Postprint of a study on the association between serum bilirubin within the normal reference range and carotid artery plaques in elderly patients with type 2 diabetes mellitus

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Abstract

Background The association between serum bilirubin and carotid plaques in elderly patients with type 2 diabetes mellitus (T2DM) remains unclear. Objective To investigate the relationship between serum bilirubin within the normal reference range and the risk of carotid plaque in elderly T2DM patients, and to explore the possible underlying mechanisms. Methods A total of 2,885 elderly T2DM inpatients (age $ $65 years) with complete clinical data, admitted to the Department of Endocrinology and Metabolism of Shanghai Jiao Tong University Affiliated Sixth People' s Hospital from 2003 to 2012, were enrolled. According to quintiles of serum unconjugated bilirubin (UCB), patients were divided into five groups: Q1 (UCB <6.0 μmol/L, 446 cases), Q2 (UCB 6.0–7.5 μmol/L, 717 cases), Q3 (UCB 7.6–8.9 μmol/L, 533 cases), Q4 (UCB 9.0–10.1 μmol/L, 607 cases), and Q5 (UCB >10.1 μmol/L, 582 cases). Detailed clinical data, physical examination findings, carotid ultrasonography results, and laboratory parameters were collected, and the prevalence of carotid plaques was compared among the five groups. Partial correlation analysis was used to assess the correlation between serum C-reactive protein (CRP) and serum bilirubin. Binary logistic regression analysis was employed to evaluate the association between serum bilirubin, including total bilirubin (TB), conjugated bilirubin (CB), UCB, and carotid plaques. Results Among the 2,885 elderly T2DM inpatients, 1,296 were male (44.9%) and 1,589 were female (55.1%), with a mean age of $(72.6\$\pm5.3) years. There were statistically significant differences among the five T2DM groups in age, sex, dura$ $lowering agents, use of insulin or its analogues, diastolic blood pressure, and lipoprotein(a) (all $P <$ $0.05). After adjustment for age, sex, and and duration of diabetes, the prevalence of carotid plaques in Q1–Q5 groups w$ P<0.001). After adjustment for age, sex, and duration of diabetes, partial correlation analysis showed that serum TB (R=-0.090, P<0.001) and UCB (R=-0.100, P<0.001) levels were negatively correlated with CRP levels. Af-

ter controlling for multiple confounders, binary logistic regression analysis indicated that serum TB (OR=0.833, 95% CI: 0.721–0.963, P=0.013) and UCB (OR=0.831, 95% CI: 0.725–0.952, P=0.008) were negatively associated with carotid plaque formation in elderly T2DM patients. Conclusion Higher serum bilirubin levels within the normal reference range may reduce the risk of carotid plaque in elderly T2DM patients. Decreased serum TB and UCB levels are independent risk factors for carotid plaque in this population, and serum bilirubin levels may be related to the inflammatory status.

Full Text

The Association between Serum Bilirubin Within the Normal Range and Carotid Plaques in Elderly Patients With Type 2 Diabetes Mellitus

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Abstract

Background: The relationship between serum bilirubin and carotid plaque in elderly patients with type 2 diabetes mellitus (T2DM) remains unclear.

Objective: To investigate the association between serum bilirubin levels within the normal range and the risk of carotid plaque in elderly T2DM patients, and to explore the potential underlying mechanisms.

Methods: A total of 2,885 elderly T2DM patients (aged $\geq$ 65 years) with complete clinical data hospitalized in the Department of Endocrinology and Metabolism, Shanghai Sixth People' s Hospital affiliated to Shanghai Jiao Tong University School of Medicine from January 2003 to December 2012 were recruited in this retrospective study. According to the quintiles of serum unconjugated bilirubin (UCB) levels, the patients were divided into five groups: Q1 (UCB<6.0 μmol/L, n=446), Q2 (UCB: 6.0-7.5 μmol/L, n=717), Q3 (UCB: 7.6-8.9 μmol/L, n=533), Q4 (UCB: 9.0-10.1 μmol/L, n=607), and Q5 (UCB>10.1 μmol/L, n=582). The detailed clinical data, physical examination findings, carotid ultrasound measurements, and laboratory test results were collected. The prevalence of carotid plaque was compared among the five groups. Partial correlation analysis was performed to examine the associations between serum

C-reactive protein (CRP) and bilirubin levels. Binary logistic regression was used to analyze the association of serum bilirubin including total bilirubin (TB), UCB, and conjugated bilirubin (CB) with the presence of carotid plaque.

