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Original Article

Investigation of the relationship between serum uric acid and atherosclerosis in newly diagnosed type 2 diabetes mellitus

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Abstract: Type 2 diabetes mellitus (T2DM) patients with cardiovascular disease (CVD) present high levels of serum uric acid (SUA), suggesting that SUA might be a necessary condition for CVD. Whether SUA is a sufficient condition for CVD in T2DM patients remains unknown. In the present study, 299 patients with newly diagnosed T2DM were investigated. Blood pressure, body mass index (BMI), serum uric acid (SUA), hemoglobin A1c (HBA1C), creatinine (CRE), blood urea nitrogen (BUN), gamma-glutamyl transpeptidase (GGT), urine albumen excretion rate (UAER) and blood lipids were measured. All participants underwent carotid ultrasonography to measure intima-media thickness (IMT) and carotid plaque. The relationship between serum uric acid level and IMT, carotid plaque was evaluated. The results revealed no significant differences in IMT or the plaque ratio among T2DM patients with different SUA levels. No significant regression was observed between IMT and SUA in women. However, multivariate regression analysis showed a significant association between IMT and SUA in men after adjusting for all cardiovascular risk factors. Taken together, SUA might be a necessary but not a sufficient condition for CVD in newly diagnosed T2DM patients.

Keywords: Carotid plaque, intimae media thickness, serum uric acid, type 2 diabetes mellitus

Introduction

Due to lifestyle changes, such as a high-fat and high-calorie diet and less physical activity, obesity is a ubiquitous problem worldwide, and the morbidity of diabetes mellitus, hyperuricemia, hyperlipidemia, hypertension, and cardiovascular disease (CVD) is increasing. These clinical/subclinical manifestations may interact with one another. An association among these manifestations would be of considerable interest [1] and provide more references for clinical applications.

Type 2 diabetes mellitus (T2DM) presents a high morbidity. Hyperuricemia and vascular atherosclerosis are very common in patients with T2DM [2]. Furthermore, there is a high risk of CVD in diabetic patients, and it is the main cause of mortality observed in these patients [3]. Previous reports have shown that hyperuricemia is closely related to CVD [4-8]. Whether CVD is induced by high levels of serum uric acid (SUA) in T2DM patients is less clear. A group of studies were conducted to investigate this issue. However, the results were contradictory. For example, Wang and co-workers [9] investigated 318 T2DM patients with or without carotid atherosclerosis and showed that the SUA level was higher in the carotid atherosclerosis group, suggesting that SUA was associated with carotid atherosclerosis in T2DM [9]. Zhang and co-workers [10] also revealed that the SUA content was significantly higher in the T2DM group with carotid atherosclerosis than that in T2DM patients without carotid atherosclerosis. Khare and co-workers [11] showed that T2DM patients with CVD had higher SUA levels than those without CVD. Based on these results, scientists have concluded that elevated SUA levels in patients with T2DM might underlie the development of carotid atherosclerosis [10]. In comparison, Yang and co-workers [12] detected no significant differences in the SUA level among T2DM patients with plaque formation, with and without atherosclerosis. However, the

degree of carotid atherosclerosis was positively correlated with the SUA level (correlation coefficient = 0.201) [12]. These inconsistent results might be attributed to unknown factors, and further investigations on patients from different areas might help to resolve this problem.

Moreover, in most studies showing a positive correlation between SUA and CVD, the authors reached their conclusions based on comparisons of SUA levels between patients with and without CVD. This kind of comparisons illustrated that high levels of SUA might be caused by CVD, but it could not demonstrate that high levels of SUA could induce CVD. To achieve a more precise understanding of the relationship between SUA levels and CVD occurrence in T2DM patients, comparisons on the morbidity of CVD among patients with different SUA levels are required.

