IJC Metabolic & Endocrine 5 (2014) 24–27

Contents lists available at ScienceDirect

IJC Metabolic & Endocrine

journal homepage: http://www.journals.elsevier.com/ijc-metabolic-and-endocrine

Impact of serum bilirubin levels on carotid atherosclerosis in patients with coronary artery disease

Yosuke Tatami [a,1], Susumu Suzuki [a,b,*,1], Hideki Ishii [a,1], Yohei Shibata [a,1], Naohiro Osugi [a,1], Tomoyuki Ota [a,1], Yoshihiro Kawamura [a,1], Akihito Tanaka [a,1], Kyosuke Takeshita [c,1], Toyoaki Murohara [a,1]

[a] Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan.
[b] Department of CKD Initiatives Internal Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan
[c] Department of Clinical Laboratory, Nagoya University Hospital, Nagoya University Graduate School of Medicine, Nagoya, Japan

ARTICLE INFO

Article history:
Received 2 May 2014
Received in revised form 11 August 2014
Accepted 17 August 2014
Available online 27 August 2014

Keywords:
Bilirubin
Carotid atherosclerosis
Coronary artery disease

ABSTRACT

Background/objectives: Bilirubin protects against oxidative stress-mediated diseases, especially atherosclerotic diseases. On the other hand, subjects with carotid atherosclerosis have a high incidence of adverse cardiovascular events. The aim of this study was to evaluate the possible relationship between serum bilirubin levels and carotid atherosclerosis in patients with coronary artery disease (CAD).
Methods: We evaluated a total of 394 patients with chronic CAD, defined as stable angina pectoris or a previous myocardial infarction. They were divided into four groups according to serum bilirubin level. Carotid intima–media thickness and plaque score (PS) in the common carotid artery were measured using an ultrasound system. Severe carotid atherosclerosis was defined as PS > 10.
Results: With increasing quartiles of serum bilirubin levels, the prevalence of severe carotid atherosclerosis significantly decreased (48.2%, 39.6%, 30.3%, and 27.0%, respectively, p for trend = 0.007). After adjusting for other risk factors, low serum bilirubin levels were independently correlated with severe carotid atherosclerosis in CAD patients (odds ratio 0.89, 95% confidence interval, 0.81–0.99, $p = 0.027$).
Conclusion: We demonstrated that low serum bilirubin levels were associated with severe carotid atherosclerosis in CAD patients. Our data suggest that serum bilirubin levels might be an independent, useful, and cost-effective tool for evaluating atherosclerotic status in CAD patients.

1. Introduction

It is commonly accepted that bilirubin, the major product of heme catabolism, has strong antioxidant properties that enable it to scavenge peroxyl radicals and to inhibit oxidation of low-density lipoprotein-derived lipids [1]. Several recent reports have demonstrated that elevated serum bilirubin levels provide important protective effects against oxidative stress-mediated diseases, especially atherosclerotic diseases [2–4].

Increased carotid intima–media thickness (IMT) is a well-established index of subclinical atherosclerosis and a risk factor for subsequent cardiovascular disease (CVD) events [5–7]. It was recently reported that greater carotid atherosclerosis is also associated with future CVD events in high-risk patients [8,9]. Therefore, evaluation of carotid atherosclerosis could be helpful in predicting future CVD events in patients with chronic ischemic heart disease. However, few studies have investigated the relationship between carotid atherosclerosis and serum bilirubin levels in CAD patients. In the present study, we examined the association between serum bilirubin levels and carotid atherosclerosis in CAD patients.

2. Methods

2.1. Study subjects

This observational study included a total of 394 patients who were treated for chronic CAD at Nagoya University Hospital between October 2011 and December 2013. Chronic CAD was defined as stable angina pectoris or a previous myocardial infarction. Patients were divided into four groups according to quartiles of total bilirubin levels. The exclusion criteria were as follows: acute cardiovascular events within 6 months before screening, previous carotid endarterectomy or carotid artery stenting, chronic liver disease, acute heart failure, and hemodialysis. Institutional ethics committee approval was obtained, and all patients

* Corresponding author at: Department of Cardiology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan. Tel.: +81 52 744 2147; fax: +81 52 744 2210.
E-mail address: sususu0531@yahoo.co.jp (S. Suzuki).
[1] All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

http://dx.doi.org/10.1016/j.ijcme.2014.08.006

Table 1
Baseline characteristics.

