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Relationship between serum uric acid and ischemic stroke in a large type 2 diabetes population in China: A cross-sectional study

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ABSTRACT

Objective: To investigate the relationship of serum UA and ischemic stroke in type 2 diabetes patients in China.
Method: We examined the above relationship using the data of the project "Comprehensive Research on the Prevention and Control of the Diabetes" (CRPCD) study. A total of 19,442 participants were enrolled in the cross-sectional study. The enrolled participants were divided into quintiles of the serum UA levels with cut off values for two age groups (<60 versus ≥60 years). Binary logistic regression analyses were used to evaluate whether the levels of serum UA were independently associated with ischemic stroke in type 2 diabetes.
Results: The serum UA levels were significantly higher in the participants with age ≥ 60 years than those with age < 60 years ($P = 0.000$). In the age group of <60 years, the odds ratio for ischemic stroke with type 2 diabetes in quintile 5 over quintile 1 was 2.420 (95% CI, 1.566–3.470) in the unadjusted model and 1.765 (95% CI, 1.097–2.840) after controlling potential confounders. However, the reverse results were observed in the age group of ≥60 years. The odds ratio in quintile 4 over quintile 1 in model 3 and model 4 were 0.767 (95% CI, 0.630–0.934) and 0.782 (95% CI, 0.640–0.957).
Conclusion: Our results indicated that serum UA levels were independently positively associated with ischemic stroke in patients aged < 60 years, but the association was U-shaped in patients aged ≥60 years.

1. Introduction

Uric acid (UA), the end product of purine metabolism, is reported to exert pro-oxidant or antioxidant properties depending on its altered concentrations in various diseases. Elevated serum UA levels can be responsible for gout arthritis due to its pro-oxidant activity [1]. On the opposite, UA exerts a strong anti-oxidant activity on the serum, where its levels can be easily measured and have been utilized as a marker of the oxidative balance with its clinical correlates. Indeed, reduced serum UA levels have been associated with worse disease outcomes in Parkinson's disease and multiple sclerosis [2,3]. In addition, several studies reported that increased serum UA levels were associated with a wide range of cardiovascular disease, including coronary heart disease, stroke and hypertension [4–6]. However, there was controversy on whether the elevated serum UA was an independent risk factor for stroke. A prospective, middle-aged population-based study firstly reported that elevated serum UA was an independent risk factor in middle-aged patients with type 2 diabetes [7], while, a nested case-control study demonstrated that serum UA was not independently associated with ischemic stroke risk in women recently [8]. Accordingly, there was no enough and consistent evidence to confirm that the serum UA was an independent risk factor for ischemic stroke.

It is a matter of controversy on the relationship of serum UA levels and type 2 diabetes patients. Various studies concluded that the serum UA levels reduced in diabetes, especially in diabetic men [9–11]. A population-based cross sectional study documented that serum UA levels were independent an risk factor in type 2 diabetes after adjusting conventional factors [12]. Based on these findings, conflict conclusions that have been drawn are due to different population-studied, sample sizes, adjusting confounders and other factors. Therefore, we conducted a population-based cross-sectional study to investigate

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the relationship of serum UA and ischemic stroke in type 2 diabetes in China.

2. Materials and methods

2.1. Study design and subject collection

This is a community-based study established in 2013 and conducted in Huai'an and Suzhou city of Jiangsu province. The data of the study were obtained from the project "Comprehensive Research on the Prevention and Control of the Diabetes (CRPCD)". The CRPCD study was approved by the Ethic Board of Jiangsu Provincial Center for Disease Control and Prevention, and all participants signed written consent. Participants in the CRPCD study were drawn from the "Basic Public Health Service" which has been implanted nationally in China since 2009. All the participants in the CRPCD study were diagnosed with type 2 diabetes mellitus. According to the criteria in the 2010 American Diabetes Association (ADA), type 2 diabetes were defined as FPG ≥ 7.0 mmol/l or HbA1c level of ≥6.5% or patients' self-report. We excluded 611 patients due to missing data on serum UA levels. Finally, the number of 19,442 participants in our study is large enough to satisfy the requirement.

2.2. Data collection

Data collection was conducted by using a standardized questionnaire by trained physicians and nurses from 2013 to 2015. Information on demographic, diabetes duration, smoking status, hypertension history and physical activity were obtained from the survey. Physical activity was classified into low, moderate and high according to the International Physical Activity Questionnaire (IPAQ 2001). Ischemic stroke events were recorded in accordance with patients' self-report.

2.3. Biochemical measurements

After an 8-h overnight fasting, venous blood samples were obtained from the antecubital vein for measuring serum UA, serum total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and HbA1c levels. Serum UA levels were measured by enzymatic methods (Roche Cobas C701, Roche Diagnostics (Shanghai) Ltd). Serum total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride concentrations were measured by standard enzymatic methods. The high-performance liquid chromatography was used for assay in HbA1C levels (TOSH G8, Roche Diagnostics (Shanghai) Ltd). The enrolled participants were divided into quintiles of the serum UA levels with cut off values for two age groups (<60 versus ≥60 years): (Q1:<230 μmo/l, Q2: 230-270 μmo/l, Q3: 271-309 μmo/l, Q4:310-359 μmo/l, Q5: >359 μmo/l in the age group of <60 years; Q1:<249 μmo/l, Q2: 249-292 μmo/l, Q3: 293-333 μmo/l, Q4:334-387 μmo/l, Q5: >387 μmo/l in the age group of ≥60 years).

