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High serum bilirubin is associated with lower prevalence of peripheral arterial disease among cardiac patients

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ABSTRACT

Several studies have shown that subjects with higher serum bilirubin may have a lower risk of cardiovascular disorders. We herein investigated whether serum bilirubin concentration is associated with lower extremity ischemia among cardiology patients. In total, 935 patients without a history of angioplasty or bypass surgery of the lower limb arteries and who had bilateral ankle–brachial index measurements were included in the study. Peripheral arterial disease (PAD) was defined to be present when ABI of either or both sides was < 0.9. Overall, the serum total bilirubin concentration ranged between 0.1 and 2.7 mg/dL (normal range, 0.1–1.0 mg/dL). Across the bilirubin tertiles, age did not differ significantly. On the other hand, male patients (median 0.6 mg/dL, interquartile range (IQR) 0.4–0.7 mg/dL) had significantly higher bilirubin levels than female patients (median 0.5 mg/dL, IQR 0.4–0.7 mg/dL, $P = 0.014$). Logistic regression analysis showed that, as compared with the lowest bilirubin tertile (0.1–0.4 mg/dL), the highest tertile (0.7–2.7 mg/dL) was significantly negatively associated with prevalent PAD after adjusting for sex, age, eGFR, white blood cell count, inorganic phosphate, HbA1C, total and HDL cholesterol, triglycerides, current smoking, diabetic medication, and statin use. This association remained significant when only those with serum bilirubin in the normal range were included in the analysis. Among cardiology patients, serum bilirubin concentration was significantly negatively associated with prevalence of PAD. The underlying mechanism and therapeutic indications should be investigated in further investigations.

1. Introduction

On the one hand, high serum bilirubin is considered to be an unfavorable prognostic factor in hepatobiliary disorders [1]. On the other hand, evidence that low serum bilirubin is associated with myasthenia gravis [2], Alzheimer's disease [3], ulcerative colitis [4], Crohn's disease [5], diabetic complications [6,7], and immunological disorders [8,9] has suggested the possibility that endogenous bilirubin, presumably owing to its antioxidant properties, may act protectively against conditions that develop or progress due to redox imbalance [10,11]. A recent study has shown that administration of bilirubin suppresses atherosclerotic formation in an animal model [12]. In humans, a relationship between serum bilirubin and atherosclerotic disorders has also been demonstrated in previous studies [13]. For example, low serum total bilirubin is associated with increased risk of coronary artery disease [14–16], carotid atherosclerosis [17,18], and arterial stiffness [19]. However, information on the association between serum bilirubin and peripheral arterial disease (PAD) seems to be limited [20,21]. To this end, by measuring the ankle–brachial index (ABI), here we analyzed the association between serum bilirubin concentrations and PAD among cardiac patients.

2. Materials and methods

2.1. Ethics statement

The current retrospective study was approved by the Ethics Committee at the Osaka Medical College and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients or their guardians.

2.2. Study population

Between November 2011 and May 2017, 5407 patients provided

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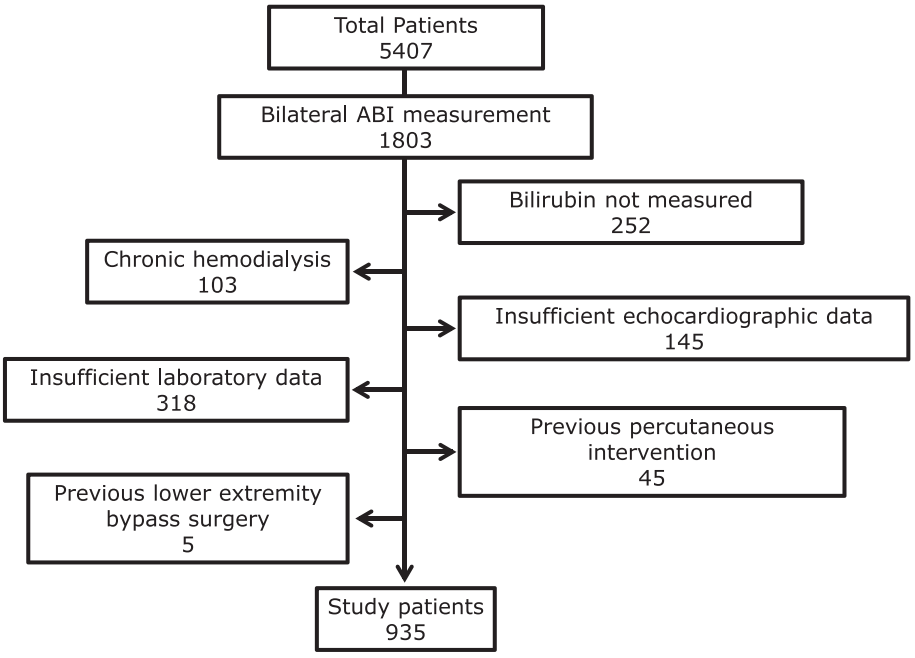

Fig. 1. Flow diagram showing selection of the patients.

written informed consent, and ABI of the bilateral sides was measured in 1803 (Fig. 1). Patients who met any of the following criteria were subsequently excluded: serum bilirubin not measured, undergoing chronic hemodialysis, insufficient echocardiographic or laboratory data, or undergone previous intervention for lower extremity ischemia. After these exclusions, 935 patients were included in the current study.

