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Dose-response relationship between serum uric acid levels and risk of incident coronary heart disease in the Dongfeng-Tongji Cohort

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ABSTRACT

Background: In prospective studies, relationship of serum uric acid (SUA) with risk of coronary heart disease (CHD) incidence is inconsistent. We evaluated the association of SUA with incident CHD and the potential modifying effect of major CHD risk factors related to SUA among a middle aged and elderly Chinese population.
Methods: We included 16, 063 participants who were free of CHD, stroke, cancer and renal diseases at baseline from Sep. 2008 to June 2010, and were followed until Oct. 2013. Cox proportional hazard model was used to estimate the hazard ratios (HR) and 95% confidence interval (95% CI) of CHD incidence in relation to SUA.
Results: The adjusted HR for incident CHD increased gradually with the increasing SUA levels (P for linear trend = 0.005), and the HR across sex-specific SUA quartile was 1.26 (95% CI: 1.09, 1.47), 1.13 (95% CI: 0.97, 1.31), 1.23 (95% CI: 1.06, 1.43) and 1.00 (reference; P for trend = 0.014), respectively. In particular, the association was more evident in individuals with normal-weight and those without hypertension or metabolic syndrome (all P for interactions < 0. 05).
Conclusions: These findings suggested that higher SUA levels were independently associated with a dose-response increased risk of CHD incidence.

1. Introduction

Serum uric acid (SUA), a final enzymatic product of purine metabolism, has been widely associated with a variety of cardiovascular conditions, including hypertension, diabetes, obesity, stroke, metabolic syndrome and more in numerous epidemiologic studies [1–5]. However, the role of SUA as an independent risk factor in coronary heart disease (CHD) incidence is still controversial [6]. Some prospective studies and two recent meta-analysis based on nine studies, showed that high SUA level or hyperuricemia may increase the risk of CHD incidence independently of traditional risk factors [7–12], whereas others studies, including an earlier meta-analysis of eight studies, indicated null associations with adjustment for possible confounders [13–19]. In addition, whether any dose-response relationship exists between SUA level and risk of CHD occurrence remains unknown. Very recently, a new meta-analysis including 29 prospective cohort studies found that hyperuricemia might increase the risk of CHD morbidity and mortality; Dose-response analysis indicated that SUA was only associated with risk of CHD mortality in females, but no significant trend was found for CHD morbidity [20].

In addition, it was observed in previous studies that the associations between high SUA or hyperuricemia and cardiovascular disease (CVD) events appear to be stronger in women [10], normotensive individuals [8], and those without metabolic risk factors [9]. SUA is also known to be associated with other important CHD risk factors. Thus, it remains unclear whether such risk factors modify the dose-response relationship between SUA level and CHD incidence.

Since hyperuricemia was common in Chinese population, and the prevalence of hyperuricemia was higher in economically developed regions than in other regions in China [21–23], the public health importance of high SUA levels or hyperuricemia as a possible CVD risk factor should not be ignored. We therefore tested the hypothesis whether SUA was associated with incident CHD in a dose-response manner and

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whether the association was modified by major CHD risk factors in a middle aged and elderly Chinese population.

2. Materials and method

2.1. Study population

Data were derived from Dongfeng-Tongji Cohort Study and the design, methods of the cohort was described in detail previously [24,25]. Briefly, 31,000 retirees at Dongfeng Motor Corporation (DMC) were invited to participate in the Dongfeng-Tongji cohort study. Except for those who did not respond to the invitation, a total of 27,009 (approximately 87% response rate) retired employees agreed and completed baseline questionnaire, medical examinations and provided fasting blood samples between September 2008 and June 2010. Five years later, the participants were invited to the follow-up survey via telephone. In total, 25,978 individuals (96.2% of those at baseline) completed the first follow-up until October 2013. At the follow-up investigation, participants repeated the questionnaire interview, physical examinations, and blood collection as those during the baseline survey. After exclusion of participants who had cancers, CHD, stroke and renal diseases at baseline ($n = 7531$), missing data of SUA ($n = 1669$) and other covariates ($n = 715$), a total of 16,063 eligible individuals were included in the analyses. The study was approved by the Ethics and Human Subject committee of the School of Public Health, Tongji Medicine College, and Dongfeng General Hospital, DMC. Written informed consents were received from all participants.

