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Association between Total Bilirubin and Hemoglobin A1c in Korean Type 2 Diabetic Patients

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Recent studies have shown that bilirubin is negatively associated with hemoglobin A1c (HbA1c) in the general population. The association between bilirubin and HbA1c in serum of diabetes patients has not yet been studied. The aim of the present study was to evaluate the association between total bilirubin and HbA1c in Korean patients with type 2 diabetes. A total of 690 of the 1,275 type 2 diabetes patients registered with the public health centers in Seo-gu, Gwangju and Gokseong-gun, Jeollanam-do participated in this study. Following an overnight fast, venous blood and urine samples were collected and analyzed. The mean HbA1c values differed significantly according to total bilirubin (≤ 0.4 mg/dL, 7.6%; 0.5 mg/dL, 7.3%; 0.6-0.7 mg/dL, 7.2%; and ≥ 0.8 mg/dL, 7.1%; *P* for trend = 0.016) after we adjusted for other confounding factors. When the odds ratio (OR) was adjusted for other confounding factors, there was a significant association between total bilirubin and HbA1c (OR, 0.4 [95% confidence interval, 0.2-0.8] for total bilirubin ≥ 0.8 mg/dL versus ≤ 0.4 mg/dL. In conclusion, total bilirubin concentrations in serum are negatively associated with HbA1c levels after adjustment for sex, age, and other confounding factors in type 2 diabetes patients.

Key Words: Bilirubin; Diabetes Mellitus Type II; Glycosylated; Hemoglobin A

INTRODUCTION

In the 20th century, cardiovascular disease (CVD) became the main cause of mortality and morbidity in Western populations, and in 2000, the global prevalence of diabetes was estimated at 171 million (1). The risk of coronary artery disease (CAD) is six times higher in type 2 diabetes patients than in the general population (2, 3). Therefore, efforts to reduce the incidence of CVD through risk factor evaluations should be the primary focus when caring for patients with diabetes.

Bilirubin, once considered simply the natural end product of heme catabolism, has emerged as an important endogenous antioxidant (4) and anti-inflammatory molecule (5). Recent studies of its physiological importance have focused on its relationship with atherosclerotic diseases (6). Many studies have reported that higher serum bilirubin levels were related to decreased risks of CAD (7, 8), carotid atherosclerosis (9), stroke (10), and peripheral arterial disease (PAD) (11).

Hemoglobin A1c (HbA1c) is a reliable marker of chronic hyperglycemia and is the test of choice for the chronic management of diabetes (12). High HbA1c levels are strongly associated with an increased risk of all-cause mortality (13). For diabetes patients, a meta-analysis of observational studies suggested that increasing levels of HbA1c are associated with a moderate increase in cardiovascular (CV) risk (14). Furthermore, in our previous study (15) HbA1c was significantly associated with carotid plaques and PAD. Some researchers hypothesize that the association of HbA1c with bilirubin may at least partly mediate the association between HbA1c and CVD. In addition, studies have demonstrated that bilirubin is negatively associated with HbA1c, independently of other CV risk factors in the general population (16, 17). However, to the best of our knowledge, the association between bilirubin and HbA1c in diabetes patients has not yet been studied. We therefore examined the cross-sectional association between total bilirubin and HbA1c in Korean type 2 diabetes patients.

MATERIALS AND METHODS

Study subjects

Between October 2008 and June 2009, 709 out of 1,275 registered type 2 diabetes patients seen at public health centers in

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Seo-gu, Gwangju and Gokseong-gun, Jeollanam-do, Korea agreed to participate in this study. The response rate was 55.6%. Nineteen subjects were excluded for the following reasons: no blood sample (n = 15), an aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level greater than three times the upper normal limit (i.e., > 120 U/L) (n = 3), and total bilirubin > 3.0 mg/dL (n = 1). In total, 690 patients participated in this study.

Study measurements

Well-trained examiners interviewed the patients using a questionnaire that includes items on cigarette smoking, the consumption of alcohol, physical activity, duration of diabetes, diabetes complications, hypertension medication, and history of cardiocerebrovascular disease (CCVD).

Weight was measured to the nearest 0.1 kg while the subjects wore light clothing; and height was measured to the nearest 0.1 cm in subjects not wearing shoes. Abdominal circumference was measured to the nearest 0.1 cm at expiration in the horizontal plane around the abdomen at the level of the midpoint between the lowest rib and the iliac crest. Blood pressure was measured twice with a standard mercury sphygmomanometer after the subjects had rested for at least 5 min.

