Archives of Medical Research 48 (2017) 284–291

ORIGINAL ARTICLE

Effects of Low-density Lipoprotein Cholesterol on Coronary Artery Calcification Progression According to High-density Lipoprotein Cholesterol Levels

Da Young Lee,[a,b] Ji Hyun Kim,[a] Se Eun Park,[a] Cheol-young Park,[a] Ki-won Oh,[a] Sung-woo Park,[a] Eun-Jung Rhee,[a] and Won-young Lee[a]

[a]*Division of Endocrinology and Metabolism, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea*

[b]*Division of Endocrinology and Metabolism, Department of Internal Medicine, Korea University College of Medicine, Ansan, South Korea*

Received for publication December 9, 2016; accepted May 19, 2017 (ARCMED-D-16-00765).

Background and Aim. Previous studies reported that many patients are at high risk for cardiovascular disease (CVD) despite achieving recommended low-density lipoprotein cholesterol (LDL-C) levels. Therefore, we investigated whether the association between LDL-C and the risk for incident CVD differed according to high-density lipoprotein cholesterol (HDL-C) levels using coronary artery calcium score (CACS) progression as a surrogate marker for predicting CVD.

Methods. We investigated 2132 Korean men in a health screening program, in which CACS was measured at baseline and after 4 years. Coronary artery calcification (CAC) progression was defined as a change in CACS $\geq$0 over 4 years. We divided the subjects into nine groups according to baseline HDL-C and LDL-C levels and compared their risks for CAC progression.

Results. After 4 years, 475 subjects (22.3%) exhibited CAC progression. We identified a positive relationship between baseline LDL-C levels and the risk for incident CAC. However, this association was attenuated by high baseline HDL-C levels. Multivariate logistic regression analysis adjusted for age, body mass index, systolic blood pressure, fasting glucose, smoking, and exercise status revealed that the odds ratios for incident CAC in the lowest HDL-C tertile were 3.08 for LDL-C tertile 3 and 2.02 for LDL-C tertile 2 compared to LDL-C tertile 1. However, these differences disappeared in the highest HDL-C tertile (HDL-C $\geq$54.0 mg/dL).

Conclusions. In this longitudinal study, we found that the positive relationship between LDL-C and the relative risk for incident CAC was attenuated by higher HDL-C levels. Therefore, HDL