Results: Among 2,885 elderly hospitalized patients with T2DM, 1,296 were men (44.9%) and 1,589 were women (55.1%), with a mean age of 72.6$\pm$5.3$years.Significantdifferenceswereobservedamongthefivegroupswithrespecttoage, sex, diabetesdu$
$lowering medications, insulinorinsulinanalogtherapy, diastolicbloodpressure, andlipoprotein(a)levels(P <$
$0.05).Afteradjustmentforage, sex, anddiabetesduration, theprevalenceofcarotidplaqueinelderlyT2DMpatie$
P<0.001). Partial correlation analysis further demonstrated that serum TB (r=-0.090, P<0.001) and UCB (r=-0.100, P<0.001) were inversely correlated with CRP levels after adjustment for age, sex, and diabetes duration. After adjusting for multiple confounders, binary logistic regression analyses showed that serum TB (OR=0.833, 95%CI=0.721-0.963, P=0.013) and UCB (OR=0.831, 95%CI=0.725-0.952, P=0.008) were independently associated with a lower risk of carotid plaque in elderly patients with T2DM.

Conclusion: Higher serum bilirubin levels within the normal range are associated with a decreased risk of carotid plaque in elderly patients with T2DM. Lower levels of serum TB and UCB are independent risk factors for carotid plaque, which may be related to inflammatory status.

Key words: Diabetes mellitus, type 2; Carotid plaque; Total bilirubin; Unconjugated bilirubin; Inflammation

Introduction

Diabetes is a well-established risk factor for atherosclerotic disease [1-2]. Type 2 diabetes mellitus (T2DM) may promote carotid plaque formation by exacerbating inflammation, increasing neovascularization, and promoting lipid core expansion [3]. The formation of carotid plaque is significantly associated with acute cerebral infarction in its territory, leading to increased risk of ischemic stroke and worse post-stroke prognosis, causing irreversible consequences [4].

As an end product of erythrocyte catabolism, serum bilirubin has been shown to be closely associated with multiple diseases, including cardiovascular disease (CVD) [5-6], T2DM [7], metabolic syndrome [8-9], hypertension [10], and obesity [11]. Bilirubin is a potent antioxidant that effectively scavenges peroxide radicals, inhibits oxidation of lipids and lipoproteins, thereby preventing plaque formation and suppressing atherosclerotic lesions [12-13]. Previous studies have demonstrated that serum bilirubin is closely associated with atherosclerosis and plaque formation. Fukui et al. [14] conducted a study of 633 T2DM patients showing that serum total bilirubin (TB) concentration was negatively correlated with pulse wave velocity (PWV), suggesting that bilirubin levels are significantly associated with subclinical atherosclerosis in T2DM patients. A longitudinal cohort study of 9,795 T2DM patients showed that higher bilirubin levels re-

duced the risk of non-traumatic lower limb amputation [15]. Amor et al. [16] studied 464 patients with familial dyslipidemia, 322 with familial hypercholesterolemia, and 142 with familial combined hyperlipidemia, finding that TB was independently and negatively associated with carotid intima-media thickness and carotid plaque formation in both familial and non-familial dyslipidemia patients. Ishizaka et al. [17] found that individuals with carotid plaque had significantly lower serum TB levels than those without carotid plaque in a health screening of 1,741 subjects.

Most previous studies have primarily compared bilirubin levels between different groups, while few have investigated the relationship between bilirubin levels within the normal range and carotid plaque, and there have been scarce studies on Chinese elderly T2DM patients. Therefore, based on a large sample population, this study investigated the relationship between serum bilirubin levels within the normal range and carotid plaque in elderly T2DM patients and explored the potential underlying mechanisms, providing new perspectives and insights for early detection and prevention of atherosclerotic lesions in elderly T2DM patients.

