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ASSOCIATION BETWEEN SERUM URIC ACID LEVEL AND CAROTID ATHEROSCLEROSIS IN CHINESE INDIVIDUALS AGED 75 YEARS OR OLDER: A HOSPITAL-BASED CASE-CONTROL STUDY

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Abstract: *Objectives:* To investigate the association between serum uric acid level and the presence and progression of carotid atherosclerosis in Chinese individuals aged 75 years or older. *Design:* Case-control study. *Setting:* In a teaching hospital. *Participants:* Five hundred and sixty-four elderlies (75 years or above) who underwent general health screening in our hospital were enrolled. *Measurements:* The detailed carotid ultrasound results, physical examination information, medical history, and laboratory test results including serum uric acid level were recorded, these data were used to analyze the relationship between serum uric acid level and carotid atherosclerosis. Then, subjects who underwent the second carotid ultrasound 1.5-2 years later were further identified to analyzed the relationship between serum uric acid and the progression of carotid atherosclerosis. *Results:* A total of 564 subjects were included, carotid plaque was found in 482 (85.5%) individuals. Logistic regression showed that subjects with elevated serum uric acid (expressed per 1 standard deviation change) had significantly higher incidence of carotid plaque (odds ratio, 1.37; 95% confidence interval, 1.07–1.75; P= 0.012) after controlling for other factors. A total of 236 subjects underwent the follow-up carotid ultrasound. Linear regression showed that serum uric acid level (expressed per 1 standard deviation change; 1 standard deviation = 95.5 μmol/L) was significantly associated with percentage of change of plaque score (P = 0.008). Multivariable linear regression showed that 1 standard deviation increase in serum uric acid levels was expected to increase 0.448% of plaque score (P = 0.023). *Conclusion:* The elevated serum uric acid level may be independently and significantly associated with the presence and progression of carotid atherosclerosis in Chinese individuals aged 75 years or older.

Key words: Carotid atherosclerosis, carotid plaque, uric acid, carotid ultrasound, elder population.

Abbreviations: DM: diabetes mellitus; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; TC: total cholesterol; BMI: body mass index.

Introduction

In China, the problem of aging population is an indisputable fact. The China Aging Development Report (2013) showed that 202 million of the population were elderly population (aged 60 years or above) in China by the end of 2012, which accounts for up 14.3% of the total Chinese population (1). By 2039, China will enter an advanced stage of aging with a total of 487 million (30.0%) of the population being elderly population. Cardiovascular and cerebrovascular diseases have become the leading causes of death in China. Their incidence increases with age (2, 3). For example, the stroke incidence in people aged over 75 years is 30 times higher than in people aged 35–44 years (3), and carotid atherosclerosis is associated with the occurrence of cardiovascular and cerebrovascular diseases (4-7).

Uric acid is a normal metabolic product of purine nucleotides. Serum uric acid may be associated with atherosclerosis through mediating inflammation, inducing endothelial dysfunction, and stimulating smooth muscle cell proliferation (8-10). Observational studies showed that high serum uric acid level may be a risk factor for carotid atherosclerosis (11, 12). The data of these studies also showed that there was a significant positive correlation between age and serum uric acid level. However, there is lack of evidence regarding the relationship between serum uric acid level and the presence and progression of carotid atherosclerosis, especially in the gradually increasing Chinese aged individuals (≥75 years old) who are at a substantially higher risk of cardiovascular and cerebrovascular diseases.

Therefore, we aimed to investigate the association between serum uric acid level and the presence and progression of carotid atherosclerosis in Chinese individuals aged 75 years or older.

Methods

Study participants

The ethics committee of the First Hospital of Jilin University approved the study design.

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We retrospectively screened individuals who underwent a general health screening in the health examination center of the First Hospital of Jilin University between January 2013 and December 2014. Elderly (75 years or above) individuals with detailed carotid ultrasound, physical examination information, medical history, and laboratory test results, including serum uric acid level were enrolled. Individuals who underwent the second carotid ultrasound 1.5–2 years later were further identified. Individuals with stroke history or taking uricosuric medication were excluded.