2.3. Assessment of PAD

ABI, together with brachial–ankle pulse wave velocity (baPWV), was measured by using a Form PWV/ABI device (Nihon Colin, Tokyo, Japan) [22]. PAD was defined as an ABI of < 0.90 in either leg. Mean ABI was defined as the arithmetic mean of values for the two sides.

2.4. Laboratory analysis

Blood samples were collected in the morning after an overnight fast. Aliquots of serum and plasma were immediately obtained and stored at − 80 degrees until analysis. High–sensitivity C–reactive protein (CRP) and BNP levels were measured by routine laboratory methods. The estimated glomerular filtration rate (eGFR) was calculated by the following Modification of Diet in Renal Disease equation for Japanese subjects: $eGFR = 194 \times (\text{serum creatinine})^{-1.094} \times (\text{age})^{-0.287}$ ($\times 0.739$, when female) [23].

2.5. Echocardiography

Echocardiographic examinations were performed with a Vivid 7 Dimension equipped with a multi–frequency transducer (GE Healthcare, Vingmed, Norway). Left ventricular (LV) end–diastolic dimension (LVDd), interventricular septal thickness (IVST) and posterior wall thickness (PWT) were measured at end diastole. LV volumes were calculated by the modified Simpson method using the apical 4–chamber view. The LVEF was defined as low when < 50%. LVM was calculated by the formula proposed by Devereux et al. [24] with the following modification: $0.8 \times 1.04 \times [(\text{LVDd} + \text{IVST} + \text{PWT})^3 - \text{LVDd}^3] + 0.6$ [25]. Body surface area (BSA) was calculated by using the following formula: $(\text{body weight})^{0.425} \times (\text{height})^{0.725} \times 0.007184$, and the LVM index (LVMI) was calculated as the ratio of LVM to BSA. When the LVMI was > 118 g/m^2 (men) or 108 g/m^2 (women), LV hypertrophy was defined as present [26].

2.6. Statistical analysis

Baseline characteristics were assessed with standard descriptive statistics. Data were expressed either as mean ± standard deviation, number (percentage) or median and interquartile range (IQR). Spearman rank correlation test was used to assess the correlation between two variables. Multivariate logistic regression analysis was performed by SPSS statistics version 22.0 (IBM, Armonk, NY).

3. Results

3.1. Patient clinical characteristics and laboratory data

Among the 935 study patients, the serum total bilirubin level ranged between 0.1 and 2.7 mg/dL with a median value of 0.5 mg/dL, and 48 patients (6.2%) had serum bilirubin higher than the upper normal value (1.0 mg/dL). Age did not differ significantly across the bilirubin tertiles; however, male patients had significantly higher bilirubin levels (median, 0.6 mg/dL; IQR, 0.4–0.7 mg/dL) as compared with female patients (median, 0.5 mg/dL; IQR, 0.4–0.7 mg/dL; $P = 0.014$, by Mann–Whitney U test). Among 109 with ASO, patients were judged to have Fontaine class 1 in 67 patients, class 2 in 39, class 3 in 1, and class 4 in 2. Serum bilirubin level did not differ significantly between those with Fontaine class 1 ASO (median, 0.5 mg/dL; IQR, 0.3–0.6 mg/dL) and those with class 2–4 ASO (median, 0.5 mg/dL; IQR, 0.4–0.6 mg/dL; $P = 0.920$, by Mann–Whitney U test) Although overall smoking status did not differ significantly across the serum bilirubin tertiles (Table 1), the prevalence of “current smoking” differed significantly with the lowest prevalence in the highest bilirubin tertile ($P = 0.041$, by χ^2 test).

Among hepatic enzymes, alanine transaminase (ALT), aspartate transaminase (AST), and gamma–glutamyl transpeptidase (GTP) were higher among those with higher serum bilirubin (Table 2). The prevalence of moderate–to–severe renal dysfunction (eGFR < 45 mL/min/1.73 m^2) was the highest among patients in the lowest bilirubin tertile (69/295, 23.4%), followed by the highest (47/303, 15.5%) and middle (37/337, 11.0%, $P < 0.001$) bilirubin tertiles. Blood hemoglobin level was higher and platelet count was lower among patients