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Mildly Elevated Serum Bilirubin Levels Are Negatively Associated with Carotid Atherosclerosis among Elderly Persons

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Abstract

Serum bilirubin may have a beneficial role in preventing oxidative changes in atherosclerosis. Limited information is available on whether serum total bilirubin is an independent confounding factor for carotid atherosclerosis (for example, intima-media thickness (IMT), plaque) measured noninvasively by B-mode ultrasonography only among elderly persons. The study subjects were 325 men aged 79±8 (mean ± standard deviation) years and 509 women aged 81±8 years that were enrolled consecutively from patients aged ≥60 years in the medical department. Carotid IMT and plaque were derived via B-mode ultrasonography. Multiple linear regression analysis showed that in men age (β = 0.199, p = 0.002), smoking status (β = 0.154, p = 0.006), GGT (β = -0.139, p = 0.039), and GGT (β = -0.133, p = 0.022) were significantly and independently associated with carotid IMT, and in women age (β = 0.186, p<0.001), systolic blood pressure (β = 0.104, p = 0.046), diastolic blood pressure (β = -0.148, p = 0.004), prevalence of antihypertensive medication (β = 0.126, p = 0.004), fasting plasma glucose (β = 0.135, p = 0.003), GGT (β = -0.104, p = 0.032), estimated glomerular filtration rate, serum bilirubin (β = -0.119, p = 0.006), and prevalence of cardiovascular disease (CVD) (β = 0.103, p = 0.017) were also independently associated with carotid IMT. The odds ratios (ORs) {95% confidence interval (CI)} of increasing serum bilirubin category were negatively associated with carotid IMT ≥1.0 mm and plaque in both genders. Compared to subjects with a serum bilirubin of Quartile-1, the multivariate-OR (95% CI) of carotid plaque was 0.25 (0.11–0.57) in the Quartile-4 male group, and 0.41 (0.21–0.78) in the Quartile-2 female group, 0.51 (0.26–0.98) in the Quartile-3 female group, and 0.46 (0.24–0.89) in the Quartile-4 female group. Our data demonstrated an independently negative association between serum bilirubin and carotid atherosclerosis in both genders.

Figures

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Introduction

Serum bilirubin, a major intravascular product of heme catabolism, is an endogenous compound that can be toxic in infants under certain conditions like excessive production of bilirubin due to hemolysis [1], but in adults a potent physiological antioxidant compound that may provide important protection against cardiovascular disease (CVD) and inflammation [2], [3]. It is generally suggested that oxidative reactions are involved in the pathophysiology of CVD processes [2], [4], [5], and that mildly increased bilirubin may have a physiologic function to protect against disease processes that involve oxygen and peroxyl radicals [6], [7].

The first report of a negative relationship between serum bilirubin levels and coronary artery disease was published as early as 1994 [8]. Since then, some studies have demonstrated that subjects with lower bilirubin levels have an increased risk of coronary artery calcification [9], ischemic stroke [10]. In a recent Taiwanese prospective study on patients with cardiac syndrome X followed for 5 years, in which patients with the lowest serum bilirubin levels had a higher incidence of non-fatal myocardial infarction, ischemic stroke, rehospitalization for unstable angina, and coronary revascularization procedures [11]. The same association was also reported in a recent United Kingdom prospective study, in which patients with the lower serum bilirubin levels had a higher incidence of CVD and death in both genders [12]. Meta analysis of studies focused on the association between serum bilirubin and atherosclerosis, an increase in serum bilirubin was associated with a decrease in CVD risk [3]. Although subjects in these studies include young persons, to our knowledge, there are few studies of which subjects are only elderly persons.

Carotid atherosclerosis (e.g., intima-media thickness (IMT), plaque) is an important and sensitive surrogate marker of CVD and can now be measured noninvasively by B-mode ultrasonography [13]–[15]. We have shown that this parameter is strongly associated with conventional cardiovascular risk factors, including age, central obesity, smoking status, metabolic syndrome (MetS), hypertension, hypertriglycerides, low high-density lipoprotein cholesterol (HDL-C) level, increased low-density lipoprotein cholesterol (LDL-C) level, uric acid, and diabetes [16]-[18]. However, limited information is available on whether serum bilirubin is an independent confounding factor for carotid atherosclerosis only among elderly persons by gender [19], [20].

Firstly, this study investigated serum bilirubin levels and their relation to potential confounding factors such as hypertension, hyperglycemia and lipids. Secondly, this study investigated whether there is an independent association of serum bilirubin with a direct and early measure of carotid atherosclerosis by B-mode ultrasonography. To examine these two issues, cross-sectional data from elderly persons were used.

