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Association of high-sensitivity C-reactive protein in middle-aged and elderly Chinese people with hyperuricaemia and risk of coronary heart disease: a cross-sectional study

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ABSTRACT

Objectives Patients with hyperuricaemia are at relatively high risk of developing coronary heart disease (CHD). The purpose of this study was to examine the relationship between high-sensitivity C-reactive protein (hs-CRP) and CHD risk in a middle-aged and elderly population with hyperuricaemia.

Design A cross-sectional study.

Setting and participants This study was conducted in a health examination centre of China. Participants were diagnosed with hyperuricaemia based on uric acid concentrations. Specifically, males with a uric acid concentration ≥416 µmol/L were included, as well as females with a concentration ≥360 µmol/L.

Main outcome measures 10-year CHD risk for each individual was evaluated using Framingham risk score based on the Adult Treatment Panel III charts.

Results A total of 517 patients with hyperuricaemia (438 males and 79 females) aged from 40 to 85 years old were included in the present study. 193 (37.3%) patients were defined with relatively high 10-year CHD risk. Compared with the lowest quintile, the crude ORs of relatively high 10-year CHD risks were 1.43 (95% CI 0.78 to 2.63, p=0.245), 2.05 (95% CI 1.14 to 3.67, p=0.016), 2.77 (95% CI 1.54 to 4.98, p=0.001), 2.12 (95% CI 1.18 to 3.80, p=0.012) in the second, third, fourth and fifth quintiles of serum hs-CRP level, respectively (p for trend=0.057). The multivariable-adjusted ORs of relatively high 10-year CHD risk were 1.40 (95% CI 0.75 to 2.61, p=0.291) in the second, 2.05 (95% CI 1.13 to 3.72, p=0.019) in the third, 2.69 (95% CI 1.47 to 4.89, p=0.001) in the fourth and 2.10 (95% CI 1.15 to 3.84, p=0.016) in the fifth quintile of serum hs-CRP level when compared with the lowest quintile (p for trend=0.068).

Conclusion This study showed that ORs of relatively high 10-year CHD risk were raised in patients with hyperuricaemia with higher serum hs-CRP level; however, there was a not significant but borderline trend association and that more research is needed.

Strengths and limitations of this study

- This is the first study exploring the association between high-sensitivity C-reactive protein (hs-CRP) and the coronary heart disease (CHD) risk in patients with hyperuricaemia in a middle-aged and elderly population with hyperuricaemia.
- The relationship of hs-CRP and the CHD risk was analysed by multivariable models.
- As result of the nature of cross-sectional design, the causal relationship cannot be established in the present study.
- Though Framingham risk score (FRS) has been used to assess the risk of cardiovascular events in Chinese population, it is noteworthy that FRS was originally constructed for the US population using a US population data.

BACKGROUND

Serum uric acid is the catabolic end-product of purine metabolism via the catalysis of xanthine oxidase. With the rapid economic development, the dietary habits of Chinese people have changed greatly towards an increasingly heavier intake of meat, dairy products and other purine enriched foods, which has led to a higher prevalence of hyperuricaemia and gout susceptibly.[1 2] A systematic review and meta-analysis involving 44 studies showed that the pooled prevalence of hyperuricaemia was 13.3% in mainland China from 2000 to 2014.[3] Some previous studies reported that an increase in serum uric acid was incriminated in the pathogenesis of metabolic syndrome,[4 5] chronic kidney disease,[6 7] stroke[8] and coronary heart disease (CHD).[9 10]

Over the past several decades, relevant studies have shown that an increased serum uric acid was significantly associated with CHD, independent of conventional CHD risk factors.[9–12] Besides, it was also demonstrated that increased uric acid was correlated with

