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Inverse relationship between fasting direct bilirubin and metabolic syndrome in Korean adults

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ABSTRACT

Background: Studies on the effects of bilirubin on cardiovascular disease have typically focused only on total serum bilirubin composed with direct bilirubin plus indirect bilirubin. In this study, we examined which type of fasting bilirubin is more associated with the metabolic syndrome (MS).

Methods: Five thousand six hundred and fifty-four individuals who visited the Center for Health Promotion for a periodic medical health check-up were screened for inclusion in the study. We excluded subjects who had a chronic viral liver disease, an alcoholic liver disease, or an abnormal liver function defined as a serum aspartate aminotransferase or alanine aminotransferase >100 IU/l, a gamma glutamyltransferase >100 IU/l, or a fasting total bilirubin level >3 mg/dl.

Results: In men, only fasting direct bilirubin levels decreased with an increase in the number of MS components ($p = 0.001$). However, all three types of fasting bilirubin decreased when the subjects had more components of MS ($p < 0.001$) in women. Both in men and women fasting direct bilirubin levels were related with the MS (p for trend = 0.003 in men and <0.001 in women) after the adjustments for age, body mass index, smoking, alcohol drinking, exercise habits, and presence of fatty liver. The odds ratio (95% confidence interval) of MS for each fasting direct bilirubin quartile was 0.88 (0.59–1.29), 0.63 (0.42–0.95), 0.61 (0.38–0.97) in men, and 0.66 (0.50–0.87), 0.52 (0.35–0.78), 0.27 (0.12–0.59) in women, respectively. However, fasting total and indirect bilirubin levels were related with the MS in women, but not in men.

Conclusion: Our findings suggest that MS is more related to the fasting direct bilirubin in Korean adults than the other types of fasting bilirubin.

1. Introduction

Metabolic syndrome (MS) is a constellation of interrelated risk factors of metabolic origin that appear to directly promote the development of cardiovascular diseases (CVD) [1]. This syndrome is also strongly associated with type 2 diabetes mellitus [2,3]. Several mechanisms have been suggested as the primary cause of MS, although the precise pathogenesis is still unknown. These mechanisms include insulin resistance [4], adipokines [5,6], and chronic inflammation [7–9].

Bilirubin is a metabolic end product of heme breakdown [10]. Recently, studies on bilirubin have suggested that it is not only a potent antioxidant, but also a cytoprotectant [11]. Individuals with Gilbert's syndrome have a reduced prevalence of CVD and they also have increased levels of circulating antioxidants and an improved resistance to serum oxidation [12]. Moreover, epidemiological studies have demonstrated that serum total bilirubin was inversely related to an increased risk of coronary artery disease [13,14]. Similarly, low bilirubin has been shown to be associated with an increased carotid intimal media thickness [15], and peripheral arterial disease [16]. The inverse relationship between serum total bilirubin and CVD has been found in prospective studies [17–19].

In addition, serum total bilirubin is independently associated with many of the cardiometabolic risk factors [20–22]. Serum total bilirubin is inversely related to adiposity, blood pressure, glucose, insulin, triglycerides and LDL-cholesterol [20,21], but directly related to HDL-cholesterol [13,14]. Moreover, Lin et al. [22] reported that serum total bilirubin is inversely associated with MS in children and adolescents. The effects of bilirubin on MS have been focused only on serum total bilirubin. However, total serum bilirubin is constituted of direct bilirubin plus indirect bilirubin. In this study, we examined which type of fasting bilirubin is more associated with the MS.

2. Materials and methods

2.1. Subjects

The study population consisted of 5654 Korean adults who visited the Center for Health Promotion for a routine health check-up from January 2006 and December 2007. Among these participants, we

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excluded 246 subjects who were positive for the hepatitis B surface antigen or the antibody to the hepatitis C virus. We also excluded 618 subjects who met one of the following exclusions; a medical history of chronic liver disease, currently taking medications for liver disease, had a daily alcohol consumption of >2 drinks (alcohol use ≥30 g/day) for men or >1.5 drinks (alcohol use ≥20 g/day) for women, or had abnormal liver functions. Abnormal liver functions were defined as a serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >100 IU/l, a serum gamma glutamyltransferase (γ-GT) > 100 IU/l, or a serum fasting total bilirubin level >3 mg/dl. The final analytic sample population contained 4790 subjects. The institutional review board of the Myongji Hospital approved this study.

2.2. Measurements

A detailed medical history and history of past and current medications were collected from the medical records of the participants. All subjects completed a lifestyle questionnaire that included smoking status, alcohol consumption, and exercise habits. A smoking habit was defined as currently smoking cigarettes. Alcohol consumption was measured according to the amount of alcohol of more than one bottle of soju (a kind of distilled spirits containing 56.8 g of pure alcohol) consumed per week. Regular exercise was defined as 30 min or more at a time, 3 times per week regularly. Body weight was measured to the nearest 0.1 kg using an electronic scale. Height was measured to the nearest 0.1 cm using a stadiometer. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Waist circumference was measured midway between the lowest rib and the iliac crest with the subjects in a standing position. A liver ultrasonography was conducted to assess the presence of fatty liver. The same operator who was blinded to the medical histories and laboratory results of the participants performed all of the ultrasounds. The ultrasounds were performed with a high resolution B-mode scanner (EnVisor HD, version C.0.1, USA).