In general, the intima-media thickness (IMT) of the carotid artery is broadly used as a predictor of CVD because IMT measured by carotid artery ultra-sound is a non-invasive marker [13-15]. However, the predictive ability of the carotid plaque score for CVD is superior to IMT [16-18]. In the present study, to understand the correlation among hyperuricemia, IMT, and carotid plaque in newly diagnosed T2DM patients, IMT and carotid plaque were used as indicators of CVD, and the levels of SUA in T2DM patients were measured. The results would clarify whether SUA had predictive ability for CVD in T2DM patients.

Materials and methods

Ethics statement

The research plan used in the present study was approved by the Research Ethics Committee of the Third Affiliated Hospital of Anhui Medical University (Hefei, China). All participants involved in the study signed the informed consent form.

Study subjects

According to the 1999 WHO guidelines [19], newly diagnosed T2DM was defined as having either fasting plasma glucose ≥ 7.0 mM and/or 2-h postprandial plasma glucose ≥ 11.1 mM with repeated observations on two occasions at least 48 h apart. People who had smoked at least one piece of cigarette daily for ≥ 1 year were defined as smokers. Family history was defined if one or more first-degree relatives had been diagnosed as T2DM.

During July 2012 to August 2015, we collected information from 377 newly diagnosed treatment-naive T2DM patients. Background information, including smoking status, family history, and medication history, were collected. Patients with malignant neoplasms, liver diseases, and/or urinary tract infection were excluded. Patients who were taking uric acid-lowering agents or diuretics were also excluded. Finally, 299 participants were eligible for the present analysis.

Anthropometry

For each patient, brachial systolic and diastolic blood pressures (DBP) were manually measured using a sphygmomanometer after resting in a relaxed sitting position for at least 5 min. Weight was determined using a metric weight scale with light clothes and without shoes. Height was measured using a standard height scale without shoes. Body mass index (BMI) was calculated using the following formula: BMI = Weight/Height^2 (kg/m^2).

Determination of serum parameters

For each patient, venous blood was collected to determine serum parameters. Standard enzymatic methods were used to determine the level of SUA, creatinine (CRE), blood urea nitrogen (BUN), cystatin (Cys-C), total cholesterol (TCH), low-density lipoprotein (LDL) cholesterol (LDL-C), triglycerides, gamma-glutamyl transpeptidase (GGT) and high-density lipoprotein (HDL) cholesterol (HDL-C) by a Beckman Coulter Unicel (DxC800). Hemoglobin A1c (HbA1c) was assessed using a high-performance liquid chromatography (Arkray HA-1880). C-peptide (C-P) was measured using a Roche E170 Ful Automatic Electrochemiluminescence Analyzer. The urine albumen excretion rate (UAER) was estimated using double optical path immune turbidimetry on a Beckman Coulter Immage 800.

Carotid ultrasonography

Carotid ultrasonography was evaluated by professionally trained and certified sonographers using high-resolution B-mode ultrasonographies (Philips-iu22). Each participant was

