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Association between serum total bilirubin levels and the risk of type 2 diabetes mellitus

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ABSTRACT

Aim: To confirm whether serum bilirubin is an independent risk factor of type 2 diabetes mellitus (T2DM) onset in patients with impaired fasting glycemia (IFG) and impaired glucose tolerance (IGT).

Methods: This was a prospective cohort study carried out at the Diabetic Identification Center of Tianjin Metabolic Diseases Hospital. Serum total bilirubin (TBIL) was measured at baseline and the patients were grouped according to baseline bilirubin quartiles. The outcome was the confirmation of T2DM by oral glucose tolerance test (OGTT) during the 3-year follow-up. Logistic regression was used to determine the risk factors for T2DM development and whether bilirubin levels are independently associated with T2DM development.

Results: Finally, 523 patients were analyzed. After 3 years, 310 participants were diagnosed with diabetes based on OGTT. Baseline quartiles of total bilirubin were inversely associated with diabetes risk, even after multivariable adjustment. The adjusted ORs for diabetes were 1.0 (reference), 0.83 (95% CI 0.74–0.96), 0.78 (95% CI 0.68–0.90), 0.74 (95% CI 0.64–0.87) for the 1st, 2nd, 3rd, and 4th quartiles of baseline serum total bilirubin, respectively ($P < 0.001$).

Conclusion: In patients with IFG or IGT, low levels of serum total bilirubin were associated with a significantly increased risk of T2DM.

1. Introduction

Type 2 diabetes in an endocrine disorder characterized by hyperglycemia resulting from variable degrees of insulin resistance and deficiency [1]. Chronic hyperglycemia can lead to multiorgan damage resulting in renal, neurologic, and cardiovascular complication [1]. The worldwide prevalence of adult T2DM is 9% in men and 7.9% in women [2]. In China, the prevalence of T2DM and pre-diabetes is 11.6% and 50.1% among individuals >18 years of age, respectively, highlighting the epidemics proportion of this problem [3]. T2DM is associated with high mortality and this mortality is directly associated with the fasting glucose levels [4]. In China, the main causes of mortality associated with diabetes are ketoacidosis, chronic kidney disease, and ischemic heart disease [5].

Bilirubin is a metabolite of heme-containing proteins. The clinical significance of bilirubin with jaundice is well known, but it is now known to be negatively associated with diabetes and its chronic complications [6–10]. Ndisang et al. [11] reported that hemin induces the up-regulation of heme

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oxygenase-1 (HO-1), improves HO-1 activity, and increases the levels of bilirubin and ferritin, leading to improved antioxidant capability and decreased oxidative stress; in addition, insulin synthesis and sensitivity are improved in rats, and GLUT4 expression is increased, which promotes the uptake of glucose into cells. In vivo studies suggest that bilirubin protects the β cells from oxidation stress and injury [12,13] and decreases systemic oxidative stress and inflammation, leading to improved insulin resistance [14–16]. Dullaart et al. [17] reported that in patients with metabolic syndrome, low serum bilirubin levels can increase the generation of inflammatory glycoprotein.

Currently, the cross-sectional [18–21] and longitudinal [22–25] studies of the association between bilirubin and T2DM in the general population report discrepant results, which are probably due to differences in age and populations. Nevertheless, Wu et al. [10] indicated that high of bilirubin levels can reduce the incidence of the metabolic syndrome in the general population of middle-age and elderly Chinese. Moreover, many cross-sectional studies have shown that bilirubin is negatively correlated with HbA1c and abdominal obesity [26–28], but this remains to be confirmed by prospective studies.

Therefore, the aim of the present prospective study was to confirm whether serum bilirubin is an independent risk factor of T2DM onset in patients with impaired fasting glycemia (IFG) and impaired glucose tolerance (IGT). The results will provide a better understanding of the pathogenesis of T2DM.

2. Design and methods

2.1. Study design and patients

This was a prospective cohort study performed at the Diabetic Identification Center of Tianjin Metabolic Diseases Hospital. The study was approved by the Ethics Committee of the hospital. All patients signed an informed consent form.