Evaluation of baseline risk factors

Basic information including sex, age, height, weight, and blood pressure was collected. Medical history including hypertension, diabetes mellitus (DM), smoking, dyslipidemia, drinking, and medical treatments for the above conditions was recorded. Laboratory tests, including those for blood glucose, hemoglobin A1C, total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and creatinine were performed in the fasting state. Hypertension was defined as a blood pressure ≥140/90 mm Hg after the individuals had rested for at least 5 minutes or when the individual was under medical treatment for hypertension. DM was defined as a fasting glucose ≥126 mg/dL or when the individual was under medical treatment for DM. Dyslipidemia was defined by total cholesterol (TC) ≥6.0 mmol/L, LDL-C ≥3.1 mmol/L, HDL-C ≤0.76 mmol/L, triglyceride ≥1.8 mmol/L, or when the individual was under medical treatment for dyslipidemia. Renal insufficiency was defined as estimated glomerular filtration rate < 60 mL/min per 1.73m2. Smoking status was categorized as never smoking, former smoking, and current smoking. Body mass index (BMI) was calculated as the ratio of weight in kilograms to the square of height in meters.

Carotid ultrasound

Carotid ultrasound was performed by experienced neurosonographers using B-mode ultrasound (Philips iU22, 9/13-MHz linear-array transducer). The supine position was used for the examination. Presence of carotid plaque and plaque score were assessed for each individual. Plaque was defined as focal thickening of ≥50% than the adjacent site (13). Plaque score was defined as the summed plaque thickness of all plaques for each individual (5, 14, 15). Most of the subjects without carotid plaque at initial examination did not have the follow-up carotid ultrasound within 1.5–2 years. For the few subjects without carotid plaque at initial examination and underwent the follow-up carotid ultrasound within 1.5-2 years, carotid plaque was not found for all of them by the follow-up carotid ultrasound. All of the subjects underwent the follow-up carotid ultrasound had carotid plaque at initial examination. Percentage of change of plaque score was calculated as the ratio of absolute difference of plaque score between the initial examination and the follow-up examination to the plaque score at initial examination.

Statistical analysis

Quantitative data were expressed as means ± SD. Qualitative data were expressed as counts and percentages. One-way ANOVA test was used for data with normal distribution. Mann–Whitney U test was used for ordered categorical data with two independent exposure groups. Kruskal-Wallis test was used for ordered categorical data with three independent exposure groups. Binary logistic regression was performed to assess the relationship between serum uric acid level and the presence of carotid plaque. Presence of carotid plaque was set as the dependent variable. Linear regression was performed to identify the relationship between serum uric acid level and the progression of carotid atherosclerosis. Percentage of change of plaque score was set as the dependent variable. Interaction between serum uric acid level and other risk factors in relation to the presence of carotid plaque and percentage of change of plaque score were assessed. SPSS 19.0 (IBM, West Grove, PA) was used to perform the analysis. The level of statistical significance was set at $P < 0.05$.

Results

A total of 564 subjects were included. Table 1 shows the baseline characteristics. The mean age was 82.3 (±4.77) years, including 314 females (55.7%). Carotid plaque was found in 482 (85.5%) individuals. The mean value of serum uric acid level was 400.6 (±86.5) μmol/L. Serum uric acid quartiles were 143 to 342 μmol/L, 343 to 395 μmol/L, 396 to 451 μmol/L, and 452 to 796 μmol/L. Older age, male sex, high BMI, hypertension, DM, increased TC, increased triglyceride, increased LDL-C, and renal insufficiency were significantly ($P < 0.05$) associated with elevated serum uric acid level according to quartiles of uric acid.

Serum uric acid level and carotid plaque

Presence of carotid plaque was found in 482 subjects (85.5%). Kruskal-Wallis test showed that higher serum uric acid level according to quartiles was associated with higher probability of carotid plaque (P for trend = 0.002). Univariate logistic regression showed that subjects with a higher level of serum uric acid (expressed per 1 standard deviation change; 1 standard deviation = 86.5 μmol/L) had significantly higher probability of having carotid plaque (OR, 1.59; 95% CI, 1.22–2.06; P = 0.001) (Table 2). After controlling for age and sex, the relationship remained significant (OR, 1.47; 95% CI, 1.14–1.90; P = 0.003) (Table 2). Additional control for other factors showed similar result (OR, 1.37; 95% CI, 1.07–1.75; P = 0.012) (Table 2).

