Impact of the Serum Uric Acid Level on Subclinical Atherosclerosis in Middle-aged and Elderly Chinese

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Aim: The carotid intima-media thickness (CIMT) is now validated as a sensitive marker of atherosclerosis and is directly associated with an increased risk of cardiovascular disease. Considering that the independent association between the serum uric acid level and CIMT remains controversial due to the complex interrelationship with other known cardiovascular risk factors, further studies are needed. The aim of the present study is to explore the association between the serum uric acid level and CIMT in a general Chinese population and determine whether the association differs according to varied metabolic status.

Methods: The present study was cross-sectional in design. A total of 10,281 community-based participants 40 years of age or older from Shanghai, China were included in the current analysis. All participants underwent a detailed questionnaire interview, anthropometric measurements and ultrasonography to assess the CIMT. Blood and urine samples were collected for the biochemical measurements.

Results: The serum uric acid levels were positively associated with obesity- and diabetes-related parameters and the CIMT. In a logistic regression model controlling for potential confounders, compared with the participants in the first quartile of the uric acid level, those in the fourth quartile had a higher odds of an elevated CIMT in both men (odds ratio [OR] = 1.37; 95% confidence interval [CI] = 1.07-1.75) and women (OR = 1.48; 95% CI = 1.12-1.94).

The subgroup analyses revealed that an association between an elevated CIMT and the serum uric acid level persisted regardless of diuretic use and the hypertension, diabetes mellitus and chronic kidney disease status. However, the association disappeared in the patients who consumed alcohol and in premenopausal women.

Conclusions: The serum uric acid level is positively associated with an elevated CIMT in middle-aged and elderly Chinese subjects, independent of known risk determinants of cardiovascular disease.


Key words: Uric acid, Atherosclerosis, Carotid intima-media thickness

Introduction

Uric acid is the end product of purine metabolism in humans¹ and its overaccumulation is considered to be related to metabolic disorders²-⁴. Although the association between serum uric acid and cardiovascular disease has been studied for decades, the relationship remains unclear and controversial. Several
prospective cohort studies, including the National Health and Nutrition Examination Survey (NHANES), have demonstrated that the uric acid level is an independent risk factor for cardiovascular disease\(^7\), while others have failed to confirm this association\(^8, 9\). Hence, it has not yet been established whether the uric acid level serves as a marker of cardiovascular diseases or as an independent risk factor. Other authors have suggested that uric acid may only play an independent role in specific populations, such as patients with hypertension\(^7\). The carotid intima-media thickness (CIMT), assessed noninvasively using ultrasonography, has been validated to be a sensitive marker of atherosclerosis\(^14\) and is directly associated with an increased risk of cardiovascular disease\(^10\). Previous studies have shown the uric acid level to be positively associated with the CIMT in various specific populations, including patients with hypertension\(^11\) or diabetes mellitus\(^12\) and post-menopausal women\(^13\). However, limited data are available regarding the relationship between the uric acid level and CIMT in the general population.

The present study aimed to explore the association between the serum uric acid level and CIMT in the general Chinese population and determine whether this association differs based on the presence of various metabolic diseases.

## Methods

### Study Population and Design

During the period of March to August, 2010, we performed a cross-sectional study in 10 nearby communities in Jiading District, Shanghai, China. A simple clustering sample design was applied, and all registered residents 40 years of age or older from these communities were invited to participate in the survey via telephone or a door-to-door visit. During the recruitment phase, a total of 10,569 inhabitants were invited, and 10,375 participants agreed to take part in the study, with a participation rate of 98.2%. All participants underwent a detailed questionnaire interview and provided fasting and OGTT 2-hour blood samples. In addition, the participants underwent neck B-mode ultrasonography to measure the CIMT.

The current study also served as a part of a multicenter observational study, the Risk Evaluation of cAncers in Chinese diabetic Individuals: a IONGitudinal (REACTION) study, which included 259,657 participants across mainland China. The registration number for the REACTION study is NCT01506869. The details of the study design have been published elsewhere\(^14\).