2.4. Statistical analysis

All continuous data including age, disease duration, BMI, serum UA, TC, TG, LDL-C, HDL-C and HbA1c levels are presented as the mean ± standard deviation or median (minimum-maximum), while all categorical variables included gender, smoking status, physical activity and hypertension were presented as percentages. Student's *t*-test was performed to compare the difference in continuous data between the two age groups. Chi-square tests were used for categorical variables. ANOVA analysis was used to analyze significance of the serum UA and albumin levels among three groups. Binary logistic regression analyses were used to evaluate whether the serum UA levels were independently associated with type 2 diabetes. The adjustment variables included age, gender, history of hypertension, HLD-C, smoking status, HbA1c, body mass index, physical activity and duration. Four models were estimated each sequentially adjusted for confounders. In Model 1, no variable was adjusted. In Model 2, age and gender variables were added. In Model 3, additional adjustment variables included history of hypertension, HLD-C were added. In Model 4, additional variables of smoking status, HbA1c, body mass index, physical activity and duration were added. Serum uric acid was modeled as quintiles variable using binary logistic regression models to estimate the association with ischemic stroke in type 2 diabetes. Odds ratios (OR) for ischemic stroke were computed across quartiles of UA using the bottom quartile as the reference category. $P < 0.05$ was considered to be statistically significant. All statistical analyses were performed with the SPSS 13.0 version statistical software.

3. Results

Of 20,053 participants, 19,442 individuals were enrolled in the final study and 611 were excluded due to missing serum UA levels and hemorrhagic stroke. The clinical baseline characteristics of type 2 diabetes patients were shown in Table 1. The mean age at baseline was 62.79 ± 9.88 years and serum UA levels was 314.97 ± 91.69 μmol/l for the participants who were divided into two groups according to age. The serum UA levels were significantly higher in the participants with age ≥ 60 yrs. than those with age < 60 yrs. ($P = 0.000$). The mean values of diabetes durations, the percentage of hypertension, SBP, the serum HLD-C levels and HbA1c levels were statistically higher in the participants with age ≥ 60 yrs. than those with age < 60 yrs. ($P = 0.000$). In contrast, the serum TG levels, BMI, WHR and the prevalence of smoking were all significantly lower in the participants aged ≥60 yrs. when compared to the participants aged < 60 yrs. ($P = 0.000$). There were no significant differences in gender, TC and LDL-C in the two groups ($P = 0.986$, $P = 0.675$, $P = 0.51$).

Table 2 showed the clinical characteristics of participants according to the quintiles of serum uric acid levels in the different age groups. There were significant differences in age, gender, smoking, hypertension, BMI, WHR, SBP, physical activity, TC, TG, HLD-C, LDL-C and HbA1c (All $P = 0.000$) except for diabetes duration ($P = 0.130$, $P = 0.082$) among various quintiles of serum UA in the participants with age < 60 yrs. and those with age ≥ 60 yrs. In addition, increasing trends for smoking, hypertension, BMI, WHR, SBP, TC, TG and LDL-C were observed in the UA quintiles of two age groups, while the reverse trends were found in HDL-C a1And HbA1c ($P = 0.000$).

Table 1
Baseline of characteristics in type 2 diabetes patients according to ages.

Variables	Total (n = 19,442)	Age < 60 years (n = 6775)	Age ≥ 60 years (n = 12,667)	*P* value
Ages (years)	62.79 ± 9.88	52.23 ± 6.07	68.45 ± 6.19	0.000
Gender (male/female)	7612/11830	2652/4123	4960/7707	0.986
Diabetes duration (years)	6.10 ± 5.66	5.12 ± 4.72	6.62 ± 6.04	0.000
Smoking status (%)	22.2	23.5	21.5	0.001
Physical activity				
Low	24.6	21.6	26.2	0.000
Moderate	68.6	72.1	66.7	0.000
High	6.8	6.3	7.1	0.000
Hypertension (%)	76.7	64.6	83.2	0.000
BMI (kg/m^2)	25.32 ± 3.46	25.49 ± 3.41	25.23 ± 3.49	0.000
WHR	0.90 ± 0.63	0.90 ± 0.63	0.89 ± 0.64	0.000
SBP (mmHg)	147.97 ± 20.61	142.40 ± 19.66	150.93 ± 20.49	0.000
TC (mmol/l)	5.30 ± 1.27	5.31 ± 1.32	5.30 ± 1.35	0.675
TG (mmol/l)	1.98 ± 1.63	2.10 ± 1.97	1.91 ± 1.41	0.000
HLD-C (mmol/l)	1.49 ± 0.44	1.46 ± 0.44	1.50 ± 0.44	0.000
LDL-C (mmol/l)	3.24 ± 1.03	3.24 ± 1.05	3.23 ± 1.01	0.51
Serum UA (μmo l)	314.97 ± 91.69	299.79 ± 88.80	323.09 ± 92.18	0.000
HbA1c	7.69 ± 1.82	7.84 ± 1.97	7.61 ± 1.72	0.000

BMI: body mass index; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides; LDL-C: low- density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; UA: uric acid.