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hypertension, diabetes mellitus, metabolic syndrome, hypertriglyceridemia and endothelial dysfunction.[6 13–19] All of this could lead to an increased risk of CHD. With the trend of population ageing, CHD has become one of the most common causes of death.[20] Therefore, it is urgent to seek effective predictors or biomarkers to identify subjects at a high risk of CHD, especially among the patients with hyperuricaemia, who are deemed a high risk group of CHD. A wide array of studies indicated that inflammation was involved in the pathogenesis of CHD.[21 22] C-reactive protein (CRP), one of the acute phase respondents, is commonly used in clinical practice to reflect chronic inflammation as an inexpensive measurement.[23] Several epidemiological studies were undertaken to clarify the relationship between CRP and CHD, but no agreement has been reached.[24–26] To the best of the authors' knowledge, there has been no study yet examining the association between high-sensitivity (hs)-CRP and the CHD risk in patients with hyperuricaemia. Meaningful outcomes in this respect would have important implications in understanding the pathophysiological mechanisms of CHD in patients with hyperuricaemia and contribute to the development of a simple and inexpensive method to predict the future CHD risk of this population.

To fill this knowledge gap, the present cross-sectional study was carried out to clarify the correlation between hs-CRP and the 10-year estimated CHD risk measured by the Framingham risk score (FRS) in the middle-aged and elderly population with hyperuricaemia, with adjustment of conventional cardiovascular risk factors.

MATERIALS AND METHODS

Study population

The participants of the present cross-sectional study were chosen from a pool of subjects who were undergoing routine medical examinations at the Department of Health Examination Center Xiangya Hospital, Central South University in Changsha, Hunan Province of China. The detailed methodology has been described in some earlier studies.[27–32] Briefly, all the qualified participants must be 40 years old or above and undergoing measurements of serum uric acid, hs-CRP, fasting plasma glucose concentration, total cholesterol, high-density lipoprotein (HDL-cholesterol) and creatinine during the specified period. In addition, the subjects should be diagnosed with hyperuricaemia (ie, the uric acid ≥416 µmol/L for male and ≥360 µmol/L for female), with availability of demographic and clinical data including age, gender, body mass index (BMI) (weight/height^2), smoking status, alcohol drinking status, activity level, medication status and so on. Initially, a total of 5994 subjects were included based on the age requirement and availability of blood biochemical assessments (serum uric acid and hs-CRP measurement) during the period of October 2013 to December 2015. Then, 3420 subjects were disqualified: 30 were lack of basic health characteristics such as blood pressure and BMI and 3390 were lack of information of health-related habits. Of the remaining 2574 subjects, only 517 were diagnosed with hyperuricaemia and were finally enrolled in the present study. The study protocol had been reviewed and approved by the local Ethics and Research Committee and the written informed consent had been obtained from all participants prior to execution.

Blood biochemistry

All blood samples were drawn from the antecubital vein using vacuum tubes after an overnight fast of ≥12 hours, and were kept at 4°C until analysis. The hs-CRP was detected by the Latex turbidity method. The fasting plasma glucose concentration was measured using the glucose oxidase enzyme method. The uric acid, total cholesterol, HDL-cholesterol and creatinine were all detected using a Beckman Coulter AU 5800 (Beckman Coulter, Brea, California, USA). The 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 were used, respectively, to evaluate the intra-assay and inter-assay coefficients of variation. 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 interassay 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. A subject was diagnosed with diabetes mellitus if his/her fasting plasma glucose level ≥7.0 mmol/L or if he/she was currently receiving medication for blood glucose control.

Assessment of other exposures

The BMI was calculated as the weight (kg) divided by the square of the height (m). The blood pressure was detected at the upper arm using an electronic sphygmomanometer after a rest of at least 10 min. Then, the status of physical activity, including the average frequency (never, one to two times per week, three to four times per week, five times and above per week) and the average duration of physical activity (within half an hour, half an hour to 1 hour, 1 to 2 hours, more than 2 hours) was collected from each subject. Last, the smoking and alcohol drinking status as well as the medication conditions of the subjects were inquired.

Assessment of 10-year CHD risk

The risk level of developing CHD was measured by the FRS according to The Adult Treatment Panel III (ATP III) charts,[33] and the FRS was calculated based on seven risk factors, which are age, gender, smoking, systolic blood pressure, use of antihypertensive medication, total cholesterol and HDL cholesterol, respectively. The specific risk scoring process is as follows: (1) calculate the number of points for each risk factor; (2) sum up the points of each risk factor to obtain the total risk score; (3) generate the estimated 10-year CHD risk for each patient. The subjects

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with the 10-year risk above 10% were classified into the high 10-year CHD risk group.