From Jan. 2012 to Dec. 2014, all patients >18 years of age and diagnosed for the first time with impaired glucose regulation (IFG or IGT) determined using an oral glucose tolerance test (OGTT) were consecutively enrolled. Diagnosis was based on the criteria by the World Health Organization (IFG was defined as an fasting glucose level of 6.1 mmol/L (110 mg/dL) to 6.9 mmol/L (125 mg/dL); IGT was defined as a glucose level of 7.8 mmol/L (140 mg/dL) to 11.0 mmol/L (199 mg/dL) during a 2-h OGTT) [29]. The exclusion criteria were: (1) viral hepatitis or serum transaminase higher than the reference value; (2) alcoholism (over 5 years, average alcohol uptake ≥40 g/day for men and ≥20 g/day for women) or mean alcohol uptake >80 g/day in the previous 2 weeks); (3) biliary calculus and cholecystitis; (4) renal insufficiency (glomerular filtration rate <60 mL/min/1.73 m^2); (5) cancer; (6) drugs influencing glucose metabolism (such as β-blocker and glucocorticoids); or (7) pregnancy or pregnancy plan in the future 3 years.

2.2. Intervention and diagnosis of diabetes

The patients were advised to control their diet and to exercise, without drug intervention. OGTT was performed again in the 3rd year to confirm the glucose metabolism status according to the same diagnostic criteria [29]. The analysis exclusion criteria were: (1) loss to follow-up; (2) refused the second OGTT; (3) received anti-diabetic drugs during the 3-year period or any other drugs known to influence glucose metabolism; or (4) pregnancy during the 3-year period.

2.3. Measurement of serum bilirubin and grouping

The venous blood was collected at baseline, stored at −70 °C, and analyzed using an automatic biochemical analyzer within 2 h (Bayer HealthCare Pharmaceuticals, Montville, NJ, USA). Total bilirubin (TBIL) levels were measured by the vanadate oxidation method. Patients were divided into quartiles (Q) of TBIL levels.

2.4. Data collection

At baseline, smoking history, alcohol consumption (never, previous drinker, actual drinker, alcohol uptake (g/week)) and diabetes family history were collected. Height, body weight, body mass index (BMI), waistline, and blood pressure were measured. Fasting blood glucose, insulin, blood lipids (total cholesterol, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), and triglycerides), creatinine, and high-sensitivity C-reactive protein were measured (hs-CRP).

2.5. Statistical analysis

Continuous data with a normal distribution are expressed as means ± standard deviation (SD) and were analyzed by analysis of variance and the LSD post hoc test. Continuous variables with a non-normal distribution are presented as medians (1st and 3rd quartiles) and were analyzed using the Wilcoxon test. Categorical data are expressed as proportions and were analyzed using the chi-square test. The patients were grouped according to the quartile of total bilirubin at baseline. The confirmation of diabetes in the 3rd year was the outcome event. A logistic regression model was used to calculate odds ratios (OR) and 95% confidence intervals (CI). Four multivariable correction models were set up: Model 1 included age, sex, and education degree. Model 2 included all the variables in Model 1 and BMI (28 kg/m^2 as cut off). Model 3 included all the variables in Model 2 and squared height (m), systolic pressure, diastolic pressure, and hs-CRP. Model 4 included all the variables in Model 3, and fasting blood glucose, blood glucose within 2 h of OGTT, and diabetes family history. SPSS 19.0 (IBM, Armonk, NY, USA) was used to analyze the data. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Characteristics of the patients

A total of 645 patients were screened in this study and all of them agreed to participate. By the end of study, 81 patients

Table 1 – Characteristics of the participants according to quartiles (Q) of serum total bilirubin at baseline.