Table 1. Characterization of the investigated participants

Indices	Level of SUA			
	Q1	Q2	Q3	Q4
SUA level	< 223	224-273.7	274.6-332.4	≥ 335
sample size	73	77	75	74
Age (year)	53.3 ± 10.7	51.3 ± 10.7	48.2 ± 12.2	45.8 ± 13.8
Male ratio	45.20%	62.30%	80%	86.50%
Smoking ratio	34.20%	39.50%	54.10%	58.10%
Ratio of family history of diabetes	34.20%	49.40%	40%	41.90%
Ratio of hypertension	16.40%	20.78%	24%	39.73%
Ratio of fatty liver	54.93%	60.87%	66.67%	76.71%
SBP (mmHg)	126.71 ± 16.78	125.87 ± 15.22	124.8 ± 14.61	132.01 ± 16.19
DBP (mmHg)	78.66 ± 9.39	80.03 ± 9.21	80.00 ± 9.42	84.49 ± 9.78
BMI (kg/m^2)	22.74 ± 3.34	24.55 ± 4.52	24.86 ± 3.15	26.88 ± 4.65
HbA1C (%)	11.4 ± 2.58	10.48 ± 2.28	10.35 ± 2.12	9.65 ± 2.57
Creatinine (μM)	51.26 ± 15.08	61.73 ± 39.61	69.01 ± 27.37	74.01 ± 20.32
Triglycerides (mM)	1.53 ± 1.35	2.12 ± 2.01	2.69 ± 2.53	3.07 ± 2.89
Total cholesterol (mM)	5.04 ± 1.07	5.29 ± 1.21	5.17 ± 0.99	5.1 ± 1.15
LDL cholesterol (mM)	3.29 ± 1.08	3.32 ± 0.99	3.09 ± 0.89	2.84 ± 0.90
HDL cholesterol (mM)	1.18 ± 0.5	1.03 ± 0.27	0.95 ± 0.30	0.92 ± 0.18
BUN (mM)	4.65 ± 1.24	4.9 ± 3.77	5.62 ± 6.96	5.36 ± 3.96
UAER (μg/min)	26.71 ± 65	26.82 ± 77	32.43 ± 118.47	19.33 ± 30.32
Cys-c (mg/L)	1.16 ± 2.43	0.88 ± 0.20	0.95 ± 0.28	0.96 ± 0.38
GGT (u/L)	27.89 ± 23.2	34.13 ± 44.33	37.04 ± 30.8	62.88 ± 74.02
C-P (nM)	0.54 ± 0.29	0.61 ± 0.35	0.76 ± 0.0.41	0.91 ± 0.38

The participants were categorized into four groups based on the level of serum uric acid. Most data are presented as means ± SD. Participants whose parents or siblings had a history of diabetes were defined as family history of diabetes.

examined in the supine position with the head slightly tilted to the opposite side. The IMT, defined as the distance between the lumen-intima interface and the media-adventitia interface of the common carotid [20], was measured on both the right and left sides of the common carotid artery. The average of these two values represents the common carotid artery IMT.

Plaque

The carotid artery plaque was defined as a localized protrusion of the internal part of the vessel wall into the lumen with ≥ 50% thicker than the surrounding area. Plaque presence was defined as ≥ 1 plaque in any of the carotid arteries [21].

Statistical analyses

The subjects were divided into quartiles according to the level of SUA (Q1, Q2, Q3, and Q4). The normality of the data in each group was examined. For normally distributed data, the differences among the four groups were compared using the Student's ANOVA. For data that were not normally distributed, the non-parametric test or Chi-square test was employed to compare differences among the four groups.

An age and gender-adjusted partial correlation analysis was performed to evaluate the association between the SUA level and other variables. Continuous variables were analyzed by analysis of covariance (ANCOVA), and categorical variables were analyzed using logistic regression. Pearson's partial correlations between carotid IMT and SUA levels in females, and Spearman's correlation between carotid IMT and SUA levels in males were also performed. The computed rank test was used to identify the relationship between SUA and the plaque ratio. Multivariable regression analyses were used to evaluate the association between the SUA level and carotid IMT or carotid plaque presence. *P* value < 0.05 was considered statistically significant. All analyses were performed using the SPSS statistical package (version 17.0).

Table 2. Correlation between serum uric acid level and other parameters in patients with newly diagnosed type 2 diabetes

Variable	Correlation coefficient	*P* value
BMI	0.400	< 0.001
SBP	0.167	0.004
DBP	0.184	0.002
TG	0.207	0.001
GGT	0.226	< 0.001
HbA1C	-0.211	< 0.001
C-P	0.329	< 0.001
HDL-C	-0.234	< 0.001
CRE	0.253	< 0.001
Cys-C		0.923
LDL-C		0.267

All correlation coefficients were calculated after adjustment for age and gender.

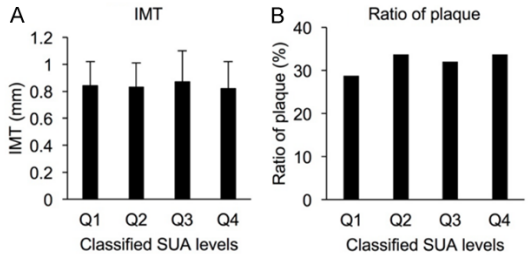

Figure 1. The IMT (A) and plaque ratio (B) in newly diagnosed T2DM patients with different SUA levels.