Serum uric acid level and the progression of carotid plaque

A total of 236 subjects who had initial carotid plaque underwent the follow-up carotid ultrasound. The mean age was 82.84 (±4.91) years, including 121 females (51.3%). The mean value of serum uric acid level was 421.98 (±95.5) μmol/L. The mean initial plaque score and mean follow-up

Table 1
Baseline characteristics of study population according to quartiles of uric acid

		Uric Acid Quartiles				
	Total (n = 564)	**Quartile 1 (n = 137)**	**Quartile 2 (n = 142)**	**Quartile 3 (n = 141)**	**Quartile 4 (n = 144)**	**P for trend**
Age (years, mean ± SD)	83.45±4.91	81.27±5.62	82.76±4.64	83.19±5.26	84.14±4.07	<0.001*
Female (n, %)	319,56.6%	91, 65.9%	85, 59.4%	77, 54.2%	66, 45.5%	<0.001
Body mass index (kg/m^2, mean ± SD)	24.43±2.33	23.81±2.10	24.14±2.48	24.49±2.45	24.56±2.27	0.003*
Smoking (n, %)						0.311†
Current	108, 19.2%	24, 17.5%	26, 18.3%	27, 19.1%	31, 21.5%	
Previous	73,12.9%	18,13.1%	16,11.3%	19,13.5%	20,13.9%	
Never	383,67.9%	95,69.3%	100,70.4%	95,67.4%	93,64.6%	
Drinking (n, %)	134, 23.8%	35, 25.5%	32, 22.5%	37,26.2%	30,20.8%	0.513
Hypertension (n, %)	254, 45.0%	51, 37.2%	57, 40.1%	66, 46.8%	80, 55.6%	0.001
Diabetes mellitus (n, %)	146, 25.9%	28, 20.4%	35, 24.6%	38, 27.0%	45, 31.3%	0.036
High TC (n, %)	87, 15.4%	16, 11.7%	19, 13.4%	23, 16.3%	29, 20.1%	0.037
High TG (n, %)	146, 25.9%	28, 20.4%	34, 23.9%	39, 27.7%	45, 31.3%	0.029
High LDL-C (n, %)	183, 32.4%	37, 27.0%	42, 29.6%	48, 34.0%	56, 38.9%	0.023
Low HDL-C (n, %)	22, 3.9%	3, 2.2%	4, 2.8%	7, 5.0%	8, 5.6%	0.093
Renal insufficiency (n, %)	122, 21.6%	22, 16.1%	27, 19.0%	32, 22.7%	41, 28.5%	0.008
Use of statin (n, %)	103, 18.3%	23, 16.8%	22, 15.5%	25, 17.7%	33, 22.9%	0.152
Use of antihypertensive medication (n, %)	180, 31.9%	40, 29.2%	44, 31.0%	45, 31.9%	51, 35.4%	0.264
Use of antidiabetic medication (n, %)	101, 17.9%	21, 15.3%	24, 16.9%	25, 17.7%	31, 21.5%	0.178
Carotid plaque (n, %)	482,85.5%	109, 79.6%	117,82.4%	124, 87.9%	132, 91.7%	0.002

TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; One-way ANOVA was used for quantitative data. Mann–Whitney U test was used for ordered categorical data with two independent exposure groups. Kruskal-Wallis test was used for ordered categorical data with three independent exposure groups.* P values for trend. † Spearman's rank correlation coefficient was -0.043 (P=0.307).

plaque score were 9.9 (±6.1) and 10.6 (±6.3), respectively. The mean percentage of change of plaque score was 7.32 (±3.56). Correlation analysis showed that serum uric acid level was significantly associated with percentage of change of plaque score (Pearson correlation coefficient = 0.173, P = 0.008). Linear regression showed that serum uric acid level (expressed per 1 standard deviation change; 1 standard deviation = 95.5 μmol/L) was significantly associated with percentage of change of plaque score (P = 0.008) (Figure 1 and Table 3). Multivariable linear regression showed that 1 standard deviation increase in serum uric acid levels was expected to increase 0.448% of plaque score (P = 0.023, Table 3).