	Q1 (n = 131) (≤8.2 μmol/L)	Q2 (n = 130) (8.3–11.1 μmol/L)	Q3 (n = 131) (11.2–14.5 μmol/L)	Q4 (n = 131) (≥14.6 μmol/L)	*P*
Age (years)	60.4 ± 5.0[a]	61.6 ± 5.3[ab]	62.7 ± 5.4[b]	64.0 ± 5.7[b]	<0.01
Sex (male (%))	99 (75.6)[a]	60 (46.2)[b]	34 (26.0)[c]	28 (21.4)[c]	<0.01
Family history of diabetes, n (%)	29 (22.1)	31 (23.8)	29 (21.9)	26 (19.7)	0.02
Smoker, n (%)	18 (13.8)[a]	20 (15.4)[ab]	17 (13.0)[a]	21 (16.3)[b]	<0.01
Weight (kg)	77.8 ± 21.3	69.8 ± 25.7	63.6 ± 23.1	60.6 ± 25.3	<0.01
Height (m)	1.70 ± 0.09	1.68 ± 0.09	1.66 ± 0.09	1.65 ± 0.08	<0.01
BMI (kg/m^2)	26.9 ± 5.0[a]	24.7 ± 5.5[ab]	23.1 ± 5.5[ab]	22.3 ± 5.7[b]	<0.01
Waist (cm)	96.7 ± 11.4[a]	95 ± 13.0[ab]	93.5 ± 13.3[b]	92.8 ± 13.9[b]	<0.01
Hypertension, n (%)	32 (24.6)	29 (22.5)	35 (26.6)	43 (32.7)	<0.01
SBP (mmHg)	122.3 ± 15.3[a]	123.9 ± 16.8[ab]	126.9 ± 18.9[b]	131.3 ± 20.6[b]	<0.01
DBP (mmHg)	72.4 ± 9.4	71.3 ± 9.4	70.8 ± 10.1	71.0 ± 10.9	<0.01
LDL (mmol/L)	3.31 ± 0.89[a]	3.26 ± 0.85[ab]	3.15 ± 0.81[b]	3.06 ± 0.84[b]	<0.01
HDL (mmol/L)	1.23 ± 0.38	1.31 ± 0.41	1.39 ± 0.44	1.43 ± 0.45	<0.01
TG > 1.7 mmol/L, n (%)	43 (32.7)[a]	43 (32.6)[ab]	36 (27.7)[b]	39 (29.4)[b]	0.001
Fasting glucose (mmol/L)	5.6 (5.2–6.1)[a]	5.5 (5.2–5.9)[ab]	5.4 (5.1–5.8)[ab]	5.3 (5.0–5.7)[b]	<0.01
OGTT 2 h glucose (mmol/L)	8.2 (7.9–11.0)	8.1 (7.9–10.9)	8.0 (7.8–10.8)	7.9 (7.8–10.6)	<0.01
Fasting insulin (ng/mL)	11.8 (8.4–16.6)[a]	10.1 (7.1–14.5)[ab]	9.1 (6.4–13.0)[ab]	8.6 (5.8–12.1)[b]	<0.01
OGTT2h insulin (ng/mL)	47.2 (33.6–66.4)	50.5 (35.5–72.6)	45.5 (32.0–65.0)	43 (29.0–60.5)	0.06
CRP (mg/L)	2.0 (0.95–4.42)[a]	2.1 (0.98–4.77)[a]	2.2 (1.0–5.0)[a]	2.6 (1.1–5.8)[b]	<0.01

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol; TG: triglycerides; OGTT: oral glucose tolerance test; CRP: C-reactive protein. 1 mmHg = 0.133 kPa.
Different letters indicate statistical difference (P < 0.05).

were lost to follow-up and 41 did not undergo the 3-year OGTT; finally, 523 (81.1%) patients completed the study.

Table 1 shows the baseline characteristics of the patients. The patients were divided into four groups according to the baseline total bilirubin quartile: Q1, TBIL ≤8.2 μmol/L; Q2, TBIL 8.3–11.1 μmol/L; Q3, TBIL 11.2–14.5 μmol/L, and Q4, TBIL ≥14.6 μmol/L. The subjects in the lowest bilirubin quartile group at baseline were younger, with higher percentage of family history of diabetes, fewer women and smokers. Compared with the subjects with the highest bilirubin quartile, they had a poor blood lipid profile, high BMI, large waistline, high fasting blood glucose, and high insulin. In addition, compared with the subjects with the highest bilirubin quartile, those with the lowest levels had low hs-CRP and systolic pressure, and the incidence of hypertension was low.

3.2. *Occurrence of T2DM*

During the 3-year follow-up, 310 new cases of diabetes were found, as diagnosed by OGTT. According to the grouping based on the baseline total bilirubin quartiles, the occurrence of diabetes was 0.67 (95% CI: 0.58–0.76) for Q1, 0.62 (95% CI: 0.53–0.71) for Q2, 0.59 (95% CI: 0.50–0.68) for Q3; and 0.54 (95% CI: 0.46–0.62) for Q4 (P < 0.01) (Fig. 1).

