Total bilirubin is negatively related to diabetes mellitus in Chinese elderly: a community study

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Background: Serum total bilirubin (TB) was used as a predictor of diabetes mellitus (DM) and this study was undertaken to investigate the relationship between serum TB and DM.

Methods: In this cross-sectional study, a total of 3,867 subjects older than 65 years were recruited from East China. The anthropometric data, lifestyle and past history were collected. The fasting blood glucose, total cholesterol (TC), triglycerides (TGs), TB and alanine aminotransferase (ALT) were detected. The prevalence of DM was calculated for every serum TB quartile. Logistic regression analysis was employed to evaluate the relationship between serum TB and DM.

Results: Serum TB was significantly higher in non-DM than DM patients (P=0.001). Serum TB was negatively related to the prevalence of DM (P=0.004). Logistic regression analysis revealed that serum TB was an independent prognostic factor of DM [odds ratio (OR): 0.876, 95% confidence interval (CI): 0.807–0.951].

Conclusions: Our results showed serum TB in physiological range is an independent risk factor of DM in old people; the prevalence of DM in old people has a linear relationship with serum TB quartiles; the prevalence of DM reduces with the increasing of serum TB within physiological range.

Keywords: Bilirubin; diabetes mellitus (DM); oxidative stress

Introduction

Disease spectrum has significantly changed in the past 100 years, and noncommunicable diseases (NCD) including diabetes mellitus (DM), cancer and cardiovascular diseases have become the major cause of death worldwide. DM has been one of the most important NCD and threatens the human health worldwide. The statistics from International Diabetes Federation (IDF) show there were 370 million DM cases worldwide in 2011, and there will be 550 million DM cases in 2030. Oxidative stress plays important roles in the occurrence and development of DM. A variety of studies have shown that glucose overload may induce oxidative stress, causing damage to cells (1-3). However, the clinical intervention with vitamin E, a widely accepted anti-oxidant, fails to achieve favorable efficacy in DM patients (4).

Bilirubin is an end product in the metabolism of heme and has been confirmed to possess potential anti-oxidative activity (5) and be negatively related to oxidative stress (6,7). Especially, in the hydrophobic cell membrane,

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bilirubin is better to preserve the stability of proteins in cell membrane as compared to glutathione. In addition, both bound and unbound bilirubin has anti-oxidative activity (8). Although bilirubin at a high level is toxic to nervous system, a large number of studies have revealed that bilirubin at appropriate elevated level is beneficial. Japanese studies have indicated that bilirubin is negatively associated with peptide C, glycated hemoglobin and type 2 DM (T2DM) in middle-aged and old people (9). There is also evidence indicating that elevated bilirubin is able to reduce the incidence of DM and metabolic syndrome (10).

The incidence of DM increases over age, and the prevalence of DM increases by 68% with an increment of 10 years after adjusting for other factors (11). However, the age-span is larger than 20 years (12) or middle-aged/old people are recruited (9) in available studies on the relationship between bilirubin and DM. In addition, some subjects in these studies have some risk factors for vascular diseases or other comorbidities (such as Gilbert syndrome and chronic kidney diseases) (13-17). Thus, this cross-sectional study was undertaken to investigate the predictive value of serum total bilirubin (TB) and to explore the relationship between serum TB and DM in people older than 65 years of East China.

Methods

Subjects

This cross-sectional study was conducted in 11 communities of Shanghai Pudong New Area between January 2014 and March 2014. People who were 65 years or older and had been residents for at least 5 years were recruited. A total of 3,876 subjects were included in this study, and the medical history was recorded (birth date, time of physical activity, smoking and drinking). Smoker was defined as smoking every day or with an interval of several days and use of more than 100 cigarettes in life. Drinking was defined as use of 20–30 g of alcohol every day for men or 10–20 g of alcohol every day for women. Subjects with a history of diseases {clinically or laboratory-proven severe systemic diseases (cancer, renal failure and heart failure), goiter, liver dysfunction [aspartate aminotransferase (AST) or alanine aminotransferase (ALT) higher than three times upper normal limit such as 120 U/L or TB higher than 17.1 µmol/L], HIV infection}, bodybuilders, professional athlete and amateur athletes were excluded from this study. The past history was collected with a standardized

questionnaire. History of DM was defined as the use of antidiabetic drugs or insulin. A history of coronary heart disease (CHD) was defined as 50% stenosis of coronary artery in coronary angiography or a history of acute myocardial infarction. Hypertension was defined as systolic blood pressure (SBP) of ≥140 mmHg, diastolic blood pressure (DBP) of ≥90 mmHg or a history of use of antihypertensive drugs. Informed consent was obtained from each subject before study.