Methods

1.1 Study Population

This study was a registered real-world study (registration number: ChiCTR 1800015893). A total of 2,885 T2DM patients hospitalized in the Department of Endocrinology and Metabolism, Shanghai Sixth People' s Hospital affiliated to Shanghai Jiao Tong University School of Medicine from 2003 to 2012 were consecutively recruited as study subjects. Inclusion criteria: (1) age $\geq$ 65 years; (2) complete clinical data; (3) serum bilirubin within the normal reference range; (4) diagnosis of T2DM according to the "Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes (2013 Edition)" [18]. Exclusion criteria: (1) no serum bilirubin test results or bilirubin exceeding the upper limit of normal; (2) lack of carotid ultrasound examination results; (3) other types of diabetes such as type 1 diabetes; (4) acute diabetic complications such as diabetic ketoacidosis; (5) diseases that may affect bilirubin such as hemolysis or biliary obstruction. This study was approved by the Ethics Committee of Shanghai Sixth People' s Hospital affiliated to Shanghai Jiao Tong University School of Medicine (approval number: 2018-KY-018(K)), and all subjects signed informed consent forms.

1.2 Data Collection

1.2.1 Data Collection Demographic and clinical data including age, sex, diabetes duration, smoking history, alcohol consumption history, hypertension history, and medication history (including lipid-lowering drugs, antihypertensive drugs, antiplatelet drugs, and insulin or analogs) were collected from all

participants. Physical examinations included height, body weight, waist circumference, hip circumference, systolic blood pressure, and diastolic blood pressure, with BMI and waist-to-hip ratio calculated accordingly.

Fasting venous blood samples were collected after 8 hours of fasting, and 2-hour postprandial blood samples were obtained to measure biochemical laboratory indicators including fasting plasma glucose (FPG), 2-hour postprandial glucose (2hPG), fasting C-peptide, 2-hour postprandial C-peptide, creatinine (Cr), serum uric acid (SUA), alanine aminotransferase (ALT), γ-glutamyltransferase (γ-GT), total bilirubin (TB), conjugated bilirubin (CB), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), lipoprotein (a), C-reactive protein (CRP), and glycated hemoglobin (HbA1c). Three independent morning urine samples collected on different days during hospitalization were used to measure 24-hour urinary microalbumin (24hAlb), with the average value calculated. Estimated glomerular filtration rate (eGFR) was calculated using the same method as in our previous studies [19-20].

1.2.2 Definitions and Standards The diagnostic criteria for smoking history, alcohol consumption history, hypertension history, and obesity were consistent with previous studies [21]. Serum TB and CB levels were measured using a LABOSPECT 008AS automatic analyzer (Hitachi, Tokyo). Serum unconjugated bilirubin (UCB) levels were obtained by subtracting CB concentration from TB concentration as described in this study [22]. Patients were divided into five groups based on quintiles of serum UCB levels: Q1 group (UCB<6.0 μmol/L, n=446), Q2 group (UCB: 6.0-7.5 μmol/L, n=717), Q3 group (UCB: 7.6-8.9 μmol/L, n=533), Q4 group (UCB: 9.0-10.1 μmol/L, n=607), and Q5 group (UCB>10.1 μmol/L, n=582). The diagnostic criteria for carotid plaque were consistent with previous studies [22].

1.2.3 Construction of Regression Models This study constructed six regression models to investigate the relationship between serum bilirubin and carotid plaque risk in elderly T2DM patients. **Model 1:** unadjusted; **Model 2:** adjusted for sex, age, and diabetes duration; **Model 3:** further adjusted for smoking history, alcohol consumption history, hypertension history, and obesity; **Model 4:** further adjusted for medication history including lipid-lowering drugs, antihypertensive drugs, antiplatelet drugs, and insulin or analogs; **Model 5:** further adjusted for systolic blood pressure, diastolic blood pressure, waist circumference, waist-to-hip ratio, and BMI; **Model 6:** further adjusted for laboratory indicators including γ-GT, ALT, TC, HDL, LDL, TG, lipoprotein (a), eGFR, SUA, 24hAlb, FPG, 2hPG, fasting C-peptide, 2-hour postprandial C-peptide, CRP, and HbA1c.