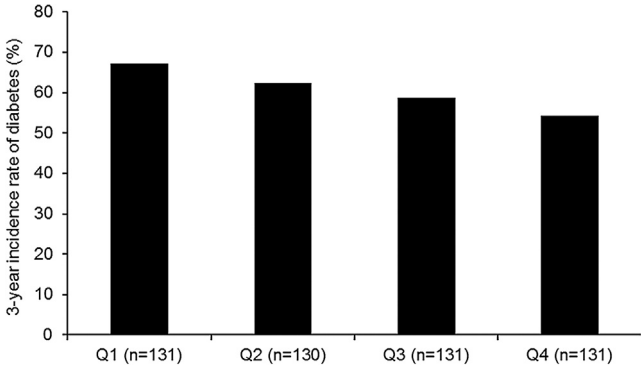

Fig. 1 – 3-year incidence rate of diabetes. Q1, total bilirubin (TBIL) ≤ 8.2 μmol/L; Q2, TBIL 8.3–11.1 μmol/L; Q3, TBIL 11.2–14.5 μmol/L, and Q4, TBIL ≥ 14.6 μmol/L. The differences of incidence rates amoung groups were statistically significant (P < 0.05).

3.3. *Risk of T2DM*

The subjects in the lowest bilirubin quartile group had a significantly increased diabetes risk. Table 2 shows the multivariable adjustments using logistic regression models. In Model 1, the OR of diabetes was 1.0 (reference), 0.87 (95% CI: 0.77–0.99), 0.75 (95% CI: 0.66–0.87), and 0.66 (95% CI: 0.58–0.78) (P < 0.01) in the 1st, 2nd, 3rd, and 4th quartile groups, respectively. After adjustment for BMI and cardiovascular risk factors, all the ORs became closer to 1.0, but the differences were still statistically significant. After further adjustment for fasting blood glucose and OGTT 2-h glucose, the risk of diabetes in all three quartile groups was still significant. Hence, bilirubin levels are associated with T2DM, even after adjustment for age, sex, BMI, smoking, systolic blood pressure, diastolic blood pressure, LDL-c, HDL-c, hs-CRP, fasting glucose, oral glucose tolerance test 2-h glucose, and family history of T2DM.

Table 2 – Adjusted odds ratios (95% confidence interval) of newly diagnosed diabetes by quartiles (Q) of total bilirubin.

	Q1 (n = 131) (≤8.2 μmol/L)	Q2 (n = 130) (8.3–11.1 μmol/L)	Q3 (n = 131) (11.2–14.5 μmol/L)	Q4 (n = 131) (≥14.6 μmol/L)	P
Model 1	1.0 (Reference)	0.87 (0.77–0.99)	0.75 (0.66–0.87)	0.66 (0.58–0.78)	<0.01
Model 2	1.0 (Reference)	0.93 (0.81–1.04)	0.82 (0.72–0.95)	0.77(0.66–0.88)	<0.01
Model 3	1.0 (Reference)	0.89 (0.78–1.00)	0.75 (0.67–0.88)	0.66 0.56–0.76)	<0.01
Model 4	1.0 (Reference)	0.83 (0.74–0.96)	0.78 (0.68–0.90)	0.74 (0.64–0.87)	<0.01

Model 1: age, sex.
Model 2: Model 1 + body mass index.
Model 3: Model 2 + smoking, systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, C-reactive protein.
Model 4: Model 3 + fasting glucose, oral glucose tolerance test 2-h glucose, and diabetes family history.

