Inverse relationship between serum total bilirubin levels and severity of disease in patients with stable coronary artery disease

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Objective **Many studies have shown that bilirubin may protect against atherosclerosis. In the present study, we assess the association between serum total bilirubin levels and the severity of coronary artery disease (CAD) assessed by angiography and the Syntax score.**

Methods **Patients from our center, who visited the center for a coronary angiography, from January 2008 to January 2011, were eligible for this analysis. Serum bilirubin levels and other blood parameters in at least 12-h fasting states were determined. The patients were divided into tertiles according to their Syntax score.**

Results **A total of 299 patients were registered for the study. The total bilirubin levels in the low Syntax score group were significantly higher than those of the other groups. After multiple logistic regression analysis, serum bilirubin levels (odds ratio = 0.155, 95% confidence interval, 0.039–0.62, *P* = 0.008) were identified as independent correlates of a high Syntax score.**

Conclusion **Serum bilirubin levels were independently and inversely associated with the severity of disease in patients with stable CAD. Serum total bilirubin level may be useful as a marker of the severity of CAD.** ***Coron Artery Dis*** **24:29–32 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Reactive oxygen species play an important role in body events such as inflammation, apoptosis, and atherosclerosis [1]. Therefore, antioxidant defense mechanisms are increasingly being investigated. Bilirubin is a final product of heme metabolism. In addition, the antioxidant effects of bilirubin are also available [2,3]. Many studies have shown that bilirubin may protect against atherosclerosis in this way [4–6]. In addition, Gilbert's syndrome is caused by a mutation that increases the level of bilirubin. The mutation carriers show a strong association with a lower risk of cardiovascular disease [7].

The Syntax score is based on a visual assessment of coronary lesions by coronary angiograms and is used to evaluate the severity of coronary artery disease (CAD). It also provides information about prognosis and appropriate revascularization [8]. Therefore, the Syntax score is important in the management of the complexity of CAD.

In the present study, we assess the association between serum total bilirubin levels and the severity of CAD assessed by angiography and the Syntax score.

Methods

Patients

Patients from our center, who visited the center for a coronary angiography, from January 2008 to January 2011, were eligible for this analysis. Patients with known hemodynamic instability, acute coronary syndrome, autoimmune disease, neoplastic disease, chronic kidney disease, chronic hepatic disease, previous coronary artery bypass surgery or percutaneous coronary intervention, chronic or current infections, presence of the thalassemia trait, and any systemic disease that could cause high bilirubin concentrations were excluded. These studies were approved by the ethics committee at our center. A clinical history of risk factors – such as age, sex, diabetes mellitus, hypertension, and smoking – was recorded.

Measurements

Blood glucose, hemoglobin, serum creatinine, high-density lipoprotein and low-density lipoprotein (LDL) cholesterol, and transaminase enzyme levels in at least 12-h fasting states were determined. Serum bilirubin concentrations were determined by the enzymatic colorimetric method using a clinical chemistry autoanalyzer.

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Two experienced physicians blinded to the study analyzed angiograms using a quantitative coronary angiographic system. Each coronary lesion with a diameter stenosis of at least 50%, in vessels of at least 1.5 mm, must be scored. The online latest updated version was used for the calculation of the Syntax scores (*http://www.Syntaxscore.com*). The patients were divided into tertiles according to their Syntax score.

Statistical analysis

All statistical analyses were carried out using the SPSS program (version 15.0; SPSS Inc., Chicago, Illinois, USA). Continuous variables are expressed as mean ± SD. Categorical variables are expressed as percentages. To compare parametric continuous variables, Student's *t*-test or analysis of variance was used; to compare nonparametric continuous variables, the Mann–Whitney *U*-test or the Kruskal–Wallis test was used. To compare categorical variables, the χ^2-test was used. Univariate and multivariate logistic regression analysis was used to evaluate the associations between the Syntax score and bilirubin level while adjusting for potential confounders.

Results

Patients who fulfilled all the inclusion and exclusion criteria (299 patients) were registered for the study. Table 1 presents the baseline clinical characteristics across the Syntax score tertiles. Compared with the other groups, group 1 was younger and had significantly lower LDL levels. However, the total bilirubin levels in this group were significantly higher than those of the other groups (Fig. 1).

Patients with high (> 17) and moderate-to-low Syntax scores (< 17) were compared in the univariate analysis. The group with a high Syntax score more frequently was older and had significantly higher fasting blood glucose, LDL, and lower total bilirubin values (Table 2).

Table 1 Baseline characteristics of the patients

	Group 1 Syntax <9	Group 2 Syntax 11–17	Group 3 Syntax >17	*P*
N	99	98	102	
Age	57±12	63±12	64±11	<0.001[a,b]
Male (%)	53.3	55.1	52	0.906
Hypertension (%)	30.3	32.3	28	0.807
DM (%)	22.2	28.6	30.4	0.395
Current smoking	20.8	30.2	29.4	0.264
Hemoglobin (mg/dl)	13.9±1.5	14.1±1.5	14±1.2	0.917
Serum creatinine (mg/dl)	0.92±0.2	0.93±0.3	0.96±0.2	0.489
ALT (U/l)	30±13	26±11	29±11	0.09
Fasting blood glucose	101±34	108±44	114±36	0.041[a]
LDL (mg/dl)	114±27	129±31	132±32	<0.001[a,b]
HDL (mg/dl)	43±10	40±7	40±9	0.07
Total bilirubin (mg/dl)	0.71±0.18	0.67±0.19	0.63±0.18	0.02[a]

ALT, alanine transaminase; DM, diabetes mellitus; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
[a]Groups 3 and 1.
[b]Groups 2 and 1.