After an overnight fast, venous blood was sampled and serum was separated on-site and stored at -70°C until analysis. The concentrations of total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, AST, ALT, γ-glutamyl transpeptidase (GGT), and total bilirubin were measured using an automatic analyzer (HITACHI-7600, Hitachi, Tokyo, Japan). The low-density lipoprotein (LDL) cholesterol level was calculated using the equation proposed by Friedewald et al. (18), except when the triglyceride level exceeded 400 mg/dL, in which case the data were treated as missing. HbA1c levels were analyzed by high-performance liquid chromatography (HPLC) with the VARIANT II system (Bio-Rad, Hercules, CA, USA). The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula (19) as follows: $186.3 \times (\text{serum creatinine}^{-1.154}) \times (\text{age}^{-0.203}) \times 0.742$ (if female), where the serum creatinine concentration was in mg/dL.

Statistical analysis

We categorized the subjects based on total bilirubin quartiles (≤ 0.40, 0.50, 0.60-0.70, and ≥ 0.80 mg/dL). Baseline differences in general and biochemical variables across the total bilirubin quartiles were compared by analysis of variance (ANOVA) for continuous variables and by chi-square test for categorical variables. Data are presented as the mean ± standard deviation (SD) or, for categorical variables, percentage. Analysis of covariance (ANCOVA) was used to compare mean HbA1c levels according to the total bilirubin quartile. Because the HbA1c distributions were skewed, data were log-transformed for ANCOVA and then back-transformed and reported as observable values. Model 1 was adjusted for sex, age, abdominal circumference, and smoking. Model 2 included the Model 1 variables plus diabetes duration, hypertension, CCVD history, HDL, LDL, triglycerides, fasting glucose, and eGFR. Model 3 included all of the Model 2 variables plus AST, ALT, and GGT. Logistic regression was used to calculate odds ratios (ORs) for HbA1c < 6.5% or ≥ 6.5% according to total bilirubin quartile. Statistical significance was defined as $P < 0.05$. Statistical analyses were performed using SPSS ver. 15.0 (SPSS Inc.).

Ethics statement

This study was conducted in accordance with the Declaration of Helsinki guidelines. The study protocol was approved by the institutional review board of Chonnam National University Hospital (No. for Seo-gu, Gwangju I-2008-11-135; No. for Gokseong-gun, Jeollanam-do I-2009-07-069). Informed consent was obtained from each subject.

RESULTS

General characteristics

The general and biochemical characteristics of the 690 subjects (225 men and 465 women) are detailed in Table 1. The mean age at diagnosis of diabetes was 59.3 ± 12.5 yr, and the mean duration of diabetes was 8.9 ± 8.0 yr. Mean systolic and diastolic BP was 130.3 ± 17.6 and 72.0 ± 9.8 mmHg, respectively. The mean total cholesterol concentration was 193.3 ± 44.1 mg/dL and the mean HDL cholesterol concentration was 47.4 ± 11.7 mg/dL. The mean AST, ALT, and GGT concentrations were 27.0 ± 12.8, 24.6 ± 14.5, and 36.6 ± 41.1 U/L, respectively. The mean HbA1c level was 7.4% ± 1.5% and the mean total bilirubin concentration was 0.6 ± 0.3 mg/dL. A total of 99 patients (14.8%) had a history of CCVD and 106 (15.6%) were current smokers.

Height, weight, diastolic BP, eGFR, AST, ALT, and GGT tended to be higher in participants with an increased total bilirubin level. In addition, these participants were more frequently male. Total cholesterol and LDL cholesterol tended to be lower in participants with an increased total bilirubin level.

Comparison of means HbA1c according to total bilirubin level

Table 2 lists the mean values (± SE) for HbA1c according to the quartile of total bilirubin. The mean HbA1c values did not differ significantly according to total bilirubin level (≤ 0.4 mg/dL, 7.5%; 0.5 mg/dL, 7.2%; 0.6-0.7 mg/dL, 7.3%; and ≥ 0.8 mg/dL, 7.3%; P for trend = 0.409) after adjustment for sex, age, abdominal circumference, and smoking. However, the mean HbA1c values differed significantly after adjustment for additional risk factors (Model 3) (≤ 0.4 mg/dL, 7.6%; 0.5 mg/dL, 7.3%; 0.6-0.7 mg/dL, 7.2%; and ≥ 0.8 mg/dL, 7.1%; P for trend = 0.016).