Anthropometric parameters

Subjects were asked to wear light clothes and stock alone during the measurement of height and body weight. Subjects were asked to rest for 10 min, the blood pressure was measured twice and a mean was calculated. Abdominal circumference was measured at the middle point between the lower edge of ribs and the iliac crest. The neck circumference was measured at the upper Adam's apple when the subject was asked to look straightly with the head horizontal. The body mass index (BMI) was calculated as body weight/height (kg/m^2).

Measurement of biomarkers

Venous blood was collected from subjects after overnight fasting and processed for the measurement of fasting blood glucose, TG and TC, TB and ALT. Blood was stored at –80 ℃.

Statistical analysis

Quantitative data with normal distribution are expressed as mean ± standard deviation, quantitative data with abnormal distribution as quartiles, qualitative data as rates. Comparisons among groups were done with analysis of variance, and qualitative data were compared with nonparametric tests. Subjects were divided into four groups with identical sample size according to the serum TB quartiles [Q1 (the lowest TB), Q2, Q3, Q4]. In every serum TB quartile [Q1, ≤8.70 (n=1,011); Q2, 8.70–10.80 (n=946); Q3, 10.80–13.30 (n=956); and Q4, 13.30–17.10 (n=963)], the prevalence of DM was calculated. Binary Logistic regression analysis was employed to explore the independent predictors of DM. A value of P<0.05 was considered statistically significant, and statistical analysis was performed with SPSS version 13.0 (SPSS, Chicago, IL, USA).

Table 1 Demographics, lifestyle, anthropometric parameters and clinical characteristics of DM and non-DM patients

Variables	Diabetes	Without diabetes	P
N	558	3,318	–
Age (years)	71.78±6.65	70.89±6.52	0.002
Gender male, n (%)	243 (43.5)	1,442 (43.5)	0.969
Alcohol use, n (%)	91 (14.8)	467 (14.3)	0.730
Current smoker, n (%)	41 (13.1)	517 (14.5)	0.510
Weight (kg)	65.59±11.20	63.48±10.72	<0.001
Height (cm)	160.90±8.72	161.24±8.49	0.378
BMI (kg/m^2)	25.31±3.66	24.38±3.43	<0.001
Clinical			
History of CHD, n (%)	93 (20.6)	465 (13.6)	<0.001
History of HBP, n (%)	440 (17.3)	115 (8.7)	<0.001
SBP (mmHg)	141.94±18.67	138.28±20.36	<0.001
DBP (mmHg)	77.80±10.25	78.34±10.47	0.252
TG (mmol/L)	4.82±1.01	4.97±0.95	<0.001
TC (mmol/L)	1.73±1.05	1.56±1.06	<0.001
FPG (mmol/L)	7.27±1.88	5.52±1.07	<0.001
ALT (U/L)	18.78±11.04	18.04±9.83	0.107
TB (µmol/L)	10.55±3.08	11.02±3.05	0.001

DM, diabetes mellitus; BMI, body mass index; CHD, coronary heart disease; HBP, high blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; FPG, fasting plasma glucose; ALT, alanine aminotransferase; TB, total bilirubin.

Results

Characteristics at baseline

A total of 3,876 subjects were recruited into this study. There were 1,685 males (43.5%) with the mean age of 71.14±6.06 years and 2,191 females with the mean age of 70.93±6.43. There were 558 DM patients. Demography, lifestyles and general clinical information of DM and non-DM patients are shown in *Table 1*. There was no difference in gender and smoking and drinking history between DM and non-DM patients. Average age, weight, and BMI were higher in DM patients than non-DM patients (P<0.005). Prevalence of CHD history and high blood pressure (HBP) history was higher in DM patients than non-DM patients (P<0.001). SBP, TC, and fasting plasma glucose (FPG) were higher in DM patients than non-DM patients (P<0.001), while TG was lower in DM patients than non-DM patients

(P<0.001). There was no difference in ALT between DM patients and non-DM patients, while there was a significant difference in TB between DM patients and non-DM patients (P=0.001).

Relationship between TB and risk for DM

According to the TB quartiles, the prevalence of DM is shown in *Table 2*. Results showed the prevalence of DM in old people had a linear relationship with TB quartiles: the prevalence of DM reduced with the increase in serum TB (P=0.004).

Independent risk factors of DM with logistic regression analysis

Binary Logistic regression analysis showed age, TB, TG,

Table 2 Relationship between prevalence of DM and TB (%)

Variable	Q1	Q2	Q3	Q4	P
History of diabetes, n (%)	164 (16.2)	146 (15.4)	134 (14.0)	114 (11.8)	0.004

DM, diabetes mellitus; TB, total bilirubin.

