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Absence of association between gallstone and coronary artery calcification

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Background and aims: Gallstone has been suggested to be associated with cardiovascular disease (CVD). Coronary artery calcification (CAC) is an excellent value to predict future CVD. The aim of this study was to evaluate the association between gallstone and CAC.
Methods: Data were analyzed from an occupational cohort of 46,893 subjects (37,557 men and 9336 women) between 2011 and 2014. Participants with cancer or CVD histories or missing data at baseline were excluded from the study. Gallstone was diagnosed by ultrasound-documentation. Multivariate logistic analysis was conducted to examine the relationship between gallstone and CAC.
Results: The total population who had gallstone was 1426 (3.1%). In multivariate analysis, odds ratios (OR) for gallstone were not different according to CAC score groups in men and women. In addition, gallstone was not associated with higher OR for CAC in men and women.
Conclusions: Gallstone was not associated with CAC in both Korean men and women.

1. Introduction

Gallstone disease is one of the major health problems in developed countries [1]. More than 80% of gallstone formations are cholesterol-based [2,3], and are associated with obesity, diabetes mellitus, dyslipidemia, metabolic syndrome, insulin resistance, and a sedentary lifestyle [1]. Hypercholesterolemia and aforementioned comorbidities have been regarded as risk factors of cardiovascular disease (CVD). Until recently, many studies have reported the association between gallstone and CVD [4–11]. However, the causal association between gallstone and CVD has not been accomplished.

Coronary artery calcification (CAC) is the presence of early atherosclerosis of coronary artery, and CAC scoring may improve cardiovascular risk prediction in asymptomatic individuals [12]. As total volume of CAC deposits is a good indicator of overall plaque burden and of future coronary events, the estimation of CAC scoring provides a useful noninvasive tool to assess risk of CV events [13]. Therefore, we hypothesized that gallstone should be significantly associated with CAC, as gallstone is a significant predictor of future CVD. We designed a cross-sectional analysis to study the association between gallstone and CAC, based on ultrasonography, to evaluate whether gallstone and CVD exhibit causal association with each other or indirect epiphenomenon.

2. Patients and methods

2.1. Study population

The study population consisted of individuals who participated in a comprehensive health-screening program and underwent coronary computed tomography (CT) scanning to establish a CAC score, from 2011 to 2014, at the clinics of the Kangbuk Samsung

Abbreviations: BMI, body mass index; CAC, coronary artery calcification; CAD, coronary artery disease; CVD, cardiovascular disease; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high sensitivity C-reactive protein.

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Hospital Total Healthcare Center in Seoul and Suwon, South Korea. The purpose of the screening program was to promote health through early detection of chronic diseases and their risk factors. Additionally, the Korean Industrial Safety and Health Law require working individuals to participate in an annual or biennial health examination. About 80% of the participants were employees of companies or local governmental organizations and their spouses, and remaining participants registered individually for the program.

Initially, 55,450 participants were included in the study. Individuals were excluded from the study if data were missing for key variables including smoking, exercise, alcohol, high sensitivity C-reactive protein (hsCRP), abdominal ultrasonographic finding, and medication (n = 6852), or if they had a history of cancer (n = 1431) or CVD (n = 766). Finally, 46,893 participants (37,557 men and 9336 women) were included in the final analysis. This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital. Requirement for informed consent was waived as de-identified information was retrieved retrospectively.

2.2. Measurements

As part of the health-screening program, individuals completed questionnaires related to their medical and social history, and medication use. Previous medical histories, including diabetes mellitus, hypertension, and others, were defined based on current usage of medication for specific disease, or positive response to the questions of medical history. Questionnaires were also used to ascertain information regarding alcohol consumption (g/day), smoking (never, ex, current), and frequency of moderate activity or exercise per week. Moderate activity was defined as >30 min of activity per day that induced slight breathlessness.

Blood samples were collected after an overnight fasting and analyzed in the same core clinical laboratory. The core clinical laboratory has been accredited and participates annually in inspections and surveys by the Korean Association of Quality Assurance for Clinical Laboratories.

Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Obesity was defined as body mass index >25 kg/m^2. Fatty liver was diagnosed based on standard criteria including hepatorenal echo contrast, liver brightness, and vascular blurring. Abdominal ultrasounds were performed using a Logic Q700 MR 3.5-MHz transducer (GE, Milwaukee, WI) by experienced radiologists, who were unaware of the aims of the study. Gallstones were defined as ultrasound-documented gallstones by the presence of strong intraluminal echoes that were gravity-dependent or that attenuated ultrasound transmission (acoustic shadowing) [14]. The inter-observer reliability and intra-observer reliability for gallstone diagnosis were excellent (κ-statistic of 0.90 and 0.96, respectively). Metabolic syndrome was defined as the 2009 joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention criteria, with waist circumference thresholds of ≥90 cm for men and ≥80 cm for women that are specific for Asian populations [15]. The 10-year Framingham risk score was calculated on the basis of age, sex, total and high-density lipoprotein cholesterol levels, smoking in the past years, blood pressure, and the use of antihypertensive medication by using the risk prediction functions of the NCEP-ATP III guidelines [16]. The homeostasis model assessment of insulin resistance (HOMA-IR) index was calculated by the following equation: HOMA-IR = (fasting insulin [mIU/mL] x fasting glucose [mmol/L])/22.5 [17].

All computed tomography scans were obtained with a LightSpeed VCT XTe 64-slice multidetector row CT scanner (GE Healthcare, Tokyo, Japan) with the same standard scanning protocol using 2.5-mm section collimation, 400-ms rotation time, 120-kV tube voltage, and 124 mAS (310 mA × 0.4 s) tube current under electrocardiogram-gated dose modulation. The quantitative coronary artery calcification scores were calculated according to the methods described by Agatston et al. [18].

2.3. Statistical analyses

Data are expressed as mean ± SD for continuous variables and as frequencies for categorical variables. The distribution of continuous variables was evaluated, and non-normally distributed variables were log-transformed to normalize the distributions for parametric statistical analysis.

Since measured values of Framingham risk score, HOMA-IR, hsCRP, and CAC score were different between men and women, sex-specific quartiles or tertiles of these risk factors for men and women were estimated. To evaluate the association between gallstone and CAC, we used a logistic regression model estimating the odds ratios (OR) with 95% confidence intervals (CI). We used stepwise models progressively to adjust for potential compounders. Model 1 was adjusted for age, center, year of screening examination, smoking status, alcohol intake, physical activity, education level, BMI, medication for hypertension, medication for diabetes, and medication for hyperlipidemia. Model 2 was adjusted for covariates in model 1 plus adjustment for HOMA-IR and fatty liver. Model 3 was adjusted for covariates in model 2 plus metabolic syndrome. Model 4 was adjusted for covariates in model 3 plus hsCRP.

Statistical analyses were performed using STATA version 11.2 (StataCorp LP, College Station, TX, USA). Reported p values were two-tailed, and $p < 0.05$ was considered statistically significant.

3. Results

Baseline characteristics of the study population by gender are presented in Table 1. Mean age of the total population was 41.3 ± 7.6 years and the male population was 37,557 (80.1%). The prevalence of gallstone in the total study population was 3.1% (2.9% in men and 3.4% in women). In case of male subjects, subjects with gallstone were significantly older and obese, and had higher prevalence of fatty liver, obesity, hypertension, diabetes, and metabolic syndrome than those without gallstone (all $p < 0.05$). Insulin resistance and inflammation presenting as HOMA-IR and hsCRP were also significantly higher in the population with gallstone. For female subjects, the differences in general characteristics and metabolic markers were similar to those in male subjects except for diabetes.

Table 2 shows the prevalence of gallstone according to quartiles or tertiles of various cardiovascular risk factors by gender. The prevalence of gallstone increased linearly according to quartiles of Framingham risk score, HOMA-IR and hsCRP both men and women ($p < 0.001$). However, there was significant linear increase of the prevalence of gallstone according to tertiles of CAC score including CAC score = 0 as a reference in men ($p < 0.001$), but not in women.

To determine the relationship between gallstone and CAC, multivariate logistic analysis was conducted. The OR for the presence of gallstone by tertile groups, including CAC score = 0 as a reference group in both men and women subjects, are presented in Table 3. In stepwise multivariate model analysis, no significant difference of OR for gallstone according to CAC score groups in both men and women was observed.

In the total study population, subjects with the presence of CAC (score > 0) were 6231 (13.3%). For male subjects, the presence of CAC was detected in 207 (18.7%) of the subjects with gallstone (n = 1106) and in 5613 (15.4%) of those without gallstone (n = 36,451). The difference of the prevalence of CAC was statistically significant ($p = 0.003$). In women, the prevalence of CAC was 4.7% (n = 15) in subjects with gallstone (n = 320) and 4.4%