Participants with missing information for the CIMT and uric acid level (\(n=88\)) and those with a history of gout (\(n=6\)) were excluded, leaving a total of 10,281 subjects who were ultimately included in the analysis.

The study protocol was approved by the Institutional Review Board of Ruijin Hospital affiliated with the Shanghai Jiao-Tong University School of Medicine. Written consent for the procedure was provided by each participant.

### Questionnaire Data and Biochemical Measurements

A standard questionnaire was used to obtain information regarding the subjects’ demographic characteristics, lifestyle factors, history of disease and medication use during face-to-face interviews conducted by trained investigators. Body weight and height were measured in light clothes without shoes to the nearest 0.1 kg and 0.1 cm, respectively. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Waist circumference was measured to the nearest 0.1 cm at the umbilical level in the standing position. Blood pressure was measured in the non-dominant arm using an automated electronic sphygmomanometer (OMRON Model HEM-752 FUZZY’ Omron Co., Dalian, China) three times consecutively with a 1-minute interval after at least five minutes of rest in the seated position. The average of the three readings was used for the analysis. The smoking and alcohol status was divided into categories of ever-smokers and never smokers and ever-drinkers and never drinkers, respectively. Ever smokers were defined as current smokers and previous smokers; never smokers were those who had never smoked. The definition of ever-drinkers and never drinkers was similar to that for the smoking status. The amount of physical activity during leisure time was estimated using the short form of the International Physical Activity Questionnaire (IPAQ) by adding questions for the frequency and duration of moderate and vigorous activity and walking\(^15\). Separate metabolic equivalent hours per week (MET-h/week) were calculated to evaluate the total physical activity. Information regarding the use of antihypertensive, antidiabetic, lipid-lowering and diuretic medications was also collected. In women, the menstrual cycle status was also obtained using a questionnaire. Menopause was defined based on the answer “yes” to the question, “Have your cycles entirely stopped?,” with an answer of “no” indicating a premenopausal status.

Overnight fasting blood samples were collected for the biochemical analysis. The blood glucose levels were measured according to the glucose oxidase method.
on an autoanalyzer (Modular P800, Roche, Basel, Switzerland). The fasting serum insulin, triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and serum creatinine levels were measured using chemiluminescence methods on the autoanalyzer (Modular E170, Roche, Basel, Switzerland). The insulin resistance index (homeostasis model assessment of insulin resistance, HOMA-IR) was calculated as follows: fasting insulin (IU/mL) × fasting glucose (mmol/L)/22.5. The estimated glomerular filtration rate (eGFR) was calculated using the following equation: eGFR = 186 × (serum creatinine × 0.011) / 1.154 × age × 0.742 if female × 1.233, where 1.233 is the modified coefficient for Chinese individuals. The urinary albumin to creatinine ratio (ACR; mg/g) was also calculated, and patients with an ACR greater than 30 mg/g were defined as having albuminuria. Chronic kidney disease was defined as an eGFR less than 60 mL/min per 1.73 m² or the presence of albuminuria.

Diabetes mellitus was defined according to a fasting glucose level of 7.0 mmol/L or higher, a 2-hour post-load glucose level of 11.1 mmol/L or higher and/or current treatment with an antidiabetic medication or insulin. The diagnosis of hypertension was determined based on a systolic blood pressure of 140 mmHg or higher, diastolic blood pressure of 90 mmHg or higher and/or the current use of antihypertensive drugs.