Statistical analysis

For statistical analysis, the continuous variables with a normal distribution were presented as mean±SD, and the category variables were described by frequency and percentage. The participants were classified into five categories based on the quintile distribution of hs-CRP, namely ≤0.50, 0.51–0.90, 0.91–1.63, 1.63–3.04 and ≥3.05 mg/L. Baseline characteristics were presented according to quintiles of hs-CRP, and their trend associations were assessed using a linear regression analysis for continuous variables or a logistic regression for category variables, with the median value of hs-CRP in each category assigned to the corresponding category. The association between hs-CRP and the CHD risk has been described as the OR and 95% CIs, which were calculated for each quintile of hs-CRP; the lowest quintile was regarded as the reference category. Then, the factors of BMI, educational background, alcohol drinking status, activity level, serum creatinine and diabetes that might affect both hs-CRP and the outcomes of interest were included in these models as adjustors. The trend for relatively high CHD risk according to quartile of hs-CRP was analysed using the linear regression model. All data analyses were performed using SPSS 18.0 (SPSS, Chicago, Illinois, USA), and the level for statistical significance was set as the p value equal to 0.05. All tests were two tailed.

Patient and public involvement

Patients and the public were not involved in setting the research question or the outcome measures, nor were they involved in the design or implementation of the study. There were no plans to disseminate the results of the research to study participants.

RESULTS

A total of 517 patients with hyperuricaemia (438 males and 79 females) aged from 40 to 85 years old were included in the present study. There were 193 (37.3%) patients were defined with relatively high 10-year CHD risk. The basic characteristics of study population based on the quintiles of hs-CRP are shown in table 1. Patients with hyperuricaemia in the highest level group of hs-CRP were more likely to have a higher BMI and lower activity level than were those in the lowest level group (p for trend <0.05 for all).

The results of the associations between hs-CRP and relatively high 10-year CHD risk (≥10%) are shown in table 2. According to the crude OR values, a higher prevalence of relatively high CHD risk was observed in the highest quintile (OR=2.12, 95% CI 1.18 to 3.80, p=0.012) of hs-CRP when comparing with the lowest quintile, and p for trend was 0.057. After adjustment for BMI, educational background, alcohol drinking status, activity level, serum creatinine and diabetes, the results did not change materially. Though ORs of relatively high CHD risk were raised in subjects with higher serum hs-CRP level, only a not significant but borderline trend association was observed; the multivariable OR based on a comparison of the highest and the lowest quintile of hs-CRP was 2.10 (95% CI, 1.15 to 3.84; p=0.016), and p for trend was 0.068.

DISCUSSION

The present cross-sectional study revealed a borderline positive association between hs-CRP and the high 10-year risk of CHD in the middle-aged and elderly population with hyperuricaemia. This correlation did not changed significantly with adjustment of several potential confounding factors such as BMI, educational background, alcohol drinking status, activity level, serum creatinine and diabetes. These findings suggested that hs-CRP could serve as a marker for the risk of CHD in patients with hyperuricaemia.

The relationship between CRP and CHD has aroused intensive arguments. Some earlier studies demonstrated that a high level of CRP concentration was positively associated with CHD and that CRP was predictive of CHD.[34–37] For example, in two nested case–control studies—the Nurses' Health Study and the Health Professionals Follow-up Study—Jennifer *et al* found that a high level of CRP was associated with an increased risk of CHD among participants with no history of cardiovascular disease and that the level of CRP could be considered as a predictor of CHD.[38] In the Cardiovascular Health Study, elevated CRP was found to be associated with an increased 10-year risk of CHD, regardless of the presence of conventional risk factors.[39] Besides, a cross-sectional study conducted in Japan demonstrated that hs-CRP was associated with the estimated risk level of CHD in the middle-aged men.[25] However, controversy remains with respect to the association of CRP with CHD, and the predictive value of CRP. According to the data obtained from the MONICA Optional Haemostasis Study, no significant correlation was observed between the CHD event rate and the plasma CRP in the European populations.[24] Similarly, it was shown that the CRP level was not significantly associated with CHD with adjustment of conventional risk factors in the postmenopausal women.[40] Meanwhile, the findings from the 1999–2004 NHANES suggested that hs-CRP was not associated with the CHD mortality.[41] The present study further revealed that CRP was borderline positively associated with CHD in patients with hyperuricaemia.