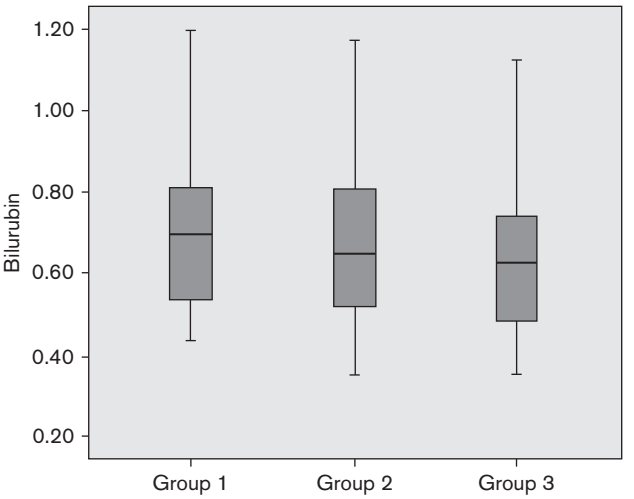
After the multiple logistic regression analysis, serum bilirubin levels (odds ratio = 0.155, 95% confidence interval, 0.039–0.62, $P = 0.008$) were identified as independent correlates of a high Syntax score (Table 3).

Discussion

To our knowledge, this is the first study to examine the relationship between total bilirubin levels and the severity of disease in patients with stable CAD. A higher baseline of serum bilirubin levels was independently associated with the coronary complexity of CAD as assessed by the Syntax score.

Coronary angiography is the best method to assess the severity of CAD. The Syntax score is calculated by coronary angiography and provides information on lesion severity and complexity [8]. Known factors that lead to

Fig. 1



Total bilirubin levels between groups.

Table 2 Univariate analysis for risk factors

	β	Significance	95% CI
Age	1.034	0.002	1.013–1.057
Fasting blood glucose	1.007	0.041	1.000–1.013
LDL (mg/dl)	1.012	0.002	1.004–1.010
Total bilirubin (mg/dl)	0.204	0.019	0.054–0.769

CI, confidence interval; LDL, low-density lipoprotein.

Table 3 Multivariate regression analysis

	β	Significance	95% CI
Age	1.035	0.003	1.012–1.058
Fasting blood glucose	1.007	0.041	1.000–1.013
LDL (mg/dl)	1.014	0.001	1.006–1.022
Total bilirubin (mg/dl)	0.155	0.008	0.039–0.619

CI, confidence interval; LDL, low-density lipoprotein.

the severity of CAD may be useful in the treatment of diseases. Many factors and biomarkers such as sex [9], fasting blood glucose [10], chronic kidney disease [11], monocyte subtypes [12], and red cell distribution width [13] have been associated with the severity of CAD. Advanced age is a classic risk factor for CAD. Zhang *et al*. [14] found that the incidence of double-vessel and multivessel diseases was more frequent in elderly patients compared with young patients. Similarly, our study and another study showed that advanced age increases the severity of CAD [15]. In addition, we found that the LDL levels and the severity of coronary involvement are associated. Other studies support our conclusion [16,17]. Moon *et al*. [18] found that lipoprotein(a) levels and small dense LDL fractions are related to the severity of CAD. Finally, in our study, we found an inverse relationship between serum total bilirubin level and the severity of CAD.

Bilirubin is the final metabolite of heme catabolism, and has been found to be an effective antioxidant [19]; it has been found to be a marker of cardiovascular risk. Schwertner *et al*. [20] found that serum bilirubin is an inverse and independent risk factor for CAD. A meta-analysis also showed a similar result [6]. Troughton *et al*. [21] found in another meta-analysis that higher total bilirubin was associated with a decreased risk of chronic hepatic disease in 10 593 middle-aged men. Ghem *et al*. [22] have shown that reduced serum bilirubin levels were shown to be associated with a higher prevalence of CAD. We found an inverse correlation between serum bilirubin levels and the Syntax score in our study. Factors (age, fasting blood glucose, LDL) that affect the severity of CAD were different between groups. However, after the multiple logistic regression analysis, serum bilirubin levels were identified as independent correlates of the severity of CAD. Our results are in agreement with those of a previous study [23]. However, that study evaluated patients with ST-segment elevation myocardial infarction and, unlike our study, included patients with stable coronary artery.

The status of bilirubin as a protective agent against atherosclerosis can be attributed to different mechanisms. Neuzil *et al*. [24] found that bilirubin inhibits oxidation of LDL lipids initiated within the lipoprotein core. Heme oxygenase (HO) is an important enzyme of bilirubin production. Increased activity of this enzyme may account for the antiatherogenic through increased elimination of heme and reducing tissue iron [25]. Increased tissue iron because of decreased HO activity can trigger inflammation. This may explain the association of low serum bilirubin levels in the atherosclerotic process. In addition, another study has reported a beneficial effect on the endothelial function of bilirubin [26].

The present investigation has several limitations. First, a small number of patients were studied. Second, information on detailed medications (i.e. lipid-affecting drugs) was unavailable.

Conclusion

Serum bilirubin levels were independently and inversely associated with the severity of disease in patients with stable CAD. This protective effect of bilirubin can be used for new treatment options. In the future, HO enzyme activity or bilirubin level can be selected as a therapeutic target. In addition, serum total bilirubin level may be useful as a marker of the severity of CAD.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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