Association of Serum Total Bilirubin with Serum High Sensitivity C-reactive Protein in Middle-aged Men

Original Article

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Background: It has been suggested that bilirubin has an inverse association with cardiovascular disease (CVD) due to its antioxidant properties. However, there are few data regarding the relationship between serum total bilirubin (sTB) and risk factors for CVD in Koreans. This study aimed to evaluate the relationship between sTB and high sensitivity C-reactive protein (hsCRP), which is an independent risk factor for CVD.

Methods: We performed a cross sectional study in 6,800 men who were examined at a health promotion center at a university hospital in Korea between May 2005 and June 2006. We grouped the subjects according to values of serum hsCRP (above or below 1.0 mg/L) and compared the characteristics of the two groups. To evaluate the relationship between sTB and hsCRP, we classified the subjects according to quartile values of sTB. Multivariate logistic regression analyses were used to analyze the relationship of levels of sTB and hsCRP after adjusting for known risk factors for CVD.

Results: Serum hsCRP was significantly associated with body mass index (BMI), smoking, diabetes, hypertension, fasting plasma glucose, systolic blood pressure, alanine aminotransferase, and total cholesterol/high density lipoprotein (TC/HDL-C) ratio, but not with age or alcohol use. As levels of sTB increased, there was a decrease in age, numbers of smokers, BMI, and TC/HDL ratio. Compared to the lowest quartile of sTB, levels of hsCRP decreased with odds ratios of 0.82 (95% CI, 0.71 to 0.96), 0.75 (95% CI, 0.65 to 0.88), and 0.63 (95% CI, 0.54 to 0.74) in the 2nd, 3rd, and 4th quartiles of bilirubin, respectively.

Conclusion: Bilirubin may be inversely associated with hsCRP.

Keywords: Bilirubin; High Sensitivity C-reactive Protein; Cardiovascular Disease

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INTRODUCTION

Atherosclerosis (AS) is a vascular disorder in which the arterial walls thicken as a result of the accumulation of fatty materials. AS is also a chronic inflammatory disease caused by the deposition of activated lymphocytes and macrophages and is promoted by low-density lipoproteins. When AS progresses, cytokines such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) increase.[1,2] High sensitivity CRP (hsCRP) is associated with instability of atheromatous plaque and is a predictive indicator

for cardiovascular morbidity.[3] Thus, an elevated level of hsCRP is associated with a risk of myocardial infarction in older people, patients with angina who have a high risk of cardiovascular disease (CVD), and also in healthy adults.[4] Additionally, similar to serum total cholesterol and the ratio of serum total cholesterol to high density lipoprotein (TC/HDL-C), an elevated level of hsCRP is an independent predictive indicator of cardiovascular morbidity[5] and is a stronger predictive risk factor for CVD than classical risk factors.[6] Schwertner et al.[7] reported that serum total bilirubin (sTB) was inversely correlated with risk of CVD, and Hunt et al.[8] found that the patients who had lower levels of sTB had up to an 80% increase in the risk of CVD compared to patients who had higher levels of sTB. However, there are few hypotheses about the relationship between sTB and CVD. According to a previous Korean study, sTB is a valuable indicator for AS of coronary arteries in patients with asymptomatic type II diabetes mellitus (DM). But there is little research regarding the relationship between sTB and CVD in Koreans. Therefore, we conducted the present study to analyze the relationship between sTB and hsCRP in middle-aged Korean men who visited a hospital health promotion center.