CIMT Measurements
A high-resolution B-mode tomographic ultrasound system (Shima dzu SDU-1200, Tokyo, Japan) equipped with a 7.5- to 10-MHz transducer was used by a specialist in ultrasonography who was unaware of the other data to evaluate sclerotic lesions in the common carotid arteries. The measurements were obtained for the far wall of the bilateral common carotid arteries 1.5 cm proximal to the site of bifurcation. The CIMT was measured at the end of diastole, as the distance from the leading edge of the first and second lines, representing the lumen-intima interface and collagen-contained upper layer of the tunica adventitia,
Antilipidemic medication use [n (%)]

Antidiabetic medication use [n (%)]

Antihypertension medication use [n (%)]

CIMT ≥ carotid intima-media thickness.

total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FBG, fasting blood glucose; 2hBG, 2-hour postprandial glucose; HOMA-IR, homeostasis model assessment of insulin resistance; eGFR, estimated glomerular filtration rate; CIMT, carotid intima-media thickness.

respectively. The mean value of bilateral measurements was calculated for the analysis. An elevated CIMT was defined as a mean CIMT of ≥90th percentile (0.7 mm).

Statistical Analysis

The general characteristics of the men and women were compared across the uric acid quartiles. Normally distributed variables are presented as the mean and standard deviation (SD), whereas variables with a skewed distribution are presented as the geometric mean and 95% CI and analyzed after logarithmic transformation. The ρ values for trends across the uric acid quartiles were calculated using a linear regression analysis for continuous variables and the Cochran-Armitage χ² test for categorical variables.

Unadjusted and adjusted logistic regression models were employed to explore the association between the uric acid quartile and an elevated CIMT separately in men and women. Adjusted variables included age, sex, smoking and drinking status, physical activity, waist circumference, SBP, DBP, TG, HDL-C, LDL-C, FBG, HOMA-IR, menopausal status (for women only) and serum creatinine. We also investigated the odds of an elevated CIMT per one SD increment in the uric acid level. The relationship between the uric acid level and CIMT was further explored in stratified analyses. The stratified factors included hypertension, diabetes mellitus, chronic kidney disease, diuretic use, drinking and menopause (for women). All analyses were per-
formed using the SAS version 9.3 software program (SAS Institute Inc., Cary, NC, USA), and a two-sided p value of less than 0.05 was the criterion for statistical significance.

Results

Characteristics of the Participants

The mean concentration of serum uric acid was 352±89 umol/L in men and 268±79 umol/L in women. The anthropometric and clinical characteristics are displayed in Table 1. BMI, waist circumference, SBP, DBP, triglycerides, total cholesterol, LDL-C, fasting insulin, HOMA-IR, serum creatinine and the rate of diuretic use increased according to the uric acid quartile in both genders (p<0.0001), whereas the HDL-C levels decreased in both genders (p<0.0001). Among men, compared with the participants in the first quartile, those in the fourth quartile were more likely to be drinkers. Among women, those in the higher quartile for uric acid were more likely to be postmenopausal.

Association between the Uric Acid Level and CIMT

As shown in Fig. 1, from quartile 1 to quartile 4, the mean CIMT value was 0.60±0.11, 0.61±0.12, 0.62±0.11 and 0.63±0.11 mm in men and 0.54±0.09, 0.55±0.09, 0.57±0.09 and 0.59±0.10 mm in women, respectively. The trend in the increase in the CIMT in association with the uric acid level was statistically significantly (p=0.0017 for men and p<0.0001 for women). When the upper 10th percentile for the CIMT was defined as an elevated CIMT value, the prevalence of an elevated CIMT increased across the uric acid quartiles. In men, the prevalence of an elevated CIMT across the quartiles was 25.8%, 29.2%, 29.5% and 32.7%, respectively (p for trend=0.0014). In women, the prevalence according to the quartiles was 8.8%, 10.3%, 12.4% and 20.1%, respectively (p for trend <0.0001) (Table 1).

