). A study of 5713 Black and White men and women aged ≥ 65 years in the USA found a 1.97-fold greater risk (95% CI=1.22–3.19) of heart failure in the gout group than in the control group, but the risk of stroke was similar in both groups (odds ratio=0.83, 95% CI=0.48–1.43) (40). The discrepancies could be attributed to variations in the country settings, factors adjusted in the analysis, definitions of outcomes, underlying conditions, study sample, and populations involved in each study.

Stratification analyses by age and sex showed that men and women aged ≥ 60 years with gout were more likely to experience stroke, heart failure, and ischemic heart disease. However, the heightened risk of ischemic heart disease was evident regardless of age and sex; the finding indicates that gout might increase the risk of ischemic heart disease at an earlier age than that of stroke or heart failure, and patients with gout should be carefully monitored for ischemic heart disease. Moreover, this study demonstrated that males and females with gout had a similar risk of stroke (9% and 22% higher, respectively), ischemic heart disease (27% and 38% higher, respectively), or heart failure (65% and 57% higher, respectively) in the overall age group. Consistently, two Taiwanese studies also found that gout-related comorbidities were associated with an elevated risk of stroke in both sexes (22, 23). However, another Taiwanese study concluded that females had a significantly greater likelihood of overall CVDs than males, with an odds ratio of 2.06 (95% CI=1.94–2.20) for females versus an odds ratio of 1.26 (95% CI=1.21–1.31) for males (11).

Individuals with a tendency of increased alcohol intake, high BMI, elevated blood pressure, high total cholesterol level, proteinuria, and high uric acid levels in the Korean population are reportedly at a high risk of developing gout (1). The same risk factors shared between gout and CVDs might be a potential source of confusion. The pathophysiological associations of gout with CVDs are yet to be fully understood; however, genetic, lifestyle, and environmental factors, together with other unidentified elements, are presumably involved. Changes in the genes related to inflammasomes and their molecular associates could probably impact hyperuricemia and the risk of developing gout, as well as other conditions, such as metabolic syndrome and CVDs (41). Genome-wide association studies indicate that genetically predisposed elevated serum urate concentrations could potentially result in an elevated risk of gout, ischemic heart disease, or heart failure (26), with a notable percentage of cardiovascular risk being possibly derived from pleiotropic genes controlling xanthin oxidase activity and urate formation (26). Additionally, chronic inflammation and interleukin (IL)-1β pathways, as well as C-reactive protein, all of which are hallmarks of gout, may be associated with the pathogenesis of CVDs (42, 43). Upon leukocyte activation, endothelial dysfunction and other common pathogenic mechanisms, NLRP3 inflammasome activation, and IL-1β production are promoted in individuals with risk factors for CVDs (44–46). Moreover, research has corroborated that inflammation speeds up aging and therefore increases the chances of heart issues in gout, and telomere length, a risk factor for gout, is an autonomous element linked to the higher recurrence rate and CVD risk (12). Thus, upregulation of these inflammatory pathways in individuals with gout could, at least in part, explain the increased risk of CVDs.

The integrity of this study is primarily based on the comprehensive and nationwide population data that have been adapted to consider socioeconomic standing, potential lifestyle-related hazards, and associated health problems. Second, to limit selection bias and improve the precision of the study, two balanced groups (22,480 participants with gout and 22,480 participants without gout) were paired according to their likelihood of having gout, which could imitate randomized experiments. Despite the high prevalence of gout in men and the elderly, a balanced distribution of age and sex was possible by equally matching 22,480 individuals with gout against the same number of non-gout participants. The heterogeneity in terms of sex differences likely reflects distinctions in the original characteristics of the research groups (20). We found that both men and women with gout were more likely to suffer from stroke, ischemic heart disease, and heart failure. Third, the data gathered from all medical and clinic services in Korea enabled a compilation of complete medical histories throughout the study, thereby enhancing the generalizability and reliability of the research results. Additionally, this 16-year follow-up study is one of the most extensive longitudinal studies on the association between gout and CVDs.

Our findings should be interpreted with a few limitations in mind. First, because this study only included Korean nationals and relied on diagnosis codes, some confounding factors might not have been taken into consideration. Second, no data regarding the family history, personal genetics, or diets for gout or heart conditions were included in the KNHIS-HSC database. Creatinine, glomerular filtration rate, or urate lowering therapies or diuretics were not provided in this study (47, 48); thus, these data were not considered in this study.

In summary, our study demonstrated that individuals with gout in the Korean population, particularly those aged ≥ 60 years, were more likely to have stroke, ischemic heart disease, or heart failure. The findings suggest that individuals diagnosed with gout should receive additional information and training regarding the potential hazards of CVDs.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

HK and N-EL: investigation, writing—original draft, and review & editing. MK: funding acquisition, writing—original draft, and review & editing. DY, KH, JH, HC, and HL: methodology. J-HK, JK, S-JC, and EN: formal analysis. HP: software. NK, SB, and JL: project administration. All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed. All authors have read and agreed to the published version of the manuscript.

Funding

This research was supported by Hallym University Research Fund. The APC was funded by Hallym University Research Fund.

Conflict of interest

Author HC was employed by the company M.D. Analytics.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1195888/full#supplementary-material

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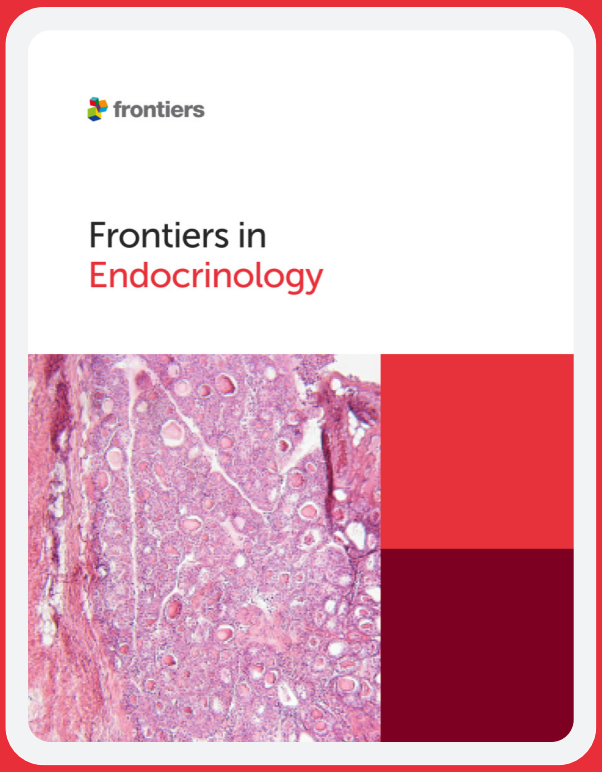

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