Relationship between hyperuricemia and risk of coronary heart disease in a middle-aged and elderly Chinese population

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Abstract

Objective: To investigate the relationship between hyperuricemia and coronary heart disease (CHD) risk based on the Framingham risk score (FRS) in a middle-aged and elderly Chinese population.

Methods: This cross-sectional study enrolled patients undergoing routine check-ups at Xiangya Hospital between October 2013 and November 2014. Hyperuricemia was defined as uric acid $\geq$416 mmol/l for males and $\geq$360 mmol/l for females. A 10-year CHD risk was calculated from FRS. A multivariable logistic analysis model was used to evaluate associations.

Results: Of the 6347 patients, 3415 (53.8%) were male, 1543 (24.3%) had a CHD risk $\geq$10% (i.e. intermediate and high risk) and the prevalence of hyperuricemia was 18.1% ($n = 1148$). After adjusting for potential confounding factors, the 10-year CHD risk was increased in patients with hyperuricemia compared with those without hyperuricemia by 0.28 times in the total population (odds ratio [OR] 1.28; 95% confidence interval [CI] 1.09, 1.48), by 0.25 times in the male population (OR 1.25; 95% CI 1.06, 1.47) and by 2.76 times in the female population (OR 3.76; 95% CI 2.08, 6.79).

Conclusion: Hyperuricemia was positively associated with a 10-year risk of CHD suggesting that it might be an independent CHD risk factor in middle-aged and elderly individuals.

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Introduction

The prevalence of hyperuricemia has been increasing worldwide over recent years.[1,2] In several Asian countries, the prevalence of hyperuricemia has been estimated to range from 13% to 26%.[3] Moreover, a study in Taiwanese aboriginals found the prevalence of hyperuricemia to be approximately 41%.[1] Several studies have suggested that hyperuricemia is strongly associated with a number of cardiovascular disease (CVD) risk factors.[4–7] In addition, research from Korea showed that an increase in serum uric acid concentration was associated with an increased Framingham risk score (FRS).[8,9] The FRS provides an integrated estimated risk of an individual developing coronary heart disease (CHD) over the next 10 years based on a set of known CVD risk factors.[8] Importantly, a meta-analysis of 26 studies demonstrated that hyperuricemia may marginally increase the risk of CHD events independently of traditional CHD risk factors.[10] However, the meta-analysis only included studies from Taiwan. To the best of our knowledge, no large-scale studies have investigated the association between hyperuricemia and the risk of CHD based on FRS in a Chinese mainland population. Therefore, a cross-sectional study was undertaken to assess the relationship between hyperuricemia and the risk of CHD calculated from the FRS.

Patients and methods

Study population

This cross-sectional study included patients who were undergoing routine check-ups at the Health Examination Centre in Xiangya Hospital, Central South University, Changsha, Hunan Province, China between October 2013 and November 2014. Participants were selected according to the following inclusion criteria: (i) aged 40 years or older; (ii) serum uric acid and other basic biochemical measurements available; (iii) availability of data on all basic characteristics, including age, sex and body mass index (BMI); and (iv) availability of data on health-related habits, such as smoking status, alcohol consumption, activity level, and medication use. The study design has been previously published.[11] Using a standardized questionnaire, independent, registered nurses interviewed all participants and collected information on demographic characteristics and health-related habits. The protocol of this study was reviewed and approved by the Ethics and Research Committee of Xiangya Hospital (no. 201312459). Verbal informed consent was obtained from each participant.