Step-adjusted models were applied to evaluate the odds of having an elevated CIMT in the different uric acid quartiles, with quartile 1 serving as the referent group (Table 2). In the unadjusted model, the risk of an elevated CIMT increased with the uric acid quartile. Compared to the participants in quartile 1, the participants in quartile 4 had a 39% (OR=1.39; 95% CI=1.15-1.69) increased risk of having an elevated CIMT among men, compared to a 162% increased risk (OR=2.62; 95% CI=2.12-3.25) among women. Following adjustment for age, the smoking and drinking status and physical activity in model 2, with further adjustment for the use of diuretics and antihyper-
The association between the uric acid level and an elevated CIMT persisted, regardless of gender, hypertension, diabetes mellitus, chronic kidney disease and diuretic use. The risk of having an elevated CIMT was 1.12 (95% CI: 1.03-1.22) for each SD increment in the uric acid level among the hypertension patients, 1.25 (95% CI: 1.09-1.43) among those without hypertension, 1.18 (95% CI: 1.03-1.36) among the subjects with diabetes mellitus, and an 18% (95% CI: 1.08-1.30) increased risk of an elevated CIMT in women.

As shown in Table 3, the risk of an elevated CIMT with each SD increment in the uric acid level was further analyzed in the different subgroups. After adjusting for age, sex, the smoking and drinking status, physical activity, waist circumference, SBP, DBP, TG, HDL-C, LDL-C, FBG, HOMA-IR, the menopausal status (for women only) and serum creatinine (except for the stratified variables), the association between the uric acid level and an elevated CIMT persisted, regardless of gender, hypertension, diabetes mellitus, chronic kidney disease and diuretic use. The risk of having an elevated CIMT was 1.12 (95% CI: 1.03-1.22) for each SD increment in the uric acid level among the hypertension patients, 1.25 (95% CI: 1.09-1.43) among those without hypertension, 1.18 (95% CI: 1.03-1.36) among the subjects with diabetes mellitus.
Discussion

The present study found that the serum uric acid level is positively associated with the CIMT in both middle-aged and elderly Chinese subjects and that this association is independent of age, sex, physical activity, waist circumference, SBP, DBP, TG, HDL-C, LDL-C, FBG, HOMA-IR, and the use of diuretics or antihypertensive, antidiabetic and antilipidemic drugs. However, this association was not detected in the participants with a current or previous history of consuming alcohol and in premenopausal women.

Several potential mechanisms may account for the link between the uric acid level and an elevated CIMT. For example, a high concentration of serum uric acid may reduce the release of nitric oxide (NO) or increase the level of mitochondrial O$_2^{-}$, which is associated with mitochondrial calcium overload, ultimately leading to endothelial cell dysfunction. In addition, uric acid acts as a pro-inflammatory cytokine and plays an important role in the proliferation of vascular smooth muscle cells and inflammatory reactions in adipose tissue, which in turn results in an increased thickness of the carotid arteries. Furthermore, a recent study found that hyperuricemia due to intestinal uric acid transport dysfunction induces deleterious metabolic sequelae, a process involved in

Table 3. Risk of an elevated CIMT with a one standard deviation increment in the uric acid level in the different subgroups