Additional analysis

Absolute values of TC, triglyceride, LDL-C, and HDL-C were significantly associated with serum uric acid levels according to quartiles of uric acid respectively (P for trend < 0.05). The absolute values of these factors were used to perform the multivariable analysis again. Multivariable logistic regression showed that the relationship between serum uric acid levels and the presence of carotid plaque remained significant (OR, 1.38; 95% CI, 1.05–1.71; P = 0.019). Multivariable linear regression showed that serum uric acid level was still significantly associated with the percentage of change of plaque score (β= 0.536, P = 0.025).

Table 2
The association between uric acid level and presence of carotid plaque

	OR	**95% CI**	**P value**
Univariate	1.59	1.22 to 2.06	0.001
Model 1	1.47	1.14 to 1.90	0.003
Model 2	1.37	1.07 to 1.75	0.012

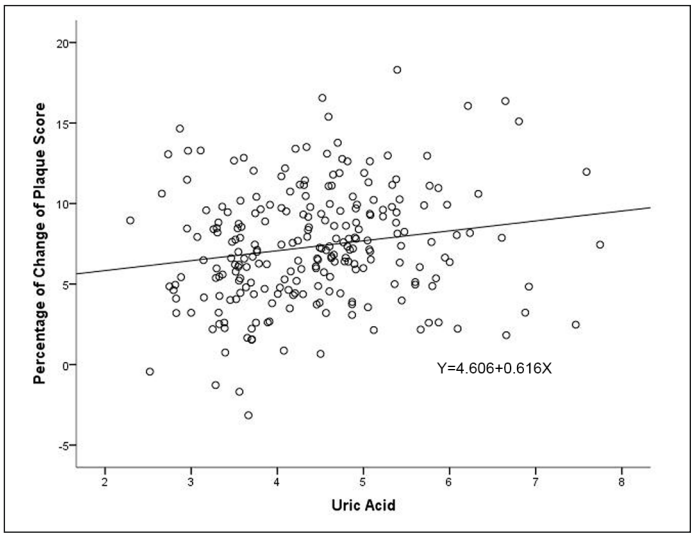
Model 1: adjusted for sex and age. Model 2: adjusted for sex, age, BMI, smoking, drinking, hypertension, diabetes mellitus, TC, TG, LDL-C, HDL-C, renal insufficiency, use of statin, use of antihypertensive medication, and use of antidiabetic medication. Binary logistic regression was used. The value of uric acid level was expressed per 1 standard deviation change (1 standard deviation = 86.5 μmol/L). BMI, body mass index; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; TC, total cholesterol; TG, triglyceride.

Table 3
The association between uric acid level and progression of carotid atherosclerosis

	β*	95% CI	P value
Univariate	0.616	0.165 to 1.068	0.008
Model 1	0.639	0.187 to 1.092	0.006
Model 2	0.448	0.063 to 0.834	0.023

Model 1: adjusted for sex and age. Model 2: adjusted for sex, age, BMI, smoking, drinking, hypertension, diabetes mellitus, TC, TG, LDL-C, HDL-C, renal insufficiency, use of statin, use of antihypertensive medication, and use of antidiabetic medication. Linear regression was used. The value of uric acid level was expressed per 1 standard deviation change (1 standard deviation = 95.5 μmol/L). Progression of carotid atherosclerosis was expressed as percentage of change of plaque score. BMI, body mass index; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride. * Unstandardized regression coefficients.

Figure 1
Linear regression for percentage of change of plaque score as a function of uric acid level. The Pearson correlation coefficient was 0.173 (p = 0.008). The value of uric acid level was expressed per 1 standard deviation change



There was no significant interaction between serum uric acid level and other risk factors (sex, age, BMI, smoking, drinking, hypertension, diabetes mellitus, TC, triglyceride, LDL-C, HDL-C, renal insufficiency, use of statin, use of antihypertensive medication, and use of antidiabetic medication) in relation to the presence of carotid plaque and percentage of change of plaque score (P≥0.151).