Blood biochemistry

All blood samples were drawn after a 12-h overnight fast and were kept at 4°C until analysis. Hyperuricemia was defined by the uric acid level $\geq 416\,\mu mol/l$ in males and $\geq 360\,\mu mol/l$ in females. Blood fasting glucose, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglyceride levels were also measured. The inter- and intra-assay coefficients of variation were tested by low concentrations (2.5 mmol/l for glucose and 118 μmol/l for uric acid) and high concentrations (6.7 mmol/l for glucose and 472 μmol/l for uric acid) of standard human samples. The intra-assay coefficients of variation were 0.98% (2.5 mmol/l) and 1.72% (6.7 mmol/l) for glucose, 1.39%

(118 μmol/l) and 0.41% (472 μmol/l) for uric acid. The inter-assay coefficients of variation were 2.45% (2.5 mmol/l) and 1.46% (6.7 mmol/l) for glucose, 1.40% (118 μmol/l) and 1.23% (472 μmol/l) for uric acid. Patients with a fasting glucose ≥7.0 mmol/l or who were currently undergoing drug treatment for blood glucose control were regarded as having diabetes mellitus. Laboratory tests were performed with a Beckman Coulter AU5800 analyser (Beckman Coulter, Brea, CA, USA).

Assessment of other exposures

The weight and height of each patient was measured to calculate BMI. Blood pressure was measured with an electronic sphygmomanometer. In addition, participants were asked about their average frequency of physical activity (i.e. never, one to two times per week, three to four times per week, five times and above per week), average duration of physical activity (i.e. half an hour or less, half an hour to 1 h, 1–2 h, more than 2 h). Smoking, alcohol consumption, educational background, occupation and medication status were ascertained by interview.

Assessment of 10-Year Risk for Coronary Heart Disease

Adult Treatment Panel III (ATP III) charts were used to calculate the FRS for each participant.[8] Information included in the risk assessment tool included age, sex, smoking, systolic blood pressure, use of antihypertensive medications, presence of diabetes mellitus, total cholesterol and HDL-C.

Statistical analyses

Continuous data were expressed as mean ± SD and categorical data were expressed as *n* of patients (%). Differences in continuous data were evaluated by

one-way analysis of variance for normally distributed data or Kruskal–Wallis H test for not normally distributed data. Differences in categorical data were assessed by the χ^2-test. Patients were classified into two categories based on their 10-year CHD risk: 0–9% (low risk) and ≥10% (intermediate/high risk). The prevalence of intermediate/high CHD risk scores were compared between patients with and without hyperuricemia. The unadjusted association between hyperuricemia and CHD risk was first examined by a logistic regression. Then a multivariable model including variables for age, BMI, creatinine level, activity level, alcohol consumption, educational background, occupation, and diabetes status was used to estimate the odds ratio (OR) and related 95% confidence interval (CI). Subgroup analyses were conducted in the male and female populations.

Sensitivity analyses were performed firstly by excluding patients with diabetes, hypolipaemic medication history or chronic kidney disease (CKD) and secondly, by adding LDL-C and triglycerides into the multivariable adjusted model. All statistical analyses were performed using the IBM SPSS® statistical package, version 19.0 (IBM Corp, Armonk, NY, USA) for Windows®. A *P*-value < 0.05 (2-tailed) was considered to indicate statistical significance.

Results

Of the 13 562 patients aged 40 years or older who were initially screened for this cross-sectional study, information on health-related habits was available for 6347 patients who were therefore eligible for the study. The mean ± SD age of the group was 53.0 ± 7.5 years; and 53.8% (3415 of 6347) of the participants were male and 2932 of 6347 (46.2%) were female. Baseline characteristics of the study population are shown in Table 1. The proportion of patients with

Table 1. Baseline characteristics of the total population and according to their coronary heart disease (CHD) risk based on the Framingham risk score.