2.2. Assessment of SUA

SUA and other biochemical indexes (such as creatinine, fasting plasma glucose, and blood lipids) were determined at the DMC-owned hospital's laboratory with ARCHITECT Ci8200 automatic analyzer (ABBOTT Laboratories. Abbott Park, Illinois, USA). SUA level was categorized into four groups according to the quartiles of gender-specific distribution: <271, 271–316, 316–370 and ≥370 μmol/L for men; <214, 214–253, 253–298 and ≥298 μmol/L for women. Hyperuricemia was defined as a SUA level ≥ 420 μmol/L (7.0 mg/dL) for men and ≥360 μmol/L (6.0 mg/dL) for women.

2.3. Assessment of covariates

Trained interviewers performed face-to-face semi-structured questionnaire interviews and collected information on socio-demographic characteristics (age, gender, education and marital status), diet, lifestyle such as smoking status (current, former, never), drinking status (current, former, never) and physical activity, occupational history, environmental exposures, family history, and medical history (diagnosed medical conditions, use of health services and use of medicines for the most recent 2 weeks). Participants who were smoking at least one cigarette per day for more than half a year were defined as current smokers; those who were drinking at least one time per week for more than half a year were considered as current drinkers. Physical activity was defined as those who regularly exercised >20 min per day over the last six months. For diet, we transformed the diet frequency into times per week uniformly according to four respondent frequency categories (daily, weekly, monthly, times per year) for four kinds of main regular food including meat and poultry, fishery product, soy products, vegetables and fruits, all of which might modify SUA levels [26,27]. We finally divided the consumption frequency per week into 3 categories: never, 1–3 times per week, and ≥4 times per week [28]. Body mass index (BMI) was calculated as mass (kg) divided by the square of height (m^2). Hypertension was defined as individuals with self-reported physician diagnosis of hypertension, or blood pressure ≥ 140/90 mmHg, or current use of antihypertensive medication [29]. Diabetes was defined as self-reported physician diagnosis of diabetes, fasting glucose level ≥ 7.0 mmol/L, or taking oral hypoglycemic medication or insulin [30]. Hyperlipidemia was defined as total cholesterol > 5.72 mmol/L or triglycerides >1.70 mmol/L at medical examination, or a previous self-reported physician diagnosis of hyperlipidemia, or taking lipid-lowering medication [31]. Metabolic syndrome, according to the new International Diabetes Federation (IDF) definition [32], was defined when the participants had central obesity (waist circumference ≥ 90 cm for Chinese men and ≥80 cm for Chinese women) plus any two of the following four factors: (1) high blood pressure: systolic ≥130 mmHg, diastolic ≥85 mmHg, or known treatment for hypertension; (2) hypertriglyceridemia: fasting serum triglycerides ≥1.7 mmol/L; (3) low HDL cholesterol: fasting HDL cholesterol <1.03 mmol/L in men and <1.29 mmol/L in women; and (4) hyperglycemia: fasting glucose level of ≥5.6 mmol/L (≥100 mg/dL) or known treatment for diabetes. The estimated glomerular filtration rate (eGFR) was calculated by using the Modification of Diet in Renal Disease (MDRD) equation applied for Chinese patients with chronic kidney disease (CKD) [33].

2.4. Ascertainment of incident CHD

All retired employees were covered by DMC's health-care service system and each participant had a unique medical insurance card number and ID, making it easy to track disease incidence and mortality. The incidence of CHD was identified through this medical insurance system and medical record reviews in the DMC-owned hospitals. The diagnosis of CHD was made based on well-accepted international standards by cardiologists in the DMC-owned hospitals. We defined incident CHD as the first hospital admission with an occurrence of an angina pectoris (ICD-10 code I20), acute myocardial infarction (AMI, I21), subsequent myocardial infarction (I22), other forms of acute (I24) or chronic (I25) heart disease, percutaneous transluminal coronary angioplasty or coronary artery bypass graft, and cardiac arrest (I46) or death with CHD (I20–I25) as the underlying cause [34].