Discussion

In this retrospective study, we found that serum uric acid level is positively and significantly associated with the presence and progression of carotid atherosclerosis in Chinese individuals aged 75 years or older. These associations were significant after controlling for other factors.

Uric acid is a normal metabolic product of purine nucleotides. Increase and decrease of serum uric acid are both associated with several diseases. Previous studies have reported that elevated level of serum uric acid is also associated with conditions such as cardiovascular disease (16, 17). However, the role of elevated uric acid as a risk factor is controversial. It may be a marker for risk, a cause of disease, or even both (16, 18).

Some studies that investigated the relationship between the level of serum uric acid and carotid atherosclerosis, but the results were inconsistent. Moreover, none of them were focused on individuals aged 75 years or older. Ishizaka et al. found that uric acid was an independent risk factor for the incidence of carotid plaque in men who did not have metabolic syndrome (19). Kawamoto et al. reported similar results; they found that uric acid was an independent risk factor for incidence of carotid intima-media thickening in men who did not have metabolic syndrome (20). However, Takayama et al. reported that the significant relationship between elevated uric acid and incidence of carotid atherosclerosis was present in both genders without metabolic syndrome (11). These significant relationships in women and in subjects with metabolic syndrome were found by other studies (21, 22). There are also studies that showed that there was no significant relationship between elevated uric acid and the incidence of carotid atherosclerosis (23). Our study not only supports the relationship in individuals aged 75 years or older, but also suggests that there is a significant relationship between elevated uric acid and progression of carotid atherosclerosis in individuals aged 75 years or older. Since there was no significant interaction between uric acid level and other factors and the sample size of our study is relatively smaller compared with that of other studies, we did not perform subgroup analysis by other factors such as sex.

Although elevated uric acid level was found to be associated with diseases such as cardiovascular disease and carotid atherosclerosis by many studies, it has not been clearly defined whether elevated uric acid is a marker for risk or a cause of disease. Because elevated uric acid is significantly associated with several risk factors such as hypertension, impaired glucose metabolism, dyslipidemia, and metabolic syndrome, it is thought that the association between elevated uric acid and cardiovascular disease or carotid atherosclerosis is merely a result of multicollinearity between uric acid and other risk factors (16, 24). Recently, a randomized, double-blind phase IIb/III trial assessed the safety and efficacy of uric acid therapy for functional outcomes at 90 days in patients with acute ischemic stroke (25). Even the primary result showed that the addition of uric acid to thrombolytic therapy was not significantly associated with excellent outcome after stroke and there are no safety concerns. A post hoc analysis showed that uric acid therapy was associated with reduced infarct growth and improved outcome in patients with hyperglycemia during

acute stroke (26). The effects probably were taken by multiple antioxidant effects such as accelerating the scavenging of peroxynitrite-derived free radicals (26). The protective effects of uric acid support the theory that hyperuricemia may be a compensatory mechanism to counteract oxidative damage related to atherosclerosis in humans (27). Hence, the cause and effect between serum uric acid and carotid atherosclerosis remain unclear.

There were several limitations of this study. First, the retrospective design of this study may increase the risk of bias and cannot elucidate the temporal order between elevated uric acid and carotid atherosclerosis. Second, only about half of the individuals with carotid plaque underwent the follow-up carotid ultrasound. Third, uric acid was closely associated with other risk factors, which makes the role of uric acid difficult to separate out. On this occasion, the statistical significance of the result may not imply that uric acid is a statistically «independent» risk factor (24).

Conclusions

In conclusion, this study suggests that elevated serum uric acid level may be significantly associated with the presence and progression of carotid atherosclerosis in Chinese individuals aged 75 years or older. These associations were significant after controlling for other factors. However, this study cannot confirm the cause and effect relation. The elevated serum uric acid level may be merely a marker for risk or a compensatory mechanism, which warrants further investigation.

Conflict of Interest: The authors declare no conflict of interest.

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Ethical standard: All experimental procedures were conducted in accordance with the guidelines in the Declaration of Helsinki and approved by the ethics committee of the First Hospital of Jilin University.

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