Characteristic	Total population $n = 6347$	Patients with 10-year CHD risk ≥ 10% $n = 1543$	Patients with 10-year CHD risk 0–9% $n = 4804$	Statistical significance[a]
Age, years	53.0 ± 7.5	56.7 ± 8.2	51.8 ± 6.8	P < 0.01
Women	2932 (46.2)	58 (3.8)	2874 (59.8)	P < 0.01
Men	3415 (53.8)	1485 (96.2)	1930 (40.2)	P < 0.01
BMI, kg/m^2	24.5 ± 3.2	25.3 ± 3.2	24.2 ± 3.2	P < 0.01
Hyperuricemia	1148 (18.1)	418 (27.1)	730 (15.2)	P < 0.01
Total cholesterol, mg/dl	205.7 ± 44.4	216.3 ± 52.2	202.2 ± 41.0	P < 0.01
HDL-C, mg/dl	58.4 ± 15.0	51.9 ± 52.2	60.5 ± 14.9	P < 0.01
LDL-C, mmol/l	3.0 ± 0.9	3.1 ± 1.0	2.9 ± 0.9	P < 0.01
Triglycerides, mmol/l	1.9 ± 1.8	2.7 ± 2.7	1.7 ± 1.3	P < 0.01
Systolic blood pressure, mmHg	126.3 ± 17.4	132.8 ± 17.9	124.2 ± 16.8	P < 0.01
Diastolic blood pressure, mmHg	80.1 ± 11.8	85.0 ± 11.7	78.5 ± 11.4	P < 0.01
Creatinine, μmol/l	85.3 ± 28.8	94.8 ± 19.6	82.2 ± 30.6	P < 0.01
Diabetes mellitus	629 (9.9)	231 (15.0)	398 (8.3)	P < 0.01
Physical activity level, h/week	2.3 ± 3.5	2.4 ± 3.7	2.3 ± 3.5	NS
Smoker	1384 (21.8)	975 (63.2)	409 (8.5)	P < 0.01
Alcohol consumption	2413 (38.0)	812 (52.6)	1601 (33.3)	P < 0.01
Education to high school or above	3025 (47.7)	783 (50.7)	2242 (46.7)	P < 0.01
Non-manual worker	5094 (80.3)	1173 (76.0)	3921 (81.6)	P < 0.01

Data are expressed as mean ± SD or n of patients (%).
[a]Kruskal–Wallis H test was used for not normally distributed continuous data and χ^2-test was used for categorical data.
BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NS, no statistically significant between-group difference ($P \geq 0.05$).

CHD risk ≥10% (i.e. intermediate and high risk) was 24.3% (1543 of 6347) and the prevalence of hyperuricemia in the total population was 18.1% (1148 of 6347).

There were statistically significant differences between the patients in the intermediate/high CHD risk group (≥10%) compared with those in the low risk CHD group (0–9%) in terms of age, BMI, total cholesterol, HDL-C, LDL-C, triglyceride, blood pressure, creatinine, smoking status, alcohol consumption, diabetes ratio, educational background, and occupation (Table 1) (P < 0.01 for all comparisons).

Unadjusted associations were observed between hyperuricemia and 10-year CHD risk in the total population and in the male and female subgroups (Table 2).

After adjusting for potential confounding factors, significant positive associations were still evident. The 10-year CHD risk was increased in patients with hyperuricemia compared with patients without hyperuricemia by 0.28 times in the total population (OR 1.28; 95% CI 1.09, 1.48; P < 0.01), by 0.25 times in the male population (OR 1.25; 95% CI 1.06, 1.47; P = 0.01), and by 2.76 times in the female population (OR 3.76; 95% CI 2.08, 6.79; P < 0.01).

Sensitivity analyses suggested similar results after excluding patients with diabetes mellitus, hypolipaemic medication history or chronic kidney disease. For the total population, the positive association between hyperuricemia and 10-year CHD risk was significant (OR 1.69; 95% CI 1.46, 1.95;

Table 2. Multivariable adjusted associations between hyperuricemia and 10-year coronary heart disease risk (≥10%) based on the Framingham risk score.

Population	Unadjusted OR (95% CI)	Statistical significance	Multivariable adjusted OR[a] (95% CI)	Statistical significance
Total	2.07 (1.81, 2.38)	$P < 0.01$	1.28 (1.09, 1.48)	$P < 0.01$
Male	1.19 (1.02, 1.39)	$P = 0.03$	1.25 (1.06, 1.47)	$P = 0.01$
Female	4.62 (2.64, 8.11)	$P < 0.01$	3.76 (2.08, 6.79)	$P < 0.01$

[a]The multivariable model was adjusted for body mass index, creatinine level, physical activity level, alcohol consumption, educational background, occupation, and diabetes mellitus status.
The prevalence of intermediate/high CHD risk scores were compared between patients with and without hyperuricemia in the total population (i.e. $n = 1148$ versus $n = 5199$), male population (i.e. $n = 855$ versus $n = 2560$) and female population (i.e. $n = 293$ versus $n = 2639$).
OR, odds ratio; CI, confidence interval.