It is interesting that, in the present study, the OR for CHD risk was lower in the highest quintile than the fourth quintile of hs-CRP. This phenomenon was also observed in several previous studies. Folsom *et al* showed that the multivariate-adjusted relative risk of CHD in the fifth quintile of CRP was lower than in the fourth quintile.[42] Similar result was observed in another study which demonstrated that multivariate-adjusted relative risk of cardiovascular events was lower in the fourth quartile than in the third quartile of CRP.[43] However, our study

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Table 1 Basic characteristics of study population based on the quintiles of hs-CRP level (n=517)

Characteristics	Quintiles of hs-CRP (mg/L) 1 (≤0.50)	2 (0.51–0.90)	3 (0.91–1.63)	4 (1.64–3.04)	5 (≥3.05)	P for trend
N	108	99	106	100	104	
Demographic characteristics						
Age (years)	50.2 (6.6)	50.2 (5.6)	51.3 (7.3)	51.4 (6.0)	51.5 (7.4)	0.165
Female (%)	13.0	13.1	13.2	19.0	18.3	0.206
Educational background (High school or above, %)	66.7	53.5	75.5	66.0	62.5	0.743
Clinical characteristics						
BMI (kg/m^2)	25.3 (3.2)	26.0 (2.6)	26.8 (3.1)	26.8 (3.0)	27.0 (3.6)	0.001
Relatively high CHD risk (≥10%, %)	25.0	32.3	40.6	48.0	41.3	0.057
Systolic blood pressure (mm Hg)	129.4 (14.3)	132.7 (15.7)	133.6 (15.5)	135.6 (16.9)	136.3 (17.4)	0.873
Diastolic blood pressure (mm Hg)	82.1 (11.0)	84.3 (11.5)	85.1 (11.3)	86.3 (11.6)	87.5 (12.2)	0.151
Diabetes (yes, %)	12.0	12.1	11.3	18.0	17.3	0.174
Biochemical characteristics						
Total cholesterol (mg/dL)	202.8 (35.6)	209.1 (37.9)	207.8 (40.9)	211.1 (41.4)	206.7 (49.6)	0.873
HDL cholesterol (mg/dL)	53.2 (13.4)	51.6 (13.5)	51.8 (9.6)	50.7 (12.1)	49.5 (10.6)	0.151
Serum creatinine (μmol/L)	100.5 (32.8)	104.4 (49.7)	98.9 (14.9)	99.5 (34.9)	99.1 (17.6)	0.528
Lifestyle characteristics						
Activity level (h/week)	2.0 (2.5)	1.3 (2.3)	1.8 (2.9)	1.6 (2.7)	1.2 (2.3)	0.047
Smoking (yes, %)	24.1	29.3	34.9	36.0	35.6	0.165
Alcohol drinking (yes, %)	53.7	61.6	63.2	61.0	52.9	0.328

Data are mean (SD), unless otherwise indicated.
BMI, body mass index; HDL, high density lipoprotein; hs-CRP, hypersensitive C-reactive protein.