METHODS

1. Study Subjects

Our study subjects were 19,747 middle-aged Korean men who visited the Health Promotion Center of Kangbuk Samsung Hospital between May 01, 2005, and June 30, 2006. Subject age ranged from 40 to 59 years old. Of the 19,475 potential subjects, we excluded 12,475 subjects who had multiple medical problems or abnormal laboratory findings. Subjects with any of the following were excluded: chronic diseases such as malignancies, chronic liver disease, and CVD, including ischemic heart disease, cerebral infarct, and peripheral vascular disease; infectious or inflammatory diseases; abnormal liver function, defined as an elevation of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) three times more than the upper normal limits, a level of serum albumin lower than 3.5 mg/dL, or sTB above 2.0 mg/dL (34.2 μmol/L, SI unit),[9] abnormal findings in the hepatobiliary tract on sonography; acute infectious diseases such as acute respiratory infection and acute hepatitis or chronic

inflammatory disease such as osteoarthritis, rheumatoid arthritis, gouty arthritis, asthma, and inflammatory bowel disease; level of hsCRP greater than 5 mg/dL; white blood cell count greater than 10,000/μL; rheumatic factor titer of more than 1:80; or the use of any medication for more than one week within one year. After applying these exclusion criteria, we enrolled 6,800 middle-aged Korean men as final subjects.

2. Data Collection

Each subject was asked to fill out a self-report questionnaire and participate in an interview with a physician who collected a history including medical problems, medications, and life habits such as smoking status and alcohol consumption. Smoking status was recorded as current smoker, ex-smoker, or non-smoker. Alcohol consumption was recorded as frequent (more than one time per week) or infrequent (less than one time per week). A nurse measured the body mass index [BMI, weight (kg)/height $(m)^2$] and blood pressure (BP) of each subject. Laboratory tests, which were performed after subjects had fasted for at least 10 hours, included serum hsCRP, sTB, fasting plasma glucose (FPG), total cholesterol (TC), HDL-C, albumin, AST, and ALT. A physician determined whether each subject had hypertension (HT) or DM by medical history. According to the American Heart Association and Centers for Disease Prevention, a person who has a level of hsCRP above 1.0 mg/L is at more than average risk of CVD and a person with an hsCRP level below 1.0 mg/L is at lower risk of CVD.[10] Therefore, we divided patients into two groups according to whether their hsCRP was above or below 1.0 mg/L.

3. Statistical Analyses

We classified all of the subjects into two groups according to their hsCRP level (above or below 1.0 mg/L) and compared each risk factor for CVD between the two groups. In addition, all of the subjects were classified into quartiles (25th, 50th, 75th percentile) according to levels of sTB and analyzed for associations between sTB level and risk factors for CVD. Clinical factors were expressed as mean ± standard deviation for continuous variables and as numbers and percentages for categorical variables. Student's t-test or ANOVA and chi-square tests were used to analyze continuous and categorical variables, respectively.

To estimate the odds ratio (OR) and 95% confidence interval

(CI) of increased hsCRP according to sTB levels, we used multivariate logistic regression models to adjust for other factors. The group that had the lowest level of sTB was used as a reference group. We used three multivariate logistic regression models according to the clinical factors included in the analysis. The first model included only age (greater or less than 45 years old). The second model included smoking status and alcohol consumption as well as age. In the third model, the following factors were added to the second model: serum ALT (greater or less than 40 mg/dL), FPG (below 100 mg/dL, 100 mg/dL to 125 mg/dL, and above 126 mg/dL), systolic BP (below 120 mm Hg, 120 mm Hg to 139 mm Hg, and above 140 mm Hg), and serum TC/HDL-C ratio (25th, 50th, 75th percentile). All analyses were performed using SPSS ver. 16.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at P-values and confidence intervals of < 0.05 and 95%, respectively.

RESULTS

Table 1 shows the baseline characteristics of the 6,800 study subjects. Subjects were classified into two groups: the low-risk group (n = 5,100; hsCRP < 1.0 mg/L) and the average to high-risk group (n = 1,789; hsCRP > 1.0 mg/L) for CVD. Compared to the average to high-risk group, the low-risk group had lower body mass index (BMI); lower prevalence of current smokers and patients with DM and HT; and lower levels of FPG, systolic BP, ALT, and TC/HDL-C ratio (all P < 0.001). Additionally, the low-risk group had a lower level of sTB than the average to high-risk group (P = 0.03).