Table 3 Binary logistic regression of risk for DM

Variables	Regression coefficient	Standard error	P	OR	95% CI
BMI	0.055	0.014	<0.001	1.056	1.029–1.085
History of CHD	0.346	0.130	0.008	1.414	1.096–1.824
History of HBP	0.721	0.116	<0.001	2.057	1.638–2.583
SBP	−0.366	0.141	0.009	0.694	0.527–0.914
TC	−0.198	0.051	<0.001	0.820	0.742–0.907
TG	0.100	0.040	0.012	1.106	1.022–1.196
TB	−0.132	0.042	0.002	0.876	0.807–0.951

DM, diabetes mellitus; OR, odds ratio; CI, confidence interval; BMI, body mass index; CHD, coronary heart disease; HBP, high blood pressure; SBP, systolic blood pressure; TG, triglyceride; TC, total cholesterol; TB, total bilirubin.

BMI and history of hypertension were the independent risk factors of DM (*Table 3*): the prevalence of DM reduced by 18% with an increment of 1 µmol/L in TB [odds ratio (OR): 0.876, 95% confidence interval (CI): 0.807–0.951; P=0.002].

Discussion

In this cross-sectional study, 3,876 people aged ≥65 years were recruited from Chinese Eastern communities to investigate the relationship between physiological serum TB and DM. Our results showed physiological serum TB was an independent risk factor of DM in old people; the prevalence of DM in old people was linearly related to TB quartile; the prevalence of DM reduced with the increase in physiological serum TB.

Ko *et al.* for the first time reported the negative relationship between serum bilirubin and impaired glucose tolerance in 1996 (18). A variety of studies confirm that elevated bilirubin may reduce the risk for DM and improve the outcome of DM patients (12,19,20). In recent years, a large epidemiological study from Korea investigated 93,909 subjects and results showed high serum bilirubin level was closely related to low risk for DM (21). The NHANES study of USA also indicates that the incidence of DM in subjects with serum bilirubin higher than 10 micromole/liter is reduced by 20% as compared to those

with serum bilirubin of <10 micromole/liter (12). However, both studies focused on the adolescents and old people. In this study, people older than 65 years were recruited, and results showed physiological serum bilirubin was negatively related to the prevalence of DM in them. This indicates that bilirubin plays a protective role in the occurrence and development of DM. Clinical and observational studies have revealed that the increased bilirubin may reduce the risk for DM by 26–31% (12,22). In the present study, the increased TB reduced the risk for DM by 18%. In our study, subjects with prior diagnosis of DM were included, and those with newly diagnosed DM were excluded. In addition, the serum bilirubin was in physiological range in our study, and subjects with comorbidities (such as Gilbert syndrome) were also excluded in the analysis of relationship between bilirubin and DM.

The protective role of bilirubin in DM is mainly ascribed to the anti-oxidative activity of bilirubin (23-26). Available studies have shown that TB in the physiological range may inhibit the damage of hyperglycemia-induced free radicals to cells (27). In addition, bilirubin may prevent vascular endothelial cells against oxidative stress (28,29). In animal experiments, biliverdin, the precursor of bilirubin, was found to prevent impaired glucose tolerance from deteriorating (30). In adults with normal serum bilirubin, bilirubin accounts for about 10% of total anti-oxidative

capacity and is negatively related to the serum markers of oxidative stress (31,32). These findings provide biological basis for the negative relationship between serum TB and DM. Bilirubin as an endogenous antioxidant (26,32,33) is negatively related to oxidative stress (7,34). Thus, the reduced prevalence of DM may be ascribed to the anti-oxidative activity of bilirubin.

Patients with T2DM usually have concomitant dyslipidemia (35). Some cross-sectional studies confirm that T2DM patients have a high incidence of dyslipidemia (36,37). Dyslipidemia may facilitate the development of atherosclerosis, which increases the risk of cardiovascular events in T2DM patients (38). Our findings were inconsistent with previously reported, which might be ascribed to the wide use of statins. Active lipid-lowering treatment is needed for DM patients, and serum lipid in physiological range is beneficial for DM patients.

There were still limitations in this study. First, this was a cross-sectional study which may not explain the causal relationship. Second, aminotransferase, γ-glutamate transferase and markers of viral hepatitis were not detected in this study, and thus we could not evaluate the influence of liver injury on our results. Third, the history of statins treatment was not recorded. Hemoglobin A1c (HbA1c) was not collected in DM patients. In addition, although the information about lifestyle (such as drinking and smoking) was collected, the information was incomplete and their reliability was questioned; the TB was measured once, and repeated measurement is needed in future studies.

Conclusions

Taken together, this large community study indicates that serum TB is an independent risk factor of DM in old people of Chinese eastern communities; the prevalence of DM in old people reduces with the increase in physiological serum TB.

Acknowledgments

Footnote

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