Blood samples were collected after an overnight fast (>12 h) and were analyzed for glucose metabolism-related substances, fasting glucose (ADVIA 1650, Siemens, Tarrytown, NY, USA), fasting insulin (Roche, Indianapolis, IN), and hemoglobin A1c (HbA1c) (HLC-723GHb, TOSOH, Siba, Minaoto-ku, Japan). Insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR) index [(insulin (μIU/ml) × fasting glucose (mg/dl)/18)/22.5]. We measured high-sensitive C-reactive protein as a marker of systemic low-grade inflammation, which was measured by turbidmetric immunoassay using a Hitachi 7170S (Hitachi Hi-Tech, Tokyo, Japan). Lipid metabolite indices including total cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, and liver function tests including albumin, AST, ALT, γ-GT, total bilirubin, and direct bilirubin were measured using an ADVIA 1650 Chemistry system (Siemens, Tarrytown, NY). Method used in measuring LDL-cholesterol was direct method [23]. Measuring method of total and direct bilirubin was Vanadate oxidation method [24].

2.3. Definition of metabolic syndrome

Metabolic syndrome was defined as having ≥3 of the criteria based on the modified NCEP ATP III definition [1] and the Korean Society for the Study of Obesity [25]:

Abdominal obesity: waist circumference ≥90 cm in men and ≥85 cm in women
Hypertriglycerides: ≥150 mg/dl
Low HDL-cholesterol: <40 mg/dl in men and <50 mg/dl in women
High blood pressure: systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg or use of anti-hypertensive medication
Impaired fasting glucose: fasting glucose ≥100 mg/dl or use of insulin or hypoglycemic medication.

2.4. Statistical analyses

The 2 sample *t*-test and $\chi 2$ test were applied for continuous and categorical variables, respectively. Fasting insulin, HOMA-IR, triglycerides, γ-GT, hs-CRP, and the 3 types of bilirubin were logarithmically transformed prior to statistical analyses in order to approximate normal distributions. We analyzed the prevalence of each component of MS in both men and women according to the quartiles of the 3 types of bilirubin. Pearson correlation coefficients were calculated to evaluate a relationship between the 3 types of bilirubin and cardiometabolic variables. We performed an evaluation of the relationships between the 3 types of bilirubin and the number of components of MS in both men and women using p for trend. Logistic regression analyses for MS were performed in both sexes with the quartiles for the 3 types of bilirubin after adjustment for age, body mass index, current smoking status, alcohol consumption, regular exercise, and the presence of fatty liver. A $p<0.05$ was considered to be statistically significant. All calculations were performed using the Statistical Package for Social Sciences software, ver 15.0 (SPSS, Chicago, IL).

3. Results

3.1. Prevalence of MS and each component in the 3 types of bilirubin

The clinical characteristics of the subjects are presented in Table 1. Body mass index, waist circumference, blood pressure, presence of fatty liver, and the use of anti-hypertensive or hypoglycemic agents were higher in subjects with MS. In contrast, subjects without MS have tendency to drink less and exercise more. In both men and women, prevalence of MS were relatively decreased as the quartiles of the 3 types of bilirubin increased, except for indirect bilirubin in men. Among MS components, direct bilirubin was related with all the components in women, but was not related with waist circumference and high blood pressure in men (Fig. 1).

3.2. Relationships between the 3 types of bilirubin and cardiometabolic risk factors

Direct bilirubin levels were negatively correlated with waist circumference, glucose metabolism-related variables and triglyceride, but positively correlated with HDL-cholesterol in both men and women. However, direct bilirubin levels were negatively correlated with blood pressure in women, but were not correlated in men. Total and indirect bilirubin levels were not associated with blood pressure

Table 1
Clinical characteristics of subjects.

Variables	With MS[a] (N = 950)	Without MS (N = 3840)	P-value
Age (y)	52.8 ± 11.0	45.6 ± 11.6	<0.001
Gender (male), n (%)	489 (51.5)	1809 (47.1)	0.016
Anthropometrics			
Body mass index (kg/m^2)	26.3 ± 2.8	23.1 ± 2.9	<0.001
Waist circumference (cm)	89.7 ± 7.0	79.1 ± 8.6	<0.001
Blood pressure (mm Hg)			
Systolic	139.7 ± 14.5	123.9 ± 15.7	<0.001
Diastolic	80.9 ± 9.2	72.2 ± 10.3	<0.001
Current smoker, n (%)	175 (18.4)	747 (19.5)	NS
Alcohol drinking, n (%)	255 (26.8)	778 (20.3)	<0.001
Regular exercise, n (%)	257 (27.1)	1997 (52.0)	<0.001
Fatty liver, n (%)	686 (72.2)	1045 (27.2)	<0.001
Hypertension, n (%)	277 (29.2)	284 (7.4)	<0.001
Diabetes mellitus, n (%)	149 (15.7)	67 (1.7)	<0.001

Data are shown as means ± SD.
[a] MS: metabolic syndrome.