2.5. Statistical analyses

Baseline characteristics of the participants were reported as mean ± SD for continuous variables and numbers (percentages) for categorical variables. Trends were evaluated with linear or logistic regression using the median value of SUA for each quartile as an ordinal variable adjusted for age and sex. We applied Cox proportional models to evaluate the relationship of SUA quartiles, hyperuricemia, or continuous serum uric acid (per 100 μmol/L increasement) with risk of incident CHD after adjusting for potential confounders. We fitted two multivariate proportional hazard models. Model 1 adjusted for age, gender, BMI, smoking status (current, former, never), drinking status (current, former, never), physical activity, education levels, hypertension, diabetes, hyperlipidemia, and family history of CHD. Model 2 further adjusted for use of diuretics, eGFR, and diet frequency categories (including meat and poultry, fishery products, soy products, vegetables and fruits). Test for linear trend was performed using the median SUA concentration for each quartile as a continuous variable in the multivariate model. Additionally, nonlinear trends of the relationship between SUA levels and risk for incident CHD was tested by restricted cubic spline Cox regression using 4 knots placed at the 5th, 35th, 65th, and 95th percentiles of SUA levels respectively, with 200 μmol/L (approximate the first sex-specific quartile) as the reference group. Stratified analyses were also performed by major baseline characteristics. Moreover, we tested potential interactions by adding the products of these covariates with SUA levels in total population, respectively. All statistical analyses were carried out using SAS version 9.3 (SAS institute Inc., Cary, NC). A 2-sided P value < 0.05 was considered to be statistically significant.

3. Results

3.1. Characteristics of study population

Baseline characteristics of participants by sex-specific quartiles of SUA levels are presented in Table 1. Compared with those in the lowest quartile, participants in the highest quartile were older and more likely to be males, overweight and presented a greater proportion of hypertension, diabetes, hyperlipidemia and metabolic syndrome. In addition, higher SUA levels were associated with a lower eGFR.

3.2. Relationship between SUA and CHD incidence

As shown in Table 2, we found that increasing SUA quartiles were independently associated with elevated risk of CHD incidence after adjustment for age, gender, BMI, education levels, smoking, drinking, physical activity, hypertension, diabetes, hyperlipidemia and family history of CHD. Compared with the first quartile of SUA levels, the adjusted HRs for CHD incidence from the second to the highest SUA quartile were 1.25 (95% CI: 1.08, 1.46), 1.16 (95% CI: 1.00, 1.35) and 1.33 (95% CI: 1.15, 1.54; P for trend = 0.001). Additional adjustment for use of diuretics, eGFR, and diet frequency categories did not substantially change the association. The adjusted HR for each 100 μmol/L increasement in SUA levels was 1.14 (95% CI: 1.01, 1.29) for CHD incidence. Hyperuricemia was also associated with a 14% increased risk of incident CHD (HR = 1.14; 95% CI: 1.01, 1.29). The restricted cubic splines showed that the risk of CHD incidence increased gradually with continuous SUA levels (P for linear trend = 0.005, Fig. 1). The significant linear trend test implied that there was dosage effects and no obvious evidence of a threshold effect on the risk of CHD incidence.

3.3. Stratified analyses for association of SUA with incident CHD

We subsequently conducted stratification analyses by major characteristics of the study population. The significant relationship between SUA levels and CHD incidence was more evident in individuals with normal-weight, normal renal function (>90 mL/min/1.73 m^2), and those without hypertension or metabolic syndrome (Table 3). In addition, the significant interactions were found between SUA levels and overweight, hypertension and metabolic syndrome (all P for interactions < 0.05).