4. Discussion

Many cross-sectional [18–21] and longitudinal [22–25] studies have shown that bilirubin is negatively correlated with HbA1c, abdominal obesity, and the metabolic syndrome in the general population, but the association between serum total bilirubin levels and the risk of type 2 diabetes mellitus in patients with IFG and IGT remains to be confirmed by prospective studies. When considering the longitudinal studies, Oda et al. [22] showed in a general Japanese population that total bilirubin levels were inversely associated with the metabolic syndrome (a precursor state of T2DM), but is not a risk factor for the development of the metabolic syndrome. On the other hand, Lee et al. [23] showed in a general Korean population that total bilirubin levels were negatively associated with the 4-year incidence of the metabolic syndrome. In a general British population, the risk of T2DM was inversely associated with the total bilirubin levels [24]. Another study in a general Korean population revealed that total bilirubin levels were inversely associated with T2DM [25]. The present study adds to these results by examining whether serum bilirubin is an independent risk factor of T2DM onset in patients with IFG and IGT. The results strongly suggest that in patients IFG or IGT, low levels of serum total bilirubin are associated with a significantly increased risk of T2DM. Indeed, among patients with impaired glucose regulation, low levels of bilirubin are associated with an increased risk of T2DM. Even after adjustment for the traditional risk factor of T2DM and fasting blood glucose, the association is still observed. The results were consistent between sex and across BMI. These results are consistent with the cross-sectional [18–21] and longitudinal [22–25] studies carried out in general populations. Furthermore, these results are supported by *in vivo* experiments that suggest that bilirubin possesses antioxidant and anti-inflammatory effects that play a role in the development of T2DM [12–16].

Available data on the role of bilirubin levels in diabetes are limited. Recently, it has been indicated that serum bilirubin levels of patients with T2DM were relatively low, and that the cardiovascular combination risk of patients with diabetes and Gilbert syndrome was lower than in patients without Gilbert syndrome [30]. Ohnaka et al. [20] showed that bilirubin levels are negatively associated with C-peptide, HbA1c, and T2DM. Muhsain et al. [31] reported that the targeted regulation of HO-1 levels could be a new therapeutic target for T2DM. A prospective cohort study (Diabetes Distress and Care Registry at Tenri [DDCRT5]) from Japan indicated that serum bilirubin levels are relevant to the development of diabetic nephropathy in patients with T2DM. Moreover, low level of bilirubin is a risk factor of diabetic nephropathy and hemoglobin is associated with diabetic nephropathy and the association might play its role through bilirubin metabolism [32]. Small-scale cross-sectional studies of patients with T2DM indicated that serum bilirubin levels are negatively correlated with urinary albumin, renal function, and eGFR [19,33–35]. The Hisayama Study by Yasuda et al. [36] indicated that among patients with T2DM and those with IGT, the increase in bilirubin levels might be a protective factor. Cho et al. [37] reported that plasma homocysteine and serum bilirubin might be biomarkers for increased risk of diabetic retinopathy in patients with T2DM. The patients with T2DM and diabetic retinopathy have increased plasma homocysteine and decreased serum bilirubin [37]. Other studies also support the negative association between total bilirubin with diabetic retinopathy. A cross-sectional study from Japan indicated that among patients with T2DM, the total bilirubin levels within physiological range are relevant to the morphological change of corneal nerve fiber (CNFs) [38]. A cross-sectional study from Kim et al. [39] also reported that serum total bilirubin levels are negatively correlated with diabetic peripheral neuropathy. Chung et al. [40] indicated that the total bilirubin levels within physiological range were negatively associated with cardiac autonomic neuropathy. Hence, those previous studies consistently associated the complications of T2DM with low levels of bilirubin. The present study adds to the literature that low bilirubin levels are associated with the development of T2DM in patients with impaired glucose metabolism, i.e. patients at high risk of T2DM.

The main limitations of the study are the small sample size and the short follow-up time. OGTT was performed only in the 3rd year, which could only be used to calculate ORs instant of hazard ratios. In addition, due to differences in genetics and living habits, the conclusions of this study cannot be extended to other ethnic groups.

In conclusion, the results suggest that patients with impaired glucose regulation and low bilirubin levels have a significantly higher risk of T2DM than those with high bilirubin levels. Bilirubin may be related with the occurrence and development of T2DM. Bilirubin levels should receive more attention during routine clinical examinations of individuals, especially those at high-risk of T2DM.

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Conflict of interest

The authors declare that they have no conflict of interest.

Authors' contributions

Min Yang conceived and coordinated the study, designed, performed and analyzed the experiments, wrote the paper. Changlin Ni, Baocheng Chang, Zhenhuan Jiang, Yanjuan Zhu, Yunzhao Tang, Zhu Li, Chenguang Li and Bin Li carried out the data collection, data analysis, and revised the paper. All authors reviewed the results and approved the final version of the manuscript.

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