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Clinical significance of serum bilirubin and gamma-glutamyltransferase levels on coronary atherosclerosis assessed by multidetector computed tomography

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Abstract *Background and aims:* Low bilirubin and high gamma-glutamyltransferase (GGT), which are endogenous markers of oxidative stress, confer a higher risk of cardiovascular disease (CVD). We investigated associations between serum concentrations of bilirubin, GGT and coronary atherosclerosis.
Methods and results: A cross-sectional analysis was performed on 1520 subjects who underwent multidetector computed tomography scans. Coronary atherosclerosis was assessed by coronary artery calcium score (CACS) and obstructive coronary artery disease (OCAD), was defined as the presence of coronary artery stenosis of ≥50%. Total bilirubin (TB) level was negatively correlated with CACS and coronary stenosis whereas GGT level was positively correlated with CACS in men. However, there was no correlation between TB, GGT levels and either CACS or coronary artery stenosis in women. In a multivariate-adjusted model, TB level was inversely associated with a CACS > 100 [odds ratio (OR) per log standard deviation (SD), 0.67; 95% confidence interval (CI), 0.52–0.87], and OCAD (OR per log SD, 0.77; 95% CI, 0.62–0.95) in men. By contrast, GGT level was positively associated with a CACS > 100 (OR per log SD, 1.35; 95% CI, 1.05–1.73) but not with OCAD. Adding TB and GGT to the conventional risk factors increased predictive accuracy for CACS > 100 (net reclassification improvement index [NRI] = 13.1%, $P = 0.026$; integrated discrimination index [IDI] = 0.024, $P = 0.001$) and for OCAD (NRI = 12.6%, $P = 0.026$; IDI = 0.010, $P = 0.013$).
Conclusions: Low TB and high GGT levels were concomitantly associated with coronary atherosclerosis in Korean men. Future studies are needed to elucidate the causal associations of TB and GGT with CVD.

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide and has become a major health issue due to its increasing prevalence. Interestingly, the prevalence of CVD in Asia has been reported to be similar to or even higher than that in Europe despite of comparatively lower average body mass index (BMI) [1]. The reason for this may

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be because Asian people who are over nourished are more susceptible to diabetes, metabolic syndrome, and nonalcoholic fatty liver disease (NAFLD) with increased insulin resistance (IR) than the European people [2]. Therefore understanding the factors, other than the already known traditional risk factors, that may aggravate atherosclerosis is important, particularly for the non-obese Asian populations at worse outcomes. In this aspect, it is noteworthy that oxidative stress plays a pivotal role in the initiation and progression of cardiovascular disease. It has been previously reported that increased production of reactive oxygen species (ROS) promotes endothelial dysfunction and atherosclerosis [3].

Bilirubin and gamma-glutamyltransferase (GGT) levels increase in association with alcohol consumption and the presence of hepatobiliary disease. However, recent researches have reported consistently that low total bilirubin (TB) and high GGT levels, even when they are relatively high or low within normal ranges, are also associated with CVD [4,5]. Population-based studies have shown that low TB levels were a significant predictor of coronary artery disease, stroke, peripheral artery disease, and mortality, independent of conventional risk factors [6–9]. In addition, considerable evidence suggests that the circulating GGT level is closely linked to CVD in a dose-dependent manner and is a good predictor of cardiovascular mortality and all-cause mortality independent of conventional risk factors [10]. Current literature suggests that serum TB, GGT level may act as a biomarker for oxidative stress, which provides a plausible biological background linking TB or GGT to CVD [10,11].

Recently introduced, multidetector-row computed tomography (MDCT) is a useful, noninvasive method for evaluating coronary artery disease. MDCT allows quantification of the coronary artery calcium score (CACS), which has been validated to have a predictive value for CVD in asymptomatic individuals [12]. Further, coronary computed tomography angiography (cCTA) provides a measure of the severity and extent of the coronary artery stenosis [13]. Several studies have found significant association between low TB [14–17], high GGT levels [18–20] and CACS or coronary artery stenosis. However, to our knowledge, no study has simultaneously investigated the associations of TB or GGT levels with the CACS and coronary artery stenosis. Therefore, we aimed to analyze the association between serum concentrations of TB and GGT and the extent of coronary artery disease assessed by MDCT in a Korean population.

Methods

Study population

We retrospectively recruited subjects who underwent a cardiac CT at the Seoul St. Mary's Hospital Health Promotion Center as part of a voluntary medical check-up between March 2009 and December 2010. Among 1732 subjects over 20 years of age with data on an MDCT of coronary artery and serum levels of bilirubin and GGT, we excluded individuals with a history of cardiovascular and cerebrovascular disease, arrhythmia ($n = 73$), hepatitis B or C infection, other known liver diseases ($n = 115$), elevated liver enzymes (AST $>$ 100 IU/L or ALT 100 IU/L) ($n = 20$), and renal dysfunction (serum creatinine $\geq$ 1.5 mg/dL) ($n = 4$). A total of 1520 subjects were included in the final analysis. This study was approved by the institutional review board of Seoul St. Mary's Hospital, Seoul, Korea.

Measurement of anthropometric, biochemical parameters, and fatty liver

Medical history and social-behavioral information were collected through questionnaires completed by patients. Smoking status was categorized as current smoker, past smoker or never smoker. Alcohol consumption was categorized as $<$10 g/day, 10–20 g/day, and $>$20 g/day.

Physical examinations were performed by measuring height, weight, waist circumference (WC), and blood pressure (BP) according to standardized methods. Body mass index (BMI) was calculated by dividing weight by the height squared (kg/m^2). BP was measured in the sitting position after a 10 min rest and hypertension was defined as systolic BP $\geq$ 140 mmHg or diastolic BP $\geq$ 90 mmHg or use of antihypertension medication. The study population was categorized into the normal or over-weight group (BMI $<$ 25) or obese group (BMI $\geq$ 25), as recommended by the World health organization Asia-Pacific guidelines. Blood samples were collected after the subjects had fasted at least 10 h. Hyperlipidemia was defined as total cholesterol $\geq$ 240 mg/dL, LDL $\geq$ 130 mg/dL, HDL $\leq$ 40 mg/dL, TG $\geq$ 150 mg/dL and/or treatment with lipid lowering agents. The degree of insulin resistance assessed by homeostasis model assessment of insulin resistance (HOMA-IR) calculated as follows: HOMA-IR = fasting insulin (μU/mL) $\times$ fasting plasma glucose (FPG) (mmol/L)/22.5 and subjects were classified as being insulin resistant (top quartile of the HOMA-IR distribution). The Framingham risk score (FRS) was calculated to estimate a 10-year risk for coronary heart diseases using validated algorithms [21]. Estimated glomerular filtration rate (eGFR) was used to estimate kidney function using the abbreviated Modification of Diet in Renal Disease (MDRD) equation [22].

We determined fatty liver based on the findings of abdominal ultrasonography which was performed using a 3.5-MHz. transducer (HDI 5000, Philips, Bothell, WA, USA) by experienced radiologists who were blinded to patient history and laboratory results. Patients with hepatic steatosis were categorized into mild, moderate, and severe, based on sonographic findings (hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring) [23].

Cardiac CT: coronary artery calcium score (CACS)

Cardiac CT was performed using a 64-slice multidetector CT scanner (SOMATOM Definition; Siemens Medical Systems, Germany). Intravenous esmolol (10–30 mg) was given if patients had a heart rate of $>$70 beats per minute.