ORs for HbA1c according to total bilirubin level

The ORs for HbA1c < 6.5% and ≥ 6.5% according to total bilirubin quartile are listed in Table 3. After adjustment for the other covariates (Model 3), a total bilirubin level of ≥ 0.8 mg/dL was significantly associated with an HbA1c value of ≥ 6.5% (OR 0.4, 95% CI, 0.2-0.8) as compared with a total bilirubin level of ≤ 0.4 mg/dL.

Table 1. General characteristics of the subjects according to the bilirubin

Variables	Total bilirubin (mg/dL)				Total	*P* value
	Quartile 1 (≤ 0.4)	Quartile 2 (0.5)	Quartile 3 (0.6 to 0.7)	Quartile 4 (≥ 0.8)		
No.	154	155	235	146	690	-
Male (%)	41 (26.6)	367 (23.2)	69 (29.4)	75 (51.4)	225 (32.4)	< 0.001
Total bilirubin (mg/dL)	0.4 ± 0.1	0.5 ± 0.0	0.6 ± 0.0	1.0 ± 0.3	0.6 ± 0.3	< 0.001
Age (yr)	69.6 ± 9.7	68.9 ± 11.6	67.6 ± 9.5	66.8 ± 10.4	68.2 ± 10.3	0.064
Age at diabetic diagnosis (yr)	59.7 ± 13.3	60.2 ± 13.3	59.5 ± 11.1	57.5 ± 12.8	59.3 ± 12.5	0.262
Diabetic duration (yr)	9.8 ± 9.1	8.7 ± 7.6	8.2 ± 7.1	9.2 ± 8.7	8.9 ± 8.0	0.263
Height (cm)	153.2 ± 8.2	152.8 ± 8.2	154.6 ± 8.1	158.7 ± 9.1	154.8 ± 8.6	< 0.001
Weight (kg)	56.3 ± 9.2	57.2 ± 10.8	59.3 ± 9.6	61.4 ± 10.1	58.6 ± 10.1	< 0.001
BMI (kg/m^2)	24.0 ± 3.7	24.5 ± 3.8	24.8 ± 3.7	24.4 ± 3.7	24.5 ± 3.7	0.209
Abdomen circumference (cm)	88.4 ± 10.4	88.0 ± 9.5	89.6 ± 9.5	89.1 ± 7.9	88.9 ± 9.4	0.347
Systolic BP (mmHg)	131.9 ± 20.2	127.5 ± 16.7	131.2 ± 16.6	130.3 ± 16.8	130.3 ± 17.6	0.123
Diastolic BP (mmHg)	71.2 ± 9.6	70.4 ± 9.2	72.3 ± 10.1	74.1 ± 9.7	72.0 ± 9.8	0.007
Total cholesterol (mg/dL)	193.6 ± 47.5	202.1 ± 46.8	191.7 ± 40.4	186.0 ± 41.7	193.3 ± 44.1	0.014
Triglycerides (mg/dL)	188.4 ± 76.2	192.2 ± 88.6	169.9 ± 68.5	185.3 ± 129.6	182.3 ± 90.9	0.070
HDL cholesterol (mg/dL)	45.4 ± 10.3	47.0 ± 11.8	48.5 ± 12.4	48.0 ± 11.7	47.4 ± 11.7	0.070
LDL cholesterol (mg/dL)	111.5 ± 36.9	116.6 ± 36.8	109.3 ± 32.9	102.8 ± 32.8	110.1 ± 34.9	0.008
Fasting plasma glucose (mg/dL)	129.0 ± 44.0	134.6 ± 48.3	140.3 ± 52.5	142.5 ± 51.8	137.0 ± 49.7	0.064
HbA1c (%)	7.5 ± 1.5	7.3 ± 1.3	7.4 ± 1.6	7.5 ± 1.6	7.4 ± 1.5	0.906
eGFR (mL/min per 1.73 m^2)	61.4 ± 18.1	63.9 ± 15.3	67.1 ± 16.4	66.2 ± 14.0	64.9 ± 16.2	0.005
AST (U/L)	24.4 ± 10.0	26.3 ± 12.2	27.1 ± 10.4	30.4 ± 17.8	27.0 ± 12.8	0.001
ALT (U/L)	21.9 ± 13.5	22.9 ± 14.6	24.9 ± 13.6	28.9 ± 16.1	24.6 ± 14.5	< 0.001
GGT (U/L)	32.4 ± 30.0	38.4 ± 67.7	39.3 ± 71.0	46.0 ± 53.6	36.6 ± 41.1	0.020
CCVD history	19 (12.8)	22 (14.5)	31 (13.7)	27 (19.1)	99 (14.8)	0.419
Current smoker (%)	27 (17.9)	21 (13.5)	32 (13.8)	26 (18.3)	106 (15.6)	0.482
Hypertension (%)*	102 (78.5)	98 (80.3)	147 (78.2)	99 (81.1)	446 (79.4)	0.913