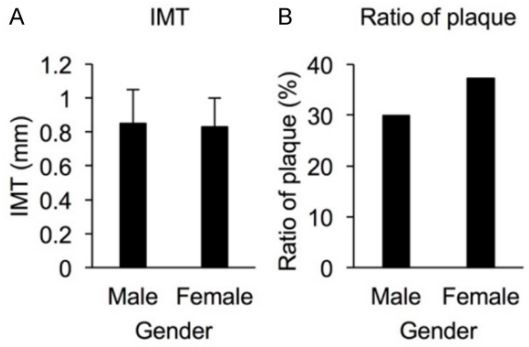

Figure 2. The IMT (A) and plaque ratio (B) in male and female newly diagnosed T2DM patients.

Results

Based on the level of SUA, the 299 participants were divided into four groups, Q1, Q2, Q3, and Q4, in which the level of SUA increased sequentially. The ranges of SUA levels and the statistical values of other indicators within each group are listed in **Table 1**.

With an increasing SUA level, the ratio of males, smoking, family history of diabetes, hypertension and fatty liver all increased significantly. Moreover, in the patients with higher SUA levels, diastolic blood pressure (DBP), body mass index (BMI), creatinine (CRE), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), gamma-glutamyl transpeptidase (GGT), and C-P showed an increasing trend, but age, HbA1C and HDL-C displayed a decreasing trend. However, there were no significant differences in the total cholesterol (TCH), blood urea nitrogen (BUN), UAER, and cystatin (Cys-C) among patients with different levels of SUA.

After adjustment for age and gender, partial correlation analysis exhibited that SUA was significantly positively correlated to BMI, systolic blood pressure (SBP), DBP, TG, GGT, C-P, and CRE, and significantly negatively correlated to HbA1C and high-density lipoprotein cholesterol (HDL-C) ($P < 0.05$). No significant relationship was observed between the SUA level and LDL-C or Cys-C after adjusting for age and gender (**Table 2**).

The IMT and plaque ratio were compared among the different SUA groups, and no significant differences were detected (**Figure 1**). T-tests revealed that IMT ($P = 0.324$) and the plaque ratio ($P = 0.175$) did not significantly differ between male and female patients (**Figure 2**).

After adjustment of other factors, linear regression analyses and multivariate regression analyses between SUA and IMT/plaque were performed (**Table 3**). A significant association was only detected between SUA and IMT in male patients after adjusting for age, smoking status, fatty liver, UAER, family history of diabetes, SBP, DBP, BMI, HBA1C, CRE, BUN, GGT, C-P, and history of hypertension. No linear regression was observed between SUA and IMT or the plaque ratio in female patients using either linear or multivariate regression analysis, or in male patients using linear regression analysis (**Table 3**).

Discussion

As a metabolic disease, hyperuricemia and T2DM result from an unhealthy lifestyle and poor dietary habits. People with an unhealthy lifestyle (such as smoking, hypertension, fatty liver, and a high SBP, DBP or BMI) clearly had high SUA levels in the present study.

Table 3. *P* value for the regression analysis between serum uric acid and IMT/plaque in patients with newly diagnosed type 2 diabetes

	Male		Female	
	IMT (mm)	plaque	IMT (mm)	plaque
Linear regression	0.419	0.834	0.996	0.151
Multivariate-adjusted[a]	0.211	1.003	0.702	1.007
Multivariate-adjusted[b]	0.048	1.006		0.996

[a]. Adjusted for age, smoking status, fatty liver, UAER, and family history ratio of diabetes. [b]. Adjusted for age, smoking status, fatty liver, UAER, family history of diabetes, SBP, DBP, BMI, HBA1C, CRE, BUN, GGT, C-P, and history of hypertension.

