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Interactive effect of serum uric acid and total bilirubin for micro-vascular disease of type 2 diabetes in China

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ABSTRACT

Aims: Serum uric acid (SUA) and bilirubin at high levels had both pro-oxidant and anti-oxidant properties. The present study aimed to examine additive interactions between SUA and total bilirubin (TBIL) for the risk of micro-vascular disease (MVD) in type 2 diabetes mellitus (T2DM).
Methods: A cross-sectional survey of 6713 inpatients with T2DM was conducted in 81 tertiary care hospitals in China. MVD was defined as having either prior diabetic retinopathy (DR) or diabetic nephropathy (DN). Binary logistic regression was used to estimate odds ratios of SUA and TBIL for MVD. Additive interaction was measured by three indices, i.e., relative excess risk due to interaction, attributable proportion due to interaction and synergy index.
Results: Among 6713 inpatients, 408 (6.08%) suffered from MVD. SUA ≥ 283 μmol/l (i.e., its media) was defined as high SUA, and TBIL <11.5 μmol/l ($n = 2290$ or 34.11%) was defined as low TBIL. Overall, 621 patients were exposed to co-presence of high SUA and low TBIL. The co-presence of both factors greatly increased the effect sizes from 1.03(95%CI: 0.72–1.46) (high SUA alone) or 0.70(95%CI: 0.48–1.05) (low TBIL alone) to 1.90 (95%CI: 1.26–2.87) for MVD in multivariable analysis. The additive interaction of both factors was significant for MVD in both univariable analysis and multivariable analysis.
Conclusions: Co-presence of both high SUA and low TBIL indentified a group of patients at a markedly increased risk of MVD in high-risk Chinese patients with T2DM.

1. Introduction

Life style transition and population aging have led to a rapid increase in the prevalence of diabetes worldwide,[1] and more and more people are suffering from its complications. How to reduce the burden of diabetes and its complications has become a health priority in many parts of the world. Diabetic retinopathy (DR) and diabetic nephropathy (DN) are two of the chronic micro-vascular complications of diabetes. DR is a major cause of vision loss in adults[2] while DN is the leading cause of life-threatening end-stage renal disease (ESRD).[3] Identification of novel risk factors is certain to contribute to a further reduction in the risk of micro-vascular disease (MVD) in type 2 diabetes mellitus (T2DM). In this regard, serum uric acid (SUA) and bilirubin were recently reported to be associated with MVD in diabetes[4,5] but it remains unknown whether the two risk factors have a synergistic or interactive effect on the risk of MVD in T2DM.

Uric acid, a metabolic end-product of purine degradation, possesses pro-oxidant property in human and is also a promoter of oxidative and inflammatory processes.[6] The levels of SUA are influenced by a variety of factors, including dietary intake, and its rates of production and renal excretion. Elevated serum uric acid levels may stem from imbalance between production and excretion. Because of lack of consensus in the diagnostic criteria for hyperuricemia, most studies defined hyperuricemia as SUA >7.0 mg/dl in man and 6.0 mg/dl in women.[7,8] Accumulation of monosodium urate crystals in the joint fluid and periarticular tissue may result in gout, one of major consequence of hyperuricemia. Recent studies revealed that hyperuricemia was associated with increased risks of cardiovascular disease, chronic kidney disease, diabetes and its complications.[5,9–11] Elevated SUA even in the normal range is associated with increased risks of diabetes and vascular complications.[12,13]

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Bilirubin is an end product of heme metabolism and considered to be a toxic metabolite in jaundice, particularly in neonates. However, recent studies found that bilirubin exhibited a cytoprotectant effect and possessed both antioxidant and anti-inflammatory properties on the vasculature.[14,15] Several cross-sectional and longitudinal studies revealed that bilirubin in human may have beneficial effects on hypertension, atherosclerosis, metabolic syndrome, cardiovascular disease and diabetes.[16–20] In patients with diabetes, serum bilirubin levels are not only inversely associated with risk of cardiovascular disease but also associated with risk of MVD[4,21] and severity of these complications.[21] A prospective study demonstrated a U-shaped relationship between bilirubin levels and the risk of coronary heart disease.[22]

Given to the anti-oxidative and anti-inflammatory properties of SUA and serum bilirubin, and their associations with MVD, it is worthwhile to explore possible interactive effects of high SUA and low TBIL on the risk of MVD in T2DM. The current study used the data from a cross sectional survey of inpatients with T2DM from Chinese 81 top tertiary care hospitals to examine 1) full-range associations of SUA and TBIL with MVD; 2) to test interactive effects of both factors on the risk of MVD in Chinese patients with T2DM.

