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Decreased urine uric acid excretion is associated with diabetic retinopathy but not with lower limb atherosclerosis in hospitalized patients with type 2 diabetes

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ABSTRACT

Objective: To explore the associations between urine uric acid excretion (UUAE) and diabetic retinopathy (DR)/lower limb atherosclerotic lesions in hospitalized Chinese patients with type 2 diabetes.
Methods: This cross-sectional study was conducted in 2529 hospitalized Chinese patients with type 2 diabetes. UUAE was determined enzymatically using a single 24-h urine collection. The subjects were stratified into quartile based on UUAE levels. DR was determined by digital fundus photography. Lower limb atherosclerotic lesions were assessed by Doppler ultrasound. Both DR and lower limb atherosclerosis were compared among the UUAE quartile groups, respectively.
Results: There was a significant decrease in the prevalence of DR in patients across the UUAE quartiles after adjustment for sex, age and diabetic duration (35.0%, 30.7%, 26.1%, and 21.5%, respectively, $p = 0.000001$ for trend). A fully adjusted multiple logistic regression analyses revealed that UUAE quartiles were markedly inversely associated with the presence of DR ($p = 0.030$). The prevalence of lower limb plaque (73.9% vs. 62.6%, $p = 0.000044$) and stenosis (16.3% vs. 9.7%, $p = 0.000015$) was markedly higher in the diabetics with DR than in those without DR. However, there was no statistical association between the UUAE and lower limb atherosclerotic lesions in type 2 diabetes.
Conclusions: Decreased UUAE was an independent risk factor for DR but not for lower limb atherosclerosis in hospitalized Chinese patients with type 2 diabetes. In selected populations, such as those with type 2 diabetes, the role of uric acid in atherosclerosis may be result from other concomitantly atherosclerotic risk factors, such as DR.

1. Introduction

Serum uric acid (SUA) is increasingly recognized as an important risk factor for diabetes mellitus and its complications such as chronic kidney diseases (CKD), diabetic neuropathy, and diabetic retinopathy (DR) [1–6]. Among diabetic complications, DR is a chronic microvascular complication and has been considered as a major cause of visual impairment and vision loss in patients with diabetes [7]. In recent decades, epidemiologic evidence supports a link between SUA and DR in patients with diabetes [1,3,8,9]. For example, Bjornstad et al. reported that SUA levels were independently associated with the development of DR over 6 years in adults with type 1 diabetes [8].

However, the role of uric acid in atherosclerosis remains controversial. In some studies, an association between SUA and atherosclerosis did not remain significant after adjustment for concomitant risk factors for atherosclerosis [10–12]. Our previous study also demonstrated that SUA was independently associated with hypertension (HTN) and metabolic syndrome but not with

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atherosclerosis in type 2 diabetes [12]. Therefore, substantial uncertainties regarding the importance of uric acid in the evaluations of the risks of atherosclerosis remain.

Furthermore, a variety of studies have examined the relationships between SUA and atherosclerosis/DR, but few studies have investigated the associations of urine uric acid excretion (UUAE) with atherosclerosis and DR. In a recent study, we found that UUAE was independently associated with CKD but not with carotid atherosclerosis in hospitalized patients with type 2 diabetes [13]. Therefore, in this context, the aims of this study were to examine the association of UUAE levels with DR and lower limb atherosclerosis in hospitalized Chinese patients with type 2 diabetes.

2. Methods

2.1. Subjects and study design

The data of the current study was partly resulted from our previous studies [12–18]. Briefly, between January 2007 and June 2009, 3598 patients with type 2 diabetes hospitalized in Department of Endocrinology and Metabolism, Shanghai Jiaotong University Affiliated Sixth People's Hospital were consecutively observed. Of the 3598 subjects, 591 subjects were excluded because of a lack of the data of UUAE. Of the remaining 3007 patients, retinal photographs were available for 2701 individuals. Of these, photographs of five subjects could not be evaluated. Additionally, the patients taking any drug that might influence uric acid metabolism, such as losartan, allopurinol and furosemide were excluded from the study. The patients who did not undergo lower limb ultrasound examination and those without complete clinical data were also excluded. Ultimately, 2529 patients were included in the final analyses. The patients were divided into four groups according to the UUAE quartile. All subjects received a diabetic diet and avoided excessive purine intake and alcohol consumption after admission to the hospital.