Table 2 shows the baseline characteristics of the four sTB groups (quartiles), which were analyzed using ANOVA and chi-square tests. The mean age of the group with the lowest sTB (sTB < 13.58 μmol/L) was significantly lower than the highest sTB group (sTB > 20.70 μmol/L) (44.31 ± 3.95 years vs. 44.09 ± 3.74 years, P < 0.001). BMI, prevalence of current smokers, and the TC/HDL-C ratio significantly decreased with increasing levels of sTB (P < 0.012 and P = 0.01, respectively). Levels of hsCRP also significantly decreased with increasing levels of sTB (P < 0.001). However, the frequency of alcohol consumption, percentage of patients who had DM or HT, levels of FPG, systolic BP, and ALT were not significantly different among the four groups.

Table 1. Mean and prevalence (%) of baseline variables according to hsCRP level.

	hsCRP (mg/L) (n = 6,800)		
	Low risk (<1.0) (n = 5,011)	Average to high risk (≥1.0) (n = 1,789)	P-value*
Age (y)	44.13 (3.78)	43.99 (3.61)	0.19
BMI (kg/m²)	24.05 (2.43)	25.23 (2.64)	<0.001
Smoking status			<0.001
Non-smoker	1,593 (31.8)	456 (25.5)	
Ex-smoker	1,395 (27.8)	499 (27.9)	
Current smoker	2,023 (40.4)	834 (46.6)	
Alcohol intake			0.25
Frequent drinker	2,250 (44.9)	775 (43.3)	
Infrequent drinker	2,761 (55.1)	1,014 (56.7)	
Diabetes mellitus	100 (2.0)	79 (4.4)	<0.001
Hypertension	618 (12.3)	298 (16.7)	<0.001
FPG (mg/dL)	96.70 (13.0)	99.53 (18.59)	<0.001
SBP (mm Hg)	114.69 (14.10)	116.82 (14.76)	<0.001
ALT (mg/dL)	27.26 (11.60)	31.51 (13.84)	<0.001
Chol/HDL ratio	3.91 (0.87)	4.22 (0.89)	<0.001
Total bilirubin (μmol/L)	17.82 (5.29)	16.78 (4.99)	0.03

Values are presented as mean (SD) or number (%).
BMI: body mass index calculated as weight in kilograms divided by height in meters squared, FPG: fasting plasma glucose, SBP: systolic blood pressure, ALT: alanine aminotransferase, Chol/HDL ratio: total cholesterol/ high density lipoprotein-cholesterol ratio.
*P-value from a t-test for continuous outcomes and χ^2 test for binary outcomes comparing a difference between the 2 study groups.

We performed a multivariate logistic regression analysis to estimate ORs and 95% CIs of increased hsCRP according to quartiles of sTB levels and used three logistic regression models to adjust for various factors (Table 3). In model I, which adjusted only for age, when compared to the lowest quartile of sTB, the ORs (95% CI) for hsCRP in the 2nd, 3rd, and 4th sTB quartiles were 0.82 (0.70 to 0.95), 0.73 (0.63 to 0.85), and 0.61 (0.52 to 0.71), respectively, and these were statistically significant (P for trend < 0.001). In both model II (adjusted for age, smoking status, and alcohol consumption) and model III (adjusted for BMI, ALT, FPG, systolic BP, and TC/HDL-C ratio as well as the factors in

Table 2. Mean and prevalence (%) of baseline variables according to quartiles of total bilirubin (μmol/L).