2. Methods

2.1. Patients

Chinese Hospital Association conducted a hospital-based cross-sectional survey from May 2013 to August 2013 as a quality improvement effort in the management of patients with T2DM in tertiary care hospitals in China. A total of 81 top tertiary care hospitals from 21 provinces in China participated in the survey. The inclusion criteria were 1) patients with T2DM and admitted to the division of endocrinology; 2) agreed the treatment scheme of basal bolus plus meal time insulin after admission; 3) between the ages of 18 to 80 years. The exclusion criteria were 1) with alanine aminotransferase or aspartate aminotransferase ≥100 U/l; 2) with serum creatinine ≥110 μmol/l in female and ≥125 μmol/l in male or chronic kidney disease; 3) during pregnancy or lactation or both; and 4) unable to communicate in a normal way. The detailed patient inclusion and exclusion criteria were available elsewhere.[23]

During the 6-month fieldwork period, a total of 6800 inpatients with T2DM were consecutively recruited. Among them, 87 patients were excluded due to missing key variables or meeting exclusion criteria. The remaining 6713 patients were used in the final analyses. The ethics approval was granted by the People's Liberation Army (PLA) General Hospital Clinical Research Ethics Committee and written informed consent was obtained from every patient before data collection.

2.2. Data collection and clinical measurements

Postgraduate medical students or research nurses conducted the fieldwork after being trained in a workshop to standardize all the data collection procedures. Patients were asked to fill out a structured questionnaire to collect data on demographics, lifestyle and medical history. Case notes were reviewed to record clinical characteristics and laboratory measurements, and then transformed the data into the questionnaire. The demographic and clinical characteristics included age, gender, duration of diabetes, body height, weight, blood pressure (BP), and self-monitoring of blood glucose (SMBG). Blood pressure was taken in the seated position using standardized sphygmomanometers. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Measurements of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), glycated hemoglobin ($HbA1_c$), SUA, TBIL, liver function and renal function were performed in the laboratory of local hospitals. Overnight fasting blood (at least 8 h of fasting) was taken and plasma was used in the above measurements. First morning urine was collected to test both albuminuria and creatinine. Use of drugs at admission and during stay in the hospital was documented, including antidiabetes drugs (oral antidiabetes drugs, insulin and glucagon-like peptide-1 based drugs and combined use of these drugs), antihypertensive drugs (calcium antagonists, renin angiotensin system inhibitors and β- receptor antagonists), and lipid lowering drugs (statins and other lipid lowing drugs). The complications of diabetes were documented in details, including macro- and micro- vascular disease. Macro-vascular disease (CVD) was defined as having any of coronary heart disease (CHD), stroke or peripheral arterial disease (PAD). The detailed definitions of CHD, stroke and PAD were published previously.[23]

2.3. Definition of micro-vascular disease

DN was diagnosed by presence of persistent proteinuria, i.e., urinary albumin (UA) ≥ 30 mg/24 h or urinary albumin excretion rate (UAER) ≥ 20 μg/min for at least three consecutive readings after excluding blood urine, urinary system infection and kidney damage from other causes. At least one ophthalmologist conducted ophthalmoscopy and fluorescein angiography by dilated pupils in the hospital, where patients had ever seen the doctor. DR was defined as background of retinopathy, pre-proliferative, proliferative, and maculopathy. Considered that the mechanism of peripheral neuropathy may be different from DR and DN,[24,25] micro-vascular disease was defined as having either DN or DR in this study.

2.4. Statistical analysis

SAS 9.3 (SAS Institute, Inc., Cary, NC, USA) was used in the current analysis. Continuous variables were expressed as medians and interquartiles or means and standard deviations where appropriate. Categorical variables were expressed as numbers and percentages. P-P plot and Q-Q plot were used to determine normal distribution of continuous variables. Categorical variables between patients with MVD and without MVD were compared using Chi-square test or Fisher's exact-test where appropriate. Continuous variables between two groups were compared by two-sample Wilcoxon rank test if normal distribution was rejected or Student *t*-test otherwise. Binary logistic regression was used to estimate associations of TBIL and SUA with MVD. A structured adjustment scheme was used to adjust for confounding effects of covariables. First, OR(95%CI)s of variables under investigation for MVD were estimated in univariable models. Then, we performed multivariable analysis to obtain adjusted OR(95%CI)s of TBIL and SUA for MVD. Adjusted variables included age, gender, duration of diabetes, BMI, systolic blood pressure, diastolic blood pressure, SMBG, HbA_{1c}, LDL-C, HDL-C, TG, use of drugs (oral antidiabetes drugs, insulin, lipid lowering drugs and antihypertensive drugs), and complications of diabetes(macro-vascular disease, sensory neuropathy, and other complications).

We used restricted cubic splines (RCS) in binary logistic regression analyses to check full-range associations of SUA and TBIL with MVD. Four knots (5%, 35%, 65% and 95%) were selected in RCS analysis as suggested by Harrell.[26] Cutoff points were chosen based on visual checking of the curves, i.e., where the risk of MVD rapidly increased or decreased after the cutoff points. Then, SUA and TBIL were stratified into binary categorical variables if appropriate. Additional binary logistic regression analyses were performed to ascertain the effect sizes of high versus low SUA (or low versus high TBIL).

Additive interactions were tested by three measures, i.e., relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP) and synergy index (S). Significant RERI (95%CI) >0, AP (95% CI) >0, or S (95%CI) >1 indicates significant additive interaction between the two variables.[27] P values < 0.05 from two-sided tests were considered to be statistically significant.

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