Values are given as the mean ± standard deviation or No (%). *Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or taking antihypertension medication. BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, glycated hemoglobin; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyl transpeptidase; CCVD, cardio-cerebrovascular disease.

Table 2. Comparison of means of HbA1c according to total bilirubin

	Categorized total bilirubin (mg/dL)	Model 1*	Model 2†	Model 3‡
		Mean (95% CI)	Mean (95% CI)	Mean (95% CI)
HbA1c	Quartile 1 (≤ 0.4)	7.5 (7.2-7.7)	7.6 (7.4-7.8)	7.6 (7.4-7.8)
	Quartile 2 (0.5)	7.2 (7.0-7.4)	7.3 (7.1-7.5)	7.3 (7.1-7.5)
	Quartile 3 (0.6 to 0.7)	7.3 (7.1-7.4)	7.2 (7.0-7.4)	7.2 (7.1-7.4)
	Quartile 4 (≥ 0.8)	7.3 (7.1-7.5)	7.1 (6.9-7.3)	7.1 (6.9-7.3)
	P for trend	0.409	0.015	0.016

*Adjusted by sex, age, abdominal circumstance and smoking; †Adjusted by Model 1 plus diabetic duration, hypertension, CCVD history, HDL, LDL, triglyceride, fasting glucose and eGFR; ‡Adjusted by Model 2 plus AST, ALT and GGT. HbA1c, glycated hemoglobin.

Table 3. ORs for HbA1c according to total bilirubin

	Categorized total bilirubin (mg/dL)	Model 1*	Model 2†	Model 3‡
HbA1c	Quartile 1 (≤ 0.4)	1.0	1.0	1.0
	Quartile 2 (0.5)	0.8 (0.5-1.5)	0.7 (0.4-1.4)	0.7 (0.4-1.4)
	Quartile 3 (0.6 to 0.7)	0.7 (0.5-1.2)	0.6 (0.3-1.1)	0.6 (0.3-1.0)
	Quartile 4 (≥ 0.8)	0.7 (0.4-1.2)	0.5 (0.2-0.9)§	0.4 (0.2-0.8)§
	P for trend	0.152	0.024	0.008

*Adjusted by sex, age, abdominal circumstance and smoking; †Adjusted by Model 1 plus diabetic duration, hypertension, CCVD history, HDL, LDL, triglyceride, fasting glucose and eGFR; ‡Adjusted by Model 2 plus AST, ALT and GGT; §$P < 0.05$. HbA1c, glycated hemoglobin; HbA1c was dichotomized according to HbA1c < 6.5 or HbA1c ≥ 6.5.

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DISCUSSION

This study examined whether total bilirubin is associated with HbA1c in Korean patients with type 2 diabetes. The data suggest that total bilirubin concentrations are negatively associated with HbA1c levels after adjustment for sex, age, and other confounding factors.

Bilirubin has emerged as an important endogenous antioxidant (4) and anti-inflammatory molecule (5) that scavenges free radicals in vitro and in vivo (4). In addition to its radical-scavenging activity, bilirubin has a potent inhibitory effect on the activity of NADPH oxidase, which is likely an important source of reactive oxygen species (ROS) production (20). Recent studies indicate that bilirubin can protect cells from a 10,000-fold increase in oxidative stress caused by hydrogen peroxide (21, 22).

Oxidative stress is a key factor in the development of atherosclerosis (23). The development of atherosclerosis involves several oxidative processes, including formation of oxygen and peroxyl radicals and LDL oxidation (24-26). The uptake of oxidized LDL by intimal macrophages leads to the accumulation of lipid-rich foam cells in the vascular intima (23). In addition, free radicals can disrupt the function of various cells including endothelial cells (27). Bilirubin may protect against atherosclerosis and coronary heart disease by protecting lipids and lipoproteins from oxidation. Oxidative stress also has a detrimental role in the pathogenesis of diabetes and its complications (28). Oxidative stress and ROS activate multiple serine kinase cascades, which potentially target the insulin signaling pathway, including the insulin receptor and its substrate proteins (29). In addition, oxidative stress may contribute to progressive beta-cell damage (30). Therefore, bilirubin likely has protective effects against the development of diabetes mellitus and CVD by reducing oxidative stress.