	1st quartile ≤13.85 (n = 1,668)	2nd quartile 13.86−16.76 (n = 1,678)	3rd quartile 16.77−20.69 (n = 1,750)	4th quartile ≥20.70 (n = 1,704)	P-value*
Age[†] (y)	44.31 (3.95)	44.24 (3.76)	44.04 (3.50)	44.09 (3.74)	<0.001
BMI[‡] (kg/m^2)	24.51 (2.54)	24.32 (2.50)	24.40 (2.55)	24.23 (2.54)	0.01
Smoking status[§]					<0.001
Non-smoker	414 (24.8)	463 (27.6)	579 (33.1)	576 (33.8)	
Ex-smoker	400 (24.0)	472 (28.1)	523 (29.9)	498 (29.2)	
Current smoker	854 (51.2)	743 (44.3)	648 (37.0)	630 (37.0)	
Alcohol intake					0.67
Frequent drinker	887 (53.2)	972 (57.9)	989 (56.5)	929 (54.5)	
Infrequent drinker	781 (46.8)	706 (42.1)	761 (43.5)	775 (45.5)	
Diabetes mellitus	38 (2.3)	44 (2.6)	51 (2.9)	46 (2.7)	0.45
Hypertension	212 (12.7)	221 (13.2)	236 (13.5)	245 (14.4)	0.14
FPG (mg/dL)	97.21 (12.64)	97.48 (14.63)	97.25 (14.80)	97.45 (14.73)	0.59
SBP (mm Hg)	114.73 (13.99)	115.38 (14.20)	115.04 (14.60)	115.85 (14.38)	0.13
ALT (mg/dL)	28.86 (12.48)	28.41 (12.21)	28.17 (12.31)	28.08 (12.50)	0.26
Chol/HDL ratio[§]	4.04 (0.87)	4.01 (0.89)	3.97 (0.88)	3.94 (0.89)	0.01
hsCRP[‖] (mg/L)	0.92 (0.91)	0.83 (0.82)	0.76 (0.75)	0.73 (0.74)	<0.001

Values are presented as mean (SD) or number (%).
BMI: body mass index calculated as weight in kilograms divided by height in meters squared, FPG: fasting plasma glucose, SBP: systolic blood pressure, ALT: alanine aminotransferase, Chol/HDL ratio: total cholesterol/high density lipoprotein-cholesterol ratio.
*P-value from an ANOVA test for continuous outcomes and χ^2 test for binary outcomes comparing differences among 4 study groups. Turkey HSD used for Post Hoc analysis. [†]Statistically different between 1st quartile, 2nd quartile vs. 3rd quartile, 4th quartile. [‡]Statistically different between 1st quartile vs. 4th quartile. [§]Statistically different between 1st quartile vs. 2nd quartile vs. 3rd quartile, 4th quartile. [‖]Statistically different between 1st quartile vs. 2nd quartile, 3rd quartile, 4th quartile and 2nd quartile vs. 4th quartile.

Table 3. Adjusted odds ratios (aOR) and 95% confidence intervals (CI) of increased hsCRP by quartiles of total bilirubin. high density lipoprotein.

Total bilirubin (μmol/L)	aOR and 95% CI of increased hsCRP		
	Model I	Model II	Model III
≤13.85	1	1	1
13.86−16.76	0.82 (0.70−0.95)	0.82 (0.71−0.96)	0.83 (0.71−0.97)
16.77−20.69	0.73 (0.63−0.85)	0.75 (0.65−0.88)	0.76 (0.65−0.89)
≥20.70	0.61 (0.52−0.71)	0.63 (0.54−0.74)	0.64 (0.55−0.75)
P-value for trend	<0.001	<0.001	<0.001

Values are presented as adjusted odds ratio (95% CI).
Increased high sensitivity C-reactive protein (hsCRP): categorization of hsCRP as < 1.0 mg/L and ≥ 1.0 mg/L.
Model I: age-adjusted odds ratio, Model II: adjusted for age, smoking status, drinking frequency, Model III: body mass index, alanine aminotransferase, fasting plasma glucose, systolic blood pressure, total cholesterol/high density lipoprotein-cholesterol ratio are added to Model II.

model II), when compared to the lowest quartile of serum total bilirubin, the ORs (95% CI) for hsCRP in the 2nd, 3rd, and 4th sTB quartiles significantly decreased (all P for trend < 0.001).

DISCUSSION

In this study, hsCRP was inversely associated with sTB. In addition, hsCRP had significant positive associations with BMI; smoking status; medical history of DM and HT; and levels of systolic BP, FPG, ALT, and the TC/HDL-C ratio, but was not associated with age or alcohol consumption.