Materials and Methods

Subjects

Subjects for this investigation were recruited from among consecutive elderly patients aged ≥60 years that visited the internal medical department of Seiyo Municipal Nomura Hospital. Participants with serum total bilirubin ≥2.1 mg/dL or alanine transaminase (ALT) ≥80 IU/L or gamma glutamyl transpeptidase (GGT) ≥80 IU/L were excluded to avoid confounding factors due to the high possibility of potential Gilbert syndrome and hepatobiliary disease. We additionally excluded participants with severe cardio-renal failure or nutritional disorders that would affect blood pressure, lipid and glucose metabolisms were also excluded. Exclusion criteria were severe hypotension as defined by systolic blood pressure (SBP) <80 mmHg; renal failure with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m²; total cholesterol

Table 1. Characteristics of subjects by gender.

Characteristics	Men N=325	Women N=509	*P*-value*
Age (years)	79±8	81±8	**0.006**
Body mass index† (kg/m^2)	21.2±3.5	21.5±3.8	0.280
Smoking status‡, N	148/14/23/140	502/1/1/5	**<0.001**
Systolic blood pressure (mmHg)	135±26	140±23	**0.004**
Diastolic blood pressure (mmHg)	75±14	77±14	0.280
Antihypertensive medication, N (%)	152 (46.8)	300 (58.9)	**0.001**
Triglycerides (mg/dL)	73 (59–97)	79 (62–109)	**0.036**
HDL cholesterol (mg/dL)	54±18	57±18	**0.003**
LDL cholesterol (mg/dL)	101±34	111±35	**<0.001**
Antidyslipidemic medication, N (%)	16 (4.9)	52 (10.2)	**0.006**
Fasting plasma glucose (mg/dL)	119 (100–146)	114 (99–142)	0.332
Antidiabetic medication, N (%)	69 (21.2)	76 (14.9)	**0.024**
eGFR § (mL/min/1.73 m^2)	66.3±21.5	60.8±19.1	**<0.001**
Alanine aminotransferase (IU/L)	16 (11–22)	14 (10–19)	**0.006**
Gamma-glutamyltransferase (IU/L)	23 (16–34)	16 (12–24)	**<0.001**
Serum bilirubin (mg/dL)	0.73 (0.54–1.03)	0.68 (0.52–0.89)	**0.023**
Cardiovascular disease, N (%)	151 (46.5)	210 (41.3)	0.152
Ischemic stroke, N (%)	136 (41.8)	177 (34.8)	**0.040**
Ischemic heart disease, N (%)	30 (9.2)	52 (10.2)	0.721
Carotid intima-media thickness (mm)	1.05±0.22	0.98±0.21	**<0.001**
Plaque, N (%)	243 (74.8)	356 (69.9)	0.135

Data are means ± standard deviation. HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate. †Body mass index was calculated using weight in kilograms divided by the square of the height in meters. ‡Smoking status: daily consumption (pack) × duration of smoking (year) {never, light (<20 pack • year), moderate (20–39 pack • year), heavy (≥40 pack • year)}. §eGFR was estimated by the following equation: $=0.741\times175\times Cr^{-1.154}\times Age^{-0.203}\times0.742$ (if female). Data for triglycerides, fasting plasma glucose, alanine aminotransferase, gamma-glutamyltransferase, and serum bilirubin were skewed and are presented as median (interquartile range) values, and were log-transformed for analysis. *Student's t-test was used for the continuous data and χ^2 test for the categorical data.

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Table 2. Relationship between serum bilirubin and variables within each gender.

	Men N=325	Women N=509
Characteristics	r (*P*-value)	r (*P*-value)
Age	−0.061 (0.271)	−0.073 (0.100)
Body mass index	0.096 (0.084)	**0.087 (0.049)**
Smoking status	0.087 (0.118)	0.022 (0.625)
Systolic blood pressure	0.064 (0.249)	−0.006 (0.884)
Diastolic blood pressure	**0.143 (0.010)**	0.041 (0.357)
Antihypertensive medication (No=0, Yes=1)	−0.048 (0.391)	0.028 (0.526)
Triglycerides	−0.078 (0.158)	**−0.181 (<0.001)**
HDL cholesterol	**0.191 (0.001)**	0.079 (0.076)
LDL cholesterol	0.068 (0.222)	0.068 (0.124)
Antidyslipidemic medication (No=0, Yes=1)	−0.024 (0.669)	0.036 (0.413)
Fasting plasma glucose	0.085 (0.128)	−0.037 (0.400)
Antidiabetic medication (No=0, Yes=1)	0.027 (0.626)	−0.010 (0.814)
eGFR	0.107 (0.053)	0.035 (0.427)
Serum uric acid	−0.078 (0.162)	−0.030 (0.500)
Alanine aminotransferase	−0.001 (0.986)	0.012 (0.789)
Gamma-glutamyltransferase	0.045 (0.421)	0.067 (0.130)
Cardiovascular disease	−0.070 (0.209)	−0.030 (0.493)

r, Pearson's correlation coefficient. Data for triglycerides, fasting plasma glucose, alanine aminotransferase, gamma-glutamyltransferase, and serum bilirubin were skewed and log-transformed for analysis.

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