1.3 Statistical Methods

Data processing was performed using SPSS 15.0 statistical software. Normally distributed continuous variables were expressed as ($\bar{x}\pm s$) and compared between groups using t-tests or ANOVA. Non-normally distributed continuous variables were expressed as M(P25, P75) and compared using non-parametric tests. Categorical variables were expressed as n(%) and compared using χ^2 tests. Partial correlation analysis was used to examine the correlation between serum CRP and serum bilirubin, adjusting for age, sex, and diabetes duration. Binary logistic regression analysis was used to assess the association between serum bilirubin and carotid plaque in elderly T2DM patients. $P<0.05$ was considered statistically significant.

Results

2.1 Patient Characteristics

This study included 2,885 elderly hospitalized patients with T2DM, including 1,296 men (44.9%) and 1,589 women (55.1%), with a mean age of 72.6$±$5.3 years. Significant differences were observed among the five groups in terms of age, sex, diabetes duration, smoking history, lipid-lowering medications, insulin or analogs, diastolic blood pressure, and lipoprotein (a) ($P<0.05$). No significant differences were found among the five groups in alcohol consumption history, hypertension history, obesity, antihypertensive drugs, antiplatelet drugs, systolic blood pressure, waist circumference, waist-to-hip ratio, BMI, Cr, SUA, eGFR, 24hAlb, ALT, γ-GT, TC, TG, HDL-C, LDL-C, FPG, 2hPG, fasting C-peptide, 2-hour postprandial C-peptide, or HbA1c ($P>0.05$), as shown in Table 1 .

2.2 Comparison of Carotid Plaque Prevalence

After adjusting for age, sex, and diabetes duration, the prevalence of carotid plaque in elderly T2DM patients across Q1 to Q5 groups was 76.9% (343/446), 71.8% (515/717), 68.5% (365/533), 65.9% (400/607), and 62.2% (362/582), respectively, with a statistically significant difference among groups (χ^2=30.900, $P<0.001$).

2.3 Comparison of Serum UCB Levels

Among the 2,885 elderly hospitalized patients with T2DM, 1,985 (68.8%) had carotid plaque with serum UCB levels of 8.0 (6.3, 10.0) μmol/L, while 900 (31.2%) without carotid plaque had serum UCB levels of 8.6 (7.0, 10.0) μmol/L. Patients with carotid plaque had significantly lower serum UCB levels than those without plaque (Z=-5.401, P=0.001).

2.4 Correlation Analysis Between Serum Bilirubin and CRP

After adjusting for age, sex, and diabetes duration, partial correlation analysis showed that serum TB was negatively correlated with CRP levels (r=-0.090, P<0.001), serum UCB levels were also negatively correlated with CRP levels (r=-0.100, P<0.001), while serum CB showed no correlation with CRP levels (r=-0.021, P=0.303).

2.5 Logistic Regression Analysis of Serum Bilirubin and Carotid Plaque

Binary logistic regression analysis was performed with the presence of carotid plaque as the dependent variable (assignment: present=1, absent=0) and serum TB, CB, and UCB levels as independent variables (assignment: actual measured values). The results showed that serum TB and UCB levels were negatively associated with carotid plaque formation in Models 1-6 (P<0.05). In Model 6, after adjusting for multiple confounders, binary logistic regression analysis showed that serum TB (OR=0.833, 95%CI=0.721-0.963, P=0.013) and UCB (OR=0.831, 95%CI=0.725-0.952, P=0.008) were negatively correlated with carotid plaque formation. However, in all models, serum CB showed no correlation with carotid plaque formation (P>0.05), as shown in Table 2 .