Many studies have reported that a high bilirubin concentration is inversely associated with the prevalence of hypertension (31) and type 2 diabetes (17, 32) and is related to CVD (7, 8, 10, 11). In the present study, we examined the association between bilirubin and subclinical atherosclerosis surrogate measures, such as common carotid artery intima-media thickness (CCA-IMT), carotid plaques, brachial-ankle pulse wave velocity (baPWV), and PAD. Only carotid plaque was associated with total bilirubin. After adjusting for the other covariates, total bilirubin concentrations of 0.5 mg/dL (OR 0.5; 95% CI, 0.2-0.9) and ≥ 0.8 mg/dL (OR 0.5; 95% CI, 0.2-1.0) were significantly associated with carotid plaques as compared with a total bilirubin concentration of ≤ 0.4 mg/dL.

It is well known that high levels of HbA1c are strongly associated with an increased risk of CVD (14) and microvascular complications such as nephropathy and retinopathy (33, 34). In our previous study (15), we examined the relationship between HbA1c and surrogate measures of subclinical atherosclerosis including CCA-IMT, carotid plaques, baPWV, and PAD in Korean type 2 diabetes patients. HbA1c was significantly associated with carotid plaque and PAD, but not with CCA-IMT or baPWV.

Some researchers have studied the relationship between HbA1c and bilirubin. In a study of 4,180 members of the general population, total bilirubin was negatively associated with HbA1c independent of other cardiovascular risk factors (16). In the baseline survey of a cohort study examining 11,776 members of the general population (17), mean HbA1c became progressively lower with increasing concentration of serum bilirubin in men (≤ 0.3 mg/dL, 5.15%; 0.4 mg/dL, 5.14%; 0.5 mg/dL, 5.14%; 0.6 mg/dL, 5.08%; and ≥ 0.7 mg/dL, 5.07%; P for trend < 0.001) and women (≤ 0.3 mg/dL, 5.12%; 0.4 mg/dL, 5.12%; 0.5 mg/dL, 5.07%; 0.6 mg/dL, 5.07%; and ≥ 0.7 mg/dL, 5.04%; P for trend < 0.001). These data are consistent with our results; however, since these studies were conducted with the general population, rather than with type 2 diabetes patients, the meaning of their results differs from that of ours.

There are some plausible explanations for the mechanism linking HbA1c and bilirubin. First, bilirubin is involved in the glycation of hemoglobin. Sugars react non-enzymatically with a wide range of proteins to form early glycation products (24), and oxidative stress is involved in the glycation reaction (14). Oxidative stress can facilitate the autoxidation of glucose to dicarbonyl intermediates, which is an early step in the Maillard reaction (33). In addition, malondialdehyde, which is generated by lipid oxidation, is thought to enhance the process of protein glycation by acting as an anchor between sugar and hemoglobin moieties (27). Therefore, bilirubin may inhibit the glycation of hemoglobin by reducing oxidative stress.

Second, bilirubin may play an important role in glycemic control. Increased expression of heme oxygenase-1, the enzyme responsible for the conversion of hemoglobin to bilirubin, is associated with enhanced insulin sensitivity and glucose metabolism (32). In addition, serum bilirubin is inversely associated with insulin resistance (12) and it increases the expression of glucose transporter-1 and the rate of glucose uptake (23). However, in the present study, we did not collect data related to insulin resistance. We therefore cannot confirm the association between bilirubin and insulin resistance.

This study has some limitations. First, as mentioned above, we could not acquire data related to insulin resistance. In addition, we did not obtain information regarding medications affecting the liver or bilirubin levels. Second, the study design was cross-sectional, which prevented us from drawing conclusions regarding the temporal nature of the observed association between serum bilirubin and HbA1c. Third, the study population consisted of Korean men and women; as a result, it is not clear whether these findings apply to other ethnic groups.

In conclusion, there is a significant negative association between total bilirubin and HbA1c, which is independent of sex,

age, abdominal circumference, smoking, and other risk factors in Korean type 2 diabetes patients. Additional prospective studies are required to further evaluate the mechanisms underlying these associations in type 2 diabetes patients.

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