<table>
<thead>
<tr>
<th>Drinker</th>
<th>Participants [n]</th>
<th>Unadjusted</th>
<th>Adjusted for age, sex</th>
<th>Multivariable adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ever</td>
<td>1174</td>
<td>1.20 (1.06-1.36)</td>
<td>1.17 (1.02-1.34)</td>
<td>1.13 (0.96-1.34)</td>
</tr>
<tr>
<td>Never</td>
<td>9107</td>
<td>1.54 (1.46-1.62)</td>
<td>1.19 (1.12-1.27)</td>
<td>1.16 (1.09-1.25)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6037</td>
<td>1.40 (1.32-1.48)</td>
<td>1.15 (1.07-1.23)</td>
<td>1.12 (1.03-1.22)</td>
</tr>
<tr>
<td>No</td>
<td>4244</td>
<td>1.58 (1.44-1.73)</td>
<td>1.20 (1.07-1.34)</td>
<td>1.25 (1.09-1.43)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1851</td>
<td>1.40 (1.26-1.55)</td>
<td>1.20 (1.07-1.35)</td>
<td>1.18 (1.03-1.36)</td>
</tr>
<tr>
<td>No</td>
<td>8407</td>
<td>1.55 (1.47-1.64)</td>
<td>1.19 (1.11-1.27)</td>
<td>1.13 (1.04-1.23)</td>
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<tr>
<td>Chronic kidney disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>707</td>
<td>1.52 (1.29-1.80)</td>
<td>1.31 (1.08-1.61)</td>
<td>1.33 (1.06-1.67)</td>
</tr>
<tr>
<td>No</td>
<td>9574</td>
<td>1.53 (1.46-1.61)</td>
<td>1.18 (1.11-1.26)</td>
<td>1.13 (1.05-1.21)</td>
</tr>
<tr>
<td>Diuretic usage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1349</td>
<td>1.48 (1.31-1.68)</td>
<td>1.25 (1.09-1.44)</td>
<td>1.20 (1.01-1.42)</td>
</tr>
<tr>
<td>No</td>
<td>8532</td>
<td>1.52 (1.45-1.61)</td>
<td>1.18 (1.11-1.26)</td>
<td>1.15 (1.06-1.24)</td>
</tr>
<tr>
<td>Menopause (only in women)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4753</td>
<td>1.33 (1.24-1.43)</td>
<td>1.22 (1.12-1.31)</td>
<td>1.17 (1.07-1.30)</td>
</tr>
<tr>
<td>No</td>
<td>1339</td>
<td>1.61 (1.18-2.15)</td>
<td>1.48 (1.07-2.01)</td>
<td>1.28 (0.85-1.91)</td>
</tr>
</tbody>
</table>

Multivariable adjusted model: adjusted for sex, age, smoking and drinking status, physical activity, WC, SBP, DBP, TG, HDL-C, LDL-C, FBG, HOMA-IR, serum creatinine, menopausal status (for women only) and use of diuretics and antihypertensive, antidiabetic and antilipidemic drugs (except for the stratified variables).
the pathology of carotid atherosclerosis. Only after atherosclerosis progresses to ischemic disease or when thrombi are generated from existing plaque as a result of rupture or erosion, do symptomatic cardiovascular events occur\(^{26}\). Although not all patients with underlying atherosclerotic plaque experience clinical cardiovascular events, the degree of subclinical atherosclerosis is positively associated with a higher risk of future cardiovascular events\(^{27-31}\). In order to prevent morbidity and mortality from cardiovascular disease, there is great interest in identifying asymptomatic patients at high risk who may be candidates for more intensive, evidence-based medical interventions\(^{27, 28}\). Imaging of the arteries to identify and quantify the presence of subclinical vascular disease has been suggested to further refine subgroups of patients with high cardiovascular disease risks\(^{27, 28}\). Moreover, measuring the CIMT using B-mode ultrasound is a noninvasive, sensitive and reproducible technique for identifying and quantifying the atherosclerotic burden and may lead to interventions that may favorably alter the natural process of cardiovascular disease\(^{32, 33}\), and the CIMT has been verified to adequately reflect the early stage of atherosclerosis and serves as a good predictor of future cardiovascular disease. However, data focusing on the independent effect of hyperuricemia on the CIMT remain inconclusive. The Atherosclerosis Risk in Communities (ARIC) Study also found a correlation between the uric acid level and an elevated CIMT in men; however, that correlation was not independent of the use of diuretics\(^{34}\). In contrast, no association between the serum uric acid level and carotid atherosclerosis was observed in the Korean Multi-Rural Communities Cohort study or a cohort of hypertensive women\(^{35, 36}\); these study participants were restricted to specific populations of rural areas or females patients with hypertension. Hence, data for the general population are scare, especially in Chinese populations. In the current study, the serum uric acid was found to be associated with the CIMT in middle-aged and elderly Chinese adults, independent of conventional cardiovascular risk factors. This finding is consistent with the findings of the majority of previous studies. Recent results for a Japanese elderly population showed the serum uric acid level to be an independent risk factor for carotid atherosclerosis\(^{37}\). A positive relationship was also found in healthy Korean men. In addition to the CIMT, other atherosclerosis indicators, such as the degree of coronary artery calcification, have been shown to exhibit the same positive association with the serum uric acid level\(^{38}\). In particular, the Brisighella Heart Study population survey reported a strong independent association between the serum uric acid level and the CIMT\(^{39}\). A similar independent relationship between these two parameters also exists in certain populations, such as elderly men without metabolic syndrome\(^{40}\), postmenopausal women\(^{13}\) and patients with hypertension\(^{41}\) or diabetes\(^{12}\).