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Table 2 Associations between hs-CRP and relatively high 10-year CHD risk (≥10%) in hyperuricaemia population (n=517)

	Quintiles of hs-CRP (mg/L)					
	1 (≤0.50)	2 (0.51–0.90)	3 (0.91–1.63)	4 (1.64–3.04)	5 (≥3.05)	P for trend
Participants (n)	108	99	106	100	104	
Median hs-CRP (mg/L)	0.34	0.69	1.21	2.11	6.12	
Crude OR (95% CI)	1.00 (reference)	1.43 (0.78 to 2.63)	2.05 (1.14 to 3.67)	2.77 (1.54 to 4.98)	2.12 (1.18 to 3.80)	0.057
P values	–	0.245	0.016	0.001	0.012	
Multivariable adjusted OR (95% CI)*	1.00 (reference)	1.40 (0.75 to 2.61)	2.05 (1.13 to 3.72)	2.69 (1.47 to 4.89)	2.10 (1.15 to 3.84)	0.068
P values	–	0.291	0.019	0.001	0.016	

*Multivariable adjusted model was adjusted for BMI, educational background, alcohol drinking status, activity level, serum creatinine and diabetes.
BMI, body mass index; CHD, coronary heart disease; hs-CRP, hypersensitive C-reactive protein.

and these previous studies are all epidemiological studies which cannot establish mechanisms, and additional basic research on this interesting phenomenon is needed.

Previous in vivo and in vitro studies have suggested that CRP modulated many factors involved in atherosclerosis, which might explain the positive association between the CRP level and CHD. CRP could reduce the endothelial nitric oxide synthase both at the protein and mRNA levels and promote the production of inducible nitric oxide synthase and endothelin-1 in endothelial cells.[38 39] Besides, it was reported that the adhesion and internalisation of white blood cells onto the arterial wall were improved by CRP by inducing the expression of vascular cell adhesion molecule-1, intercellular adhesion molecule-1, E-selectin and monocyte chemoattractant protein-1.[44 45] Moreover, CRP could also induce the monocyte chemotaxis and differentiation[46 47] and facilitate the uptake of oxidised low-density lipoprotein through macrophages and monocyte-platelets aggregation.[48 49] Further evidence supported CRP as a participant in later stages of atherosclerosis with the expression of matrix metalloproteinases and collagenase activity in human monocyte-macrophages.[50 51]

The present study clarified that high hs-CRP was correlated with a high CHD risk in the middle-aged and elderly population with hyperuricaemia, while several previous study have shown that CRP was not significantly associated with CHD in general population or other population.[24 40] It is suggested that hyperuricaemia interacts synergistically with high hs-CRP subjects and may subsequently enhance the risk of CHD predictor value of hs-CRP. This has implications for clinicians to predict the CHD risk in patients with hyperuricaemia based on hs-CRP, an easily measured clinical marker, and thereby providing preventive measures accordingly. Meanwhile, it also prompts that uric acid may interact with other risk factors during the development and progression of CHD, but such conclusion needs to be validated by further study.

Several strengths and shortcomings of this study are worth being mentioned. First, this is the first study exploring the association between hs-CRP and the CHD risk in patients with hyperuricaemia in the middle-aged and elderly population. Second, multivariable models were used to analyse the aforementioned relationship by adjusting a considerable number of potential confounding factors, such as BMI, serum creatinine and diabetes. As for the limitations, first, no causal relationship can be established in the present study due to the nature of cross-sectional design. However, the primary objective of this study was to examine the association between CRP and the CHD risk rather than to prove that CRP could increase the incidence of CHD. As CRP was deemed to be correlated with the CHD risk score, it can be used to reflect this complicated index in clinical practice. Subsequently, other more complicated indexes such as the FRS could be used to examine the CHD risk. Therefore, it can be speculated that CRP may have the potential to be an easily accessible screening method in the future after further studies' confirmation. Second, though FRS has been used to assess the risk of cardiovascular events in Chinese population,[52 53] it is noteworthy that FRS was originally constructed for the US population using a US population data. Third, age, sex, blood pressure, cholesterol and smoking should be included in adjusting covariates in multivariate analyses regarding CHD risk. However, FRS was calculated based on seven risk factors: age, gender, smoking, systolic blood pressure, use of antihypertensive medication, total cholesterol and HDL cholesterol. Therefore, we excluded these impotent confounders from adjusting risk factors as previous studies did.[54 55]

CONCLUSION

This study showed that ORs of relatively high 10-year CHD risk were raised in patients with hyperuricaemia with higher serum hs-CRP level; however, there was a not significant but borderline trend association and that more research is needed.

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Competing interests None declared.

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