The relationship between serum bilirubin concentration and coronary artery ectasia

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Abstract

Introduction: The pathophysiology of coronary artery ectasia (CAE) has not been clearly identified, although multiple abnormalities including arteritis, endothelial dysfunction, and atherothrombosis have been reported. Several studies have demonstrated that higher serum bilirubin inhibits the inflammation and proliferation of vascular smooth muscle cells; also there is a relationship between serum bilirubin and cardiovascular disease. However, the relationship between bilirubin and CAE is still unknown.

Aim: We compared serum bilirubin concentration between CAE patients and controls.

Material and methods: This study included 50 CAE patients (20 male, mean age: 60.26 ±10.6 years) and 30 control persons (10 male, mean age: 57.86 ±11.6 years). These participants underwent concurrent routine biochemical tests and leukocyte count, hemoglobin, hematocrit and platelet count in whole blood. These parameters were compared between groups.

Results: No statistically significant difference was found between the two groups in terms of basic characteristics. Total, direct and indirect serum bilirubin levels were significantly lower among persons with CAE patients than controls (0.37 ±0.4 vs. 0.71 ±0.6 and 0.13 ±0.1 vs. 0.27 ±0.2 and 0.24 ±0.2 vs. 0.43 ±0.4 mg/dl; all $p < 0.001$, respectively).

Conclusions: Our study revealed a relationship between serum bilirubin and CAE.

Key words: coronary artery ectasia, bilirubin, inflammation, endothelial dysfunction.

Introduction

Coronary artery ectasia (CAE) has been characterized as a localized or diffuse non-obstructive lesion of the epicardial coronary arteries with a luminal dilation exceeding 1.5-fold the normal adjacent segment or vessel diameter [1]. The prevalence of CAE varies from 1.2% to 4.7% among patients undergoing coronary angiography [2–5].

The etiopathogenesis of this coronary enlargement is completely unknown. Although the exact mechanisms leading to CAE are not clear yet, atherothrombosis, endothelial dysfunction, inflammation and vasculitis have been suggested as possible responsible factors. Coronary artery ectasia has also been reported in association with various conditions such as congenital coronary anomalies, connective tissue diseases, and vasculitis [6, 7].

Bilirubin is an important and potent endogen antioxidant and anti-inflammatory agent. Several previously published studies have demonstrated the relationship between serum bilirubin levels and cardiovascular disease such as coronary artery disease and atrial fibrillation [8–11].

As far as we know, no study has yet been performed about the association of serum bilirubin concentration with CAE.

Aim

In our study, we compared bilirubin concentration between CAE patients and a control group.

Material and methods

The study group included 50 patients (20 male, mean age 60.26 ±10.6 years) with isolated CAE who had irregularities with ectatic coronaries without any stenotic lesions under visual assessment. The control group consisted of 30 age- and gender-matched subjects (10 male, mean age 57.86 ±11.6 years) who proved to have normal coronary angiograms. The indication for coronary angiography was either the presence of typical angina or pos-

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itive or equivocal results of noninvasive screening tests for myocardial ischemia in both groups.

Physical examination, medical history of patients, blood biochemistry and transthoracic echocardiographic examination were evaluated in both groups to exclude systemic diseases. Patients with obstructive coronary artery disease (who had coronary stenotic lesions of > 20%), chronic renal failure, chronic liver disorders, chronic lung disease, moderate or severe valvular disease, hypertension, diabetes mellitus, congenital heart disease, left ventricular systolic dysfunction on echocardiography (EF < 50%), anemia, pregnancy, obstructive sleep apnea, hematological disorders, known malignancy, thyroid dysfunction, hypercholesterolemia, electrolyte imbalance, and drug history including anti-gout agents, anti-inflammatory agents (steroid or nonsteroid), antiaggregants or anticoagulant agents were excluded from the study. Also patients with a recent history of an acute infection, high body temperature > 38°C or an inflammatory disease were excluded from the study.

The patients having a systolic blood pressure ≥ 140 mm Hg and/or a diastolic blood pressure ≥ 90 mm Hg and those taking antihypertensive drugs were accepted to be hypertensive. Diabetes was defined as a fasting blood glucose level > 126 mg/dl or current use of a diet or medication to lower blood glucose. Current cigarette smoking was defined as use of > 10 cigarettes/day at the time of diagnosis.