An important point of this study that should be addressed is that, in the subgroup analysis, the positive association between the uric acid level and the risk of an elevated CIMT was not affected by the use of diuretics or hypertension, diabetes or chronic kidney disease status. However, the serum uric acid level was not found to be associated with the CIMT in the participants who were currently or had ever consumed alcohol. Additionally, Iribarren C. et al.\(^{42}\) identified a positive trend between the risk of coronary heart disease and an increased serum uric acid level among alcohol drinkers, and previous reports have revealed that alcohol consumption may induce hyperuricemia\(^{43}\). Meanwhile, light to moderate alcohol intake has been shown to have behavioral effects on atherosclerosis\(^{44}\). Therefore, the behavioral effects of alcohol in neutralizing the adverse effects of uric acid may in part explain the disappearance of the association between the uric acid level and CIMT. Moreover, an increased level of uric acid as a result of alcohol consumption may not actually reflect a stable chronic uric acid level, which may veil the actual influence of the uric acid concentration on the carotid vessels. In addition, we found that the serum uric acid level is associated with the CIMT in postmenopausal women, whereas no association was detected in premenopausal women. Nevertheless, no significant interaction was detected between the uric acid level and menopausal status. This finding may the result of the limited sample size for premenopausal women.

The strengths of our study include the large general sample size and collection of detailed clinical information. However, several limitations should also be considered. First, due to the cross-sectional nature of the study design, no causal relationships were identified. Second, the population was restricted to middle-aged and elderly Chinese subjects; therefore, the findings may not be generalizable to younger populations or other ethnicities. Third, there was no information regarding diet, and a high-purine diet may induce elevation of the uric acid level in the blood. Hence, the confounding effects of diet were not investigated in this study.

**Conclusion**

In conclusion, the uric acid level is independently
associated with the CIMT in middle-aged and elderly general Chinese subjects, and alcohol consumption may weaken this association. In light of the importance of early prevention of carotid atherosclerosis, controlling the serum uric acid level may be beneficial for avoiding future cardiovascular risks.

**Conflicts of Interest**

The authors declare that they have no competing interests.

**Authors’ Contributions**

C.Y. designed the study, collected, analyzed and interpreted the data and wrote the manuscript. B.X., W.S., J.S., X.L., M.X., L. and Y.B. interpreted the data and revised the manuscript. T.W., W.W. and G.N. conceived of and designed the study, interpreted the data and revised the manuscript. All authors approved the final version of the manuscript.

**Acknowledgements**

The authors thank the field workers for their contribution and the participants for their cooperation. This work is supported by grants from the Key Laboratory for Endocrine and Metabolic Diseases of Ministry of Health (994DP131044), National Clinical Research Center for Metabolic Diseases of Ministry of Health (2013BAL09B13), National Key New Drug Creation and Manufacturing Program of Ministry of Science and Technology (2012ZX09303006-001), National High Technology Research and Development Program of China (863 Program, 2012AA020107) and National Natural Science Foundation of China (81321001, 81030011, 81130016, 81222008 and 81270877).

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