Serum bilirubin is known to have an antioxidant effect and an inverse relationship with the risk for CVD.[11-14] Bilirubin is a final metabolite of heme, but the function of bilirubin is not clear. Vitek et al.[15] reported that patients with Gilbert syndrome, who have a slightly elevated level of serum direct bilirubin, had a lower risk of CVD compared to healthy subjects. According to the NHANES study (1999−2004),[13] a 1.71 micromol/L (0.1 mg/dL) increment in bilirubin level was associated with a 9% reduction in the odds of stroke (OR, 0.91; 95% CI, 0.86 to 0.96) among the civilian population and with a 10% reduction in the odds of stroke (OR, 0.90; 95% CI, 0.80 to 1.00) among patients with a history of stroke. Nobotny and Vitek[14] reported that serum bilirubin in men had an inverse relationship with the severity of AS in a meta-analysis of 11 studies. We found that after adjusting for other risk factors of CVD, sTB was inversely associated with hsCRP, which is a predictive indicator for CVD, and this finding is consistent with the results of previous studies. Although this was a cross-sectional study and our participants were middle-aged Korean men who visited a health promotion center, we believe the number of study participants was sufficient to evaluate the relationship between sTB and hsCRP.

There have been several studies about the relationship between hsCRP and risk factors for CVD. Nakanishi et al.[16] reported that hsCRP had a significant relationship with age, smoking status, serum fasting glucose, BMI, BP, HDL-C, and triglycerides. In a previous Korean study,[17] hsCRP had a positive relationship with serum fasting glucose, age, and BP. However, hsCRP was not significantly associated with age in our study. This result is possibly due to the narrow age distribution of our study sample (40 to 59 years old).

Mild to moderate alcohol consumption reduces hsCRP. Several studies[18-20] reported that men who drank one to four drinks of alcoholic beverages per week had the lowest levels of hsCRP, and the relationship between alcohol consumption and hsCRP was U shaped. However, this study did not detect a significant association between alcohol consumption and hsCRP. We did not collect specific information about the amount of alcohol consumed by study subjects because of our inability to validate the information. Serum bilirubin is affected by aging, smoking status, and fasting state, among other factors, and has an inverse relationship with risk factors for CVD, such as aging, obesity, smoking, HT, and dyslipidemia.[7,21,22] We found that sTB had an inverse association with age, BMI, smoking status, and the TC/HCL-C ratio. However, in this study, sTB did not demonstrate a significant relationship with HT or systolic BP. A previous Korean study[23] reported that serum bilirubin had a significant relationship with HT in women but not in men. Therefore, we suggest that future studies about the association between sTB and BP or HT in the general population should include women and older people.

We transformed the levels of sTB measured in this study to SI units (μmol/L). The SI unit for sTB levels contains more information and is better at detecting changes of serum bilirubin within physiologic levels.[14]

However, further studies about the relationships between other forms of serum bilirubin and risk factors for CVD are necessary. It is not clear how serum bilirubin lowers the risk of CVD. One potential mechanism is the antioxidant and anti-inflammatory effects of bilirubin through inhibition of oxidation of low-density lipoprotein cholesterol (LDL-C) and oxygen radicals, which may consequently prevent AS. Another possible mechanism is the association of high-density serum bilirubin with lower levels of inflammation.[24-26]

One of the limitations of this study was that we included only the total level of serum bilirubin in the analysis to investigate the association with hsCRP and risk factors for CVD; serum direct and indirect bilirubin were not included in the analysis. Because all forms of bilirubin (free or albumin-bound) inhibit hyperoxidation of LDL-C,[27] this limitation might not have affected our results. The other limitation was the age distribution of the study sample. The study subjects were middle-aged Korean men (40−59 years old); therefore, the results may not be necessarily generalized to

other populations in or outside of Korea. The third limitation was that this study was a cross-sectional study, which makes it difficult to detect a causal relationship between sTB and hsCRP and risk factors for CVD.

In conclusion, this study showed that sTB was inversely associated with hsCRP and risk factors for CVD. Despite some limitations, this study is meaningful because it is a large study of subjects who visited a health promotion center. We anticipate that the results of this study will be used in future studies.

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