$P < 0.001$). In addition, following the inclusion of LDL-C and triglyceride into the multivariable adjusted model, the positive association between hyperuricemia and CHD risk was still significant (OR 1.44; 95% CI 1.24, 1.68; $P < 0.001$).

Discussion

The results of this present study showed that hyperuricemia is positively associated with the 10-year risk of CHD calculated using FRS and independent of some potential confounding factors (i.e. age, BMI, creatinine, activity level, alcohol consumption, educational background, occupation, and diabetes status). The relationship was valid for both the male and female subgroups. To the best of our knowledge, this is the first study to examine the correlation between hyperuricemia and CHD risk based on FRS in a middle-aged to elderly Chinese population.

Uric acid is the metabolic end product of purine metabolism.[12] It has been described as having both an extracellular antioxidant effect and an intracellular pro-oxidant effect depending on locality and presence of other factors.[12] This dual role has been described as the 'uric acid paradox'.[12] For example, low concentrations of uric acid contribute to the prevention of oxidative inactivation of endothelial enzymes and angiotensin converting enzyme and also to the preservation of nitrous oxide (NO) production.[13] However, under hyperuricemic conditions, the beneficial effects are replaced by deleterious effects that include NO reduction, endothelial dysfunction,[14] oxygen radical promotion and increased proinflammatory marker production.[15]

Although the exact mechanisms are unclear, several studies have shown that hyperuricemia is associated with CHD and is independently associated with some CHD risk factors.[9,16,17] Possible causes include damage to the vascular endothelium and vessel wall because, as previously mentioned, uric acid can exert a pro-oxidant effect and oxidative stress would promote endothelial dysfunction.[14,18] In addition, uric acid stimulates the proliferation of vascular smooth muscle cells through the renin-angiotensin system and its activation could lead in turn to the stimulation of the xanthine oxidase and nicotinamide adenine dinucleotide phosphate systems.[19,20] This phenomenon could possibly impair arterial function and cause arterial stiffening, which is a major cause of hypertension and CHD.[12] Another possible explanation of the involvement of uric acid in CHD is

impaired kidney function.[21] Elevated serum uric acid is a characteristic of CKD and decreased glomerular filtration rate and increased albuminuria, which are both components of CKD, can potentiate cardiovascular risk.[22]

This current cross-sectional study had several strengths. For example, as far as we ae aware, it is the first study to investigate the possible association of hyperuricemia with 10-year CHD risk based on FRS in a large sample ($n = 6347$) of middle-aged and elderly Chinese patients. Also, a multivariable model was used to ensure that the associations were independent of a considerable number of potentially confounding factors (i.e. BMI, creatinine, activity level, alcohol consumption, educational background, occupation and diabetes status), which improved the reliability of the results. However, the study had some limitations. First, the serum uric acid level was determined by a balance of uric acid generation, reabsorption, and excretion. Thus, it could have been influenced by various factors such as the use of diuretics, dietary purine intake, volume depletion and renal dysfunction.[23] However, these factors were not recorded and so they could not be assessed in this study. Secondly, the cross-sectional design of the study precluded analysis of causal associations and therefore, further prospective studies and intervention trials should be undertaken to establish any causal association between hyperuricemia and CHD. Finally, this study evaluated only middle-aged and elderly patients undergoing a health check-up, which limits the applicability of these results to the general population.

In conclusion, this present study demonstrated that hyperuricemia was positively associated with 10-year risk of CHD. Therefore, hyperuricemia may be an independent CHD risk factor in middle-aged and elderly Chinese patients. Additional prospective studies are required to confirm these findings.

Declaration of conflicting interests

Funding

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