Coronary angiography

Coronary angiograms were performed with a femoral approach using the Judkins technique without the use of nitroglycerin, adenosine, or a calcium channel blocker. All patients in the study population underwent elective coronary artery angiography using Siemens Axiom Artis DFC (Siemens Medical Solutions, Erlangen, Germany) following appropriate patient preparation. Coronary angiograms were judged with regard to smooth appearance, luminal wall irregularities, epicardial local or diffuse caliber reduction, and stenosis. Coronary artery ectasia was defined as dilation of the coronary artery > 1.5-fold the diameter of the adjacent normal coronary vessels according to Falsetti and Carroll [12].

Laboratory tests

Biochemical parameters were analyzed spectrophotometrically on an Architect C16000 (Abbott, USA) autoanalyzer using an enzymatic-colorimetric assay. Also C-reactive protein (CRP) was recorded in both groups.

For whole blood count (hematocrit, hemoglobin, leukocytes, and platelets), the blood samples were collected in tubes with EDTA and analyzed on a CELL-DYN 3700 (Abbott, USA) device using the impedance and optic scatter method.

Statistical analysis

The statistical program SPSS 16.0 (SPSS Inc., Chicago, IL, USA) was used for statistical study. All values are given as mean ± standard deviation. Mean values of continuous variables were compared between groups using the Student *t* test or Mann-Whitney *U* test, according to whether they were normally distributed or not, as tested by the Kolmogorov-Smirnov test. A *p* value of less than 0.05 was considered significant.

Results

Evaluating basic clinical and demographic characteristics, there was no statistically significant difference between the two groups in terms of age, gender distribution, body mass index, and smoking status (Table I).

Serum total bilirubin, direct bilirubin and indirect bilirubin were lower in patients with CAE than controls (0.37 ±0.4 mg/dl vs. 0.71 ±0.6 mg/dl and 0.13 ±0.1 mg/dl vs. 0.27 ±0.2 mg/dl and 0.24 ±0.2 mg/dl vs. 0.43 ±0.4 mg/dl;

Table I. Comparison of basic clinical, biochemical and whole blood count features of patients and controls

Parameter	Patients (*n* = 50)	Controls (*n* = 30)	Value of *p*
Age [years]	60.26 ±10.6	57.86 ±11.6	NS
Gender, male	20 (40)	10 (33)	NS
Body mass index [kg/m²]	29.8 ±5.4	28.5 ±4.6	NS
Smoking	9 (18)	6 (20)	NS
Fasting glucose [mg/dl]	95.7 ±9	97.6 ±8.5	NS
Creatinine [mg/dl]	0.75 ±0.1	0.72 ±0.2	NS
Total cholesterol [mg/dl]	211 ±45	181 ±36	NS
Triglyceride [mg/dl]	162.5 ±65	151.9 ±41	NS
TSH [μIU/ml]	1.7 ±0.6	1.6 ±0.4	NS
CRP [mg/dl]	3.33 ±2.09	2.18 ±1.5	NS
Na [mmol/l]	140.1 ±11	138 ±9.9	NS
K [mmol/l]	4.4 ±0.9	4.1 ±0.4	NS
Total bilirubin	0.37 ±0.4	0.71 ±0.6	< 0.001
Direct bilirubin	0.13 ±0.1	0.27 ±0.2	< 0.001
Indirect bilirubin	0.24 ±0.2	0.43 ±0.4	< 0.001
Leukocytes [10³/μl]	9.1 ±6.5	8.4 ±4.4	NS
Hemoglobin [g/dl]	13.8 ±1.95	13.49 ±1.15	NS
Hematocrit (%)	40.6 ±3.4	40.7 ±3.49	NS
Platelet [10³/μl]	232 ±70	234 ±63	NS

Results was presented as mean ± SD or n (%), NS – non-significant, TSH – thyroid-stimulating hormone, CRP – C-reactive protein.

Table II. Logistic regression analyses

Parameter	HR (95% CI)	Value of *p*
Total bilirubin	0.86 (0.76–0.92)	< 0.001
Direct bilirubin	0.82 (0.74–0.90)	< 0.001
Indirect bilirubin	0.88 (0.78–0.97)	< 0.001

all *p* < 0.001, respectively). C-reactive protein levels were similar in both groups. Other biochemical parameters were not statistically significantly different between the 2 groups. Also there was no statistically significant difference between the two groups with regard to leukocyte count, platelet count, hemoglobin and hematocrit level (Table I).