Variables	Quartiles of serum total bilirubin levels				*p*, Trend
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Male gender	105 (77.8)	79 (82.3)	71 (79.8)	60 (81.1)	0.85
Age (years)	70.7 ± 9.2	69.9 ± 9.7	69.2 ± 9.0	68.0 ± 9.5	0.19
BMI (kg/m^2)	23.5 ± 3.6	24.0 ± 3.9	23.1 ± 4.1	23.6 ± 3.8	0.90
Hypertension	108 (80.0)	74 (77.1)	72 (80.1)	53 (71.6)	0.47
Diabetes	58 (43.0)	37 (38.5)	44 (49.4)	27 (36.5)	0.33
Dyslipidemia	108 (80.0)	79 (82.3)	76 (85.4)	56 (75.7)	0.45
Current smoker	39 (29.5)	21 (23.6)	23 (28.0)	13 (17.6)	0.26
Multi vessel disease	105 (77.8)	69 (71.9)	57 (64.0)	54 (72.9)	0.17
Previous MI	27 (20.0)	23 (24.0)	20 (22.7)	13 (17.6)	0.74
Previous CI	21 (15.6)	12 (12.5)	11 (12.4)	10 (13.5)	0.89
AST (IU/l)	20.5 ± 5.6	21.1 ± 5.1	21.1 ± 6.2	21.2 ± 5.3	0.53
ALT (IU/l)	18.4 ± 7.6	19.1 ± 8.0	19.8 ± 8.9	18.9 ± 8.0	0.62
HDL (mg/dl)	46.9 ± 15.4	49.2 ± 13.5	46.6 ± 14.1	46.9 ± 11.2	0.39
LDL (mg/dl)	98.6 ± 30.7	104.7 ± 35.1	104.3 ± 29.3	103.6 ± 28.4	0.36
Triglycerides (mg/dl)	123 (87–176)	118 (83–163)	116 (90–168)	115 (73–149)	0.73
Fasting glucose (mg/dl)	109 (95–139)	108 (95–146)	109 (96–135)	101 (89–122)	0.12
Hemoglobin A1c (%)	6.2 ± 1.2	6.2 ± 1.1	6.2 ± 1.0	6.0 ± 1.1	0.52
Estimated GFR (ml/min/1.73 m^2)	62.3 ± 22.0	66.5 ± 19.1	69.4 ± 17.9	69.4 ± 16.1	0.01
Proteinuria	33 (25.2)	12 (12.9)	15 (17.2)	9 (12.9)	0.06
C-reactive protein (mg/dl)	0.07 (0.03–0.14)	0.06 (0.03–0.12)	0.06 (0.04–0.11)	0.05 (0.03–0.10)	0.10
ACE-I or ARB	77 (57.0)	57 (59.3)	53 (59.6)	43 (59.0)	0.98
β-Blockers	40 (29.6)	30 (31.2)	30 (34.1)	21 (28.4)	0.86
Statins	84 (62.2)	66 (68.8)	60 (67.4)	49 (66.2)	0.74
Anti-diabetes drugs	57 (42.2)	34 (35.4)	44 (49.4)	24 (32.4)	0.11

Data are presented as mean ± SD, median (interquartile range), or *n* (%).
BMI, body mass index; MI, myocardial infarction; CI, cerebral infarction; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; GFR, glomerular filtration rate; ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotension receptor blocker.

provided written informed consent. Body mass index was calculated as body weight divided by height squared (kg/m^2). After an overnight fast of 12 h, blood samples were obtained from all patients. Serum total bilirubin levels were measured by enzymatic methods using an autoanalyzer. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, and/or current antihypertensive medication use. Diabetes mellitus was defined as the use of any antihyperglycemic medication or a current diagnosis of diabetes or having a fasting plasma glucose concentration >126 mg/dl or a glycosylated hemoglobin concentration ≥6.5% (National Glycohemoglobin Standardization Program). Dyslipidemia was defined as low-density lipoprotein (LDL) cholesterol ≥140 mg/dl, high-density lipoprotein cholesterol <40 mg/dl, triglycerides ≥150 mg/dl, or receiving lipid-lowering therapy. Current smokers were defined as those who declared active smoking at all available examinations. The estimated glomerular filtration rate (eGFR) was calculated according to the new Japanese equation: eGFR (ml/min/1.73 m^2) = 194 × serum creatinine − 1.094 × age − 0.287 × 0.739 (in females) [10]. Proteinuria was defined as a dipstick urinalysis score of 1+ or higher.

2.2. Measurement of carotid atherosclerosis

Ultrasonography of the bilateral common carotid artery, carotid bifurcation, and internal carotid artery was performed using a high-resolution carotid ultrasound system with a 7.5-MHz linear array transducer (Prosound α10; Hitachi ALOKA Medical, Tokyo, Japan). IMT is defined as the distance from the leading edge of the first echogenic line to that of the second. The first line represents the lumen–intima interface, and the second line represents the collagen-containing upper layer of the adventitia. Max IMT is defined as maximal IMT of several sites in the bilateral carotid arteries [11,12]. To assess the severity of carotid atherosclerosis, plaque score (PS) was calculated by summing all plaque thicknesses in eight segments, as proposed by Handa et al. [7,12]. The severity of PS was classified as normal, mild, moderate, or severe if the total PS was <1.1, 1.1–5.0, 5.1–10.0, or >10.0, respectively. All measurements were performed by a trained physician who was blinded to the patients' clinical information. A total of 30 randomly selected persons were measured for evaluation of inter- and intra-observer agreement. The inter- and intra-observer variability of PS and max IMT were well

Table 2
Data regarding carotid ultrasonography.

Variables	Quartiles of serum total bilirubin levels				*p*, Trend
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Max IMT (mm)	2.67 ± 0.95	2.33 ± 0.95	2.36 ± 1.05	2.27 ± 0.98	0.003
PS	9.9 ± 5.0	8.3 ± 5.1	7.8 ± 4.9	7.9 ± 5.9	0.002
PS severity					0.004
Normal (<1.1)	2 (1.5)	6 (6.3)	3 (3.4)	7 (9.5)	
Mild (1.1–5)	18 (13.3)	18 (18.8)	28 (31.5)	18 (24.3)	
Moderate (5.1–10)	50 (37.0)	34 (35.4)	31 (34.8)	29 (39.2)	
Severe (>10)	65 (48.2)	38 (39.6)	27 (30.3)	20 (27.0)	

Data are presented as mean ± SD or *n* (%).
IMT, intima–media thickness; PS, plaque score.