Regarding the effects of sex and age on the level of SUA, contradictory results have been reported. Zoppini and co-workers [22] investigated 2726 outpatients attending the Diabetes Clinic at the University Hospital of Verona and detected no significant relationship between sex, age, and the level of SUA. Li and co-workers [23] surveyed 1026 patients in Shanghai City (China) and suggested an increased ratio of males to females but no clear trend in age, along with an elevated SUA level. Kanbay and co-workers [24] studied 486 patients with CKD stage 3-5 who were referred to the nephrology outpatient in the Clinic of Gulhane School of Medicine, and showed that older people had higher SUA levels. These contradictory results might be associated with the location that was investigated. Based on the data collected in the present study, along with the increasing level of SUA, the ratio of male patients increased but age decreased, suggesting that men might have a higher risk of hyperuricemia than women and that patients with hyperuricemia tended to have a younger age in Hefei City, China.

T2DM patients have a high risk of elevated SUA levels and CVD [2]. T2DM patients with CVD generally present high SUA levels [4-8]. However, this evidence remained inconclusive. The authors could only conclude that hyperuricemia was a necessary condition for CVD in T2DM patients, but whether it is a sufficient condition remains unknown. Atherosclerosis is a pathological basis of CVD, and carotid IMT is an indicator of CVD risk [25-27]. In the present study, we investigated 299 eligible patients who were initially diagnosed with T2DM in Hefei City, and then we compared the morbidity associated with carotid plaque and IMT in patients with different levels of SUA. The results revealed no significant differences among different groups, suggesting that SUA might not induce plaque in T2DM patients.

Pulse wave velocity (PWV) and carotid IMT are considered noninvasive indicators of CVD [28]. Based on the PWV, Bae and co-workers [29] found that the SUA level was associated with brachial-ankle pulse wave velocity (baPWV) in men and weakly associated in women in Korea. Zhang and co-workers [2] reported that SUA was related to carotid-femoral pulse wave velocity (cfPWV) and carotid-radial pulse wave velocity (crPWV) in newly diagnosed T2DM men. These results suggested a strong association between SUA and CVD. A few studies have examined the relationship between SUA and carotid plaque. SUA was independently associated with the prevalence of vulnerable carotid plaque after adjusting for potential confounders in middle-aged adults in a community-based cohort [30]. Tan and co-workers demonstrated that SUA was related to plaque in 116 stroke-free participants [31]. These results indicated that SUA might be associated with carotid plaque in selected populations. In comparison, Pan and co-workers [32] found no significant connection between SUA and carotid plaque after adjusting for age and gender. Similarly, Herder and co-workers [33] demonstrated that the SUA level was not associated with the total plaque area. In the present study, there was no significant relationship between the SUA level and IMT in women based on linear or multivariate regression. In men, only multivariate regression analysis detected a significant relationship between the SUA level and IMT in men after adjusting for age, smoking status, fatty liver, UAER, family history of diabetes, SBP, DBP, BMI, HBA1C, CRE, BUN, GGT, C-P, and history of hypertension. These results were consistent with Pan and co-workers [32] and Herder and co-workers [33], suggesting that the relationship between SUA and plaque was nonexistent or very weak and easily influenced by other factors in newly diagnosed T2DM patients.

In the present study, two limitations should be considered. First, our data were obtained from a single hospital, and most of the participants involved in the study were from Hefei City or nearby areas. To validate a relationship be-

tween SUA and plaque, more samples from a large area should be considered. Second, the subjects in the present study were diagnosed with T2DM for the first time. Although the effects of medication or treatment could be avoided, the duration of illness was unknown, which likely affected the results. In future analyses, every patient should be followed up, and the association between SUA and incidences of vascular events should be determined.

In conclusion, the present study showed no significant differences in IMT and carotid plaque ratio in newly diagnosed T2DM patients with different SUA levels. SUA might be a necessary but not a sufficient condition for CVD in newly diagnosed T2DM patients.

Disclosure of conflict of interest

None.

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