As a result of the forward stepwise logistic regression analysis, it was found that serum total bilirubin, direct bilirubin and indirect bilirubin levels were independent predictors of CAE (Table II).

Discussion

In the present study, we found that total serum bilirubin levels were significantly lower in the CAE patient group compared to controls. To the best of our knowledge, our study is the first to focus on the relationship between bilirubin and CAE.

The pathophysiology of CAE has not been clearly identified yet, although multiple abnormalities including inflammation, endothelial dysfunction, oxidative stress, vasculitis, and atherothrombosis have been reported [5]. Coronary artery ectasia is associated with connective tissue disorders such as scleroderma, Ehlers-Danlos syndrome, and Kawasaki disease [13].

Previous studies have demonstrated that CRP, IL-6 and neutrophil/lymphocyte ratio (NLR) were higher in patients with CAE than in control participants. The increased levels of CRP and NLR may suggest that these markers may be used in clinical practice for assessment of the inflammatory status of CAE [14–16]. We found that CRP levels were higher in patients than controls, but the difference was statistically insignificant.

Recently, low serum bilirubin levels have been proposed as a useful biomarker to predict cardiovascular risk [17]. Recent evidence suggests that bilirubin acts as a potent physiologic antioxidant and anti-inflammatory agent. Recently studies have shown that elevated serum bilirubin concentrations provide important protection against atherosclerotic diseases [18, 19].

Several authors have suggested that bilirubin plays a potential role in inhibition of lipid oxidation [20, 21].

Previous studies have shown that plasma bilirubin concentration is correlated inversely with several risk factors for coronary artery disease such as smoking, diabetes, and obesity, and correlated directly with HDL cholesterol [20, 22].

An inverse correlation between the presence of coronary artery disease, peripheral arterial disease, carotid intima-media thickness and bilirubin has been reported in several studies. Subnormal levels of plasma bilirubin are associated with premature coronary artery disease and cardiovascular morbidity [23, 24].

In a previous study, the 3-year incidence of coronary artery disease was significantly lower in patients with Gilbert syndrome [25].

Elevated concentrations of plasma bilirubin were suggested to be able to prevent atherogenesis. Strong ability to scavenge peroxyl radicals and the antioxidant capacity of bilirubin functioning even in a slightly increased concentration in the circulation have led to the concept that it may have a physiological function to protect against disease processes involving oxygen and peroxyl radicals [26, 27].

In a previous study, Gullu *et al.* found that elevated concentrations of bilirubin may serve as a protective factor in the development of coronary flow reserve impairment, coronary microvascular dysfunction, and possibly in the development of coronary atherosclerosis. They concluded that bilirubin shows the beneficial effects independent of the known coronary risk factors [28].

Induced hyperbilirubinemia was associated with a significant improvement of endothelial function in type 2 DM [29]. Also bilirubin inhibits vascular cell adhesion molecule 1 (VCAM-1) and blocks vascular smooth muscular cell proliferation [30].

As far as we know, there is no study available in the literature about the association between CAE and serum bilirubin levels. Our study is important for this reason, and we ascertained if there is an association between bilirubin and CAE.

When the 2 groups were compared in our study, serum bilirubin levels of patients having CAE were significantly lower than those of controls.

Our results may contribute to knowledge of the etiopathogenesis of CAE and pathophysiological mechanisms of increased prevalence of cardiovascular morbidity and mortality risk in these patients. The decreased concentration of bilirubin might be explained by vascular destruction, endothelial dysfunction and thrombosis in CAE patients.

Conclusions

It was found in our study that there might be an association between CAE and serum bilirubin. The measurement of bilirubin also may be used to indicate increased risk of CAE-related adverse cardiovascular events. The most important restriction of our study is the limited number of patients, and there was no obstructive coronary artery disease group. Another limitation was that angiographic diagnosis of normal coronary arteries was based on axial contrast angiograms of the vessel lumen,

which underestimates the presence of atherosclerotic plaques. Further studies are required to determine the relation between bilirubin and CAE. We have shown for the first time that patients with CAE have lower bilirubin levels compared to controls.

Conflict of interest

The authors declare no conflict of interest.

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