Discussion

This large-sample cross-sectional study investigated the association between serum bilirubin levels within the normal range and carotid plaque in elderly T2DM patients. The results showed that carotid plaque risk was negatively correlated with serum TB and UCB levels but not with CB levels. Additionally, TB and UCB were negatively correlated with CRP levels, suggesting that serum bilirubin levels may be associated with inflammatory status.

Kawamoto et al. [23] included 325 men (79$±8*years*)*and*509*women*(81±$8 years) aged >60 years for B-mode measurement of carotid intima-media thickness (CIMT) and plaque, showing that serum TB levels were independently and negatively associated with carotid atherosclerosis in both sexes. Lee et al. [24] conducted a 6-8 year cohort study of 1,381 T2DM patients, finding that 599 (43.4%) developed carotid plaque progression during follow-up, and these patients were older with higher prevalence of hypertension, abdominal obesity, and markers of chronic kidney disease, and lower TB concentration. Multivariate logistic regression showed that higher TB levels were associated with lower risk of CIMT progression (OR=0.584, 95%CI=0.392-0.870; P=0.008). Our study is consistent with these findings.

Studies have shown that compared with CB, UCB has stronger antioxidant and anti-lipid peroxidation properties [25]. Lapenna et al. [25] observed that subjects with carotid stenosis $ $90% had lower serum TB, CB, and UCB levels

than those with stenosis <90%. A retrospective cohort study in Hebei including 4,360 subjects (median follow-up time 26.76 months) showed that each 1 SD increase in serum TB and UCB was associated with 7.30% (95%CI=2.80%-11.60%) and 15.70% (95%CI=11.40%-19.80%) reduction in carotid plaque risk, respectively; while each 1 SD increase in CB increased carotid plaque risk by 24.3% (95%CI=19.7%-29.0%), indicating that TB and UCB were negatively correlated with carotid plaque formation while CB was positively correlated [26]. Our results differ from this study, as we found that carotid plaque risk was significantly negatively correlated with serum TB and UCB levels but not with CB levels, suggesting CB had no significant predictive effect on carotid plaque formation. The discrepancy may be due to age differences in the study populations, as our study included elderly T2DM patients.

CRP is generally considered a sensitive marker of chronic systemic inflammation such as atherosclerosis [27]. A retrospective cross-sectional study found that in patients with coronary atherosclerosis, TB levels were negatively correlated with inflammatory markers including CRP [28]. Yoshino et al. [29] demonstrated that serum TB levels were negatively correlated with CRP in overweight individuals, and CRP could independently predict TB levels in overweight patients. A retrospective cohort study of 8,229 Chinese elderly adults (aged 65-99 years, 4,677 men and 3,552 women) with 5-year follow-up, grouped by baseline serum CRP concentration into low-risk (<1.0 mg/L), medium-risk (1.0-3.0 mg/L), and high-risk ($ $3.0 mg/L) groups, showed that high CRP concentration was associated with increased risk of carotid plaque in Chinese elderly adults [30]. Our study is consistent with these results, showing that serum TB and UCB levels were negatively correlated with CRP in elderly T2DM patients, suggesting that besides its known antioxidant stress effects, higher serum TB levels may exhibit anti-inflammatory effects in the process of coronary and carotid plaque formation, which requires further investigation.

In summary, this study clarifies the relationship between serum bilirubin levels within the normal range and carotid plaque formation in T2DM patients, providing predictive value for carotid plaque risk and poor prognosis in T2DM patients, and offering new insights for better prevention and treatment strategies. However, this study has certain limitations. First, as a retrospective single-center study, the causal relationship between serum bilirubin levels and carotid plaque formation cannot be established. Second, the study population was limited to elderly T2DM patients without a normal control group, limiting generalizability to other populations. Therefore, large-scale prospective cohort studies are needed to determine the applicable scope of bilirubin in predicting carotid plaque risk.

Author Contributions

JIN Chunhua was responsible for data collection, collation, and statistics; ZHANG Yawen was responsible for manuscript writing; LI Lianxi was responsible for project management, supervision, and manuscript revision.

Conflict of Interest

The authors declare no conflict of interest.

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