All of the patients participated in a detailed interview and gave a histories of HTN and medication including lipid-lowering drugs (LLDs) and antihypertensive agents (AHAs) and insulin or insulin analogues (IIAs), alcohol consumption and smoking habits. Both smoking status and alcohol use were defined according to our previous criteria [14]. The study was approved by the ethics committee of the Shanghai Jiao Tong University Affiliated Sixth People's Hospital and written informed consent was obtained from all subjects.

2.2. Physical examination and laboratory measurements

The physical examination and laboratory measurements used in the present study have been described in detail previously [12–18]. In brief, height, weight, waist circumference, hip circumference, and blood pressure were examined according to a standardized protocol. The body mass index (BMI) and the waist-to-hip ratio (WHR) were calculated according to the corresponding formula [14].

Venous blood samples were collected for measurements of glycosylated hemoglobin A1C (HbA1c), fasting plasma glucose (FPG), 2-h postprandial plasma glucose (2h PPG), fasting C-peptide (FCP), 2-h postprandial C-peptide (2h PCP), blood platelet count (BPC), white blood cell count (WBCC), total triglycerides (TTG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), alanine aminotransferase (ALT), creatinine (Cr), serum uric acid (SUA), C-reactive protein (CRP).

A single 24-h urine sample was collected in the period of hospitalization, and 24-h UUAE was determined by enzymatic methods using a single 24-h urine collection. The 24-h urinary albumin excretion (UAE) was calculated as the mean of the values obtained from three separate early morning urine samples during the period of hospitalization. The estimated glomerular filtration rate (eGFR) was calculated using the following equation for Chinese individuals: $eGFR = 175 \times (\text{serum creatinine})^{-1.234} \times (\text{age})^{-0.179}$ ($\times$ 0.79 if female) [19].

2.3. Ultrasonography measurements

Lower limb artery Doppler ultrasound examination, including the measurement of atherosclerotic plaque, stenosis and femoral intima-media thickness (FIMT), has been described in detail in our previous studies [12,14,16,18]. The definition of FIMT, lower limb atherosclerotic plaque, and stenosis has been also described in detail in our previous studies [12,16,18]. The reproducibilities of measurements of lower limb atherosclerotic lesions have been also reported in the previous study [16,18].

2.4. Digital nonmydriatic fundus photography

Retinal photographs of all subjects were taken according to a standardized protocol described in detail previously [14,15].The definition of non-proliferative diabetic retinopathy (NPDR), proliferative diabetic retinopathy (PDR), and DR had been described in our previous studies [14,15]. In cases of discrepancies in the DR status (NPDR and PDR) between the two eyes of a patient, the eye with PDR was considered for analysis.

2.5. Statistical analysis

The study data were analyzed with SPSS 15.0 for Windows. The P-values less than 0.05 are considered statistically significant. Data are expressed as mean ± S.D, percentages or medians (interquartile range 25%–75%) for variables that are not normally distributed. For continuous variables with normal distribution, one-way ANOVA with LSD was used to compare data among multiple groups, and independent sample t tests were used for comparisons of variables between two groups. If the data were not distributed normally, the Mann–Whitney U test and kruskal-Wallis H test were used. The χ^2 test was used to compare the prevalence data. The general linear and binary logistic regressions were applied to assess differences in the variables while adjusting for other factors. We constructed three models to assess the association between UUAE and DR by logistic regression: model 1 included adjustment for age, sex, diabetes duration (DD), HTN, smoking, alcohol drinking, and the use of LLDs and AHAs and IIAs; model 2 had additional adjustment for systolic blood pressure (SBP), diastolic blood pressure (DBP), BMI, and WHR; and model 3 had additional adjustment for laboratory results including ALT, TC, TTG, LDL-C, HDL-C, CRP, HbA1C, and FPG, 2h PPG, FCP, 2h PCP, Cr, eGFR, BPC, WBCC, and SUA.

3. Results

3.1. Characteristics of the study subjects

The characteristics of the study subjects according to UUAE quartiles are showed in Table 1. The patients were stratified into quartiles based on the UUAE levels with the cutoff limits of <2212, 2212–2831, 2832–3572, and >3572 μmol/24 h. After controlling for age and sex, the patients with type 2 diabetes in the higher UUAE quartiles were more likely to be male, younger, smokers and drinkers; have shorter DD; have higher DBP, BMI, WHR, FPG, 2h PPG, FCP, 2h PCP, TG, ALT, UAE and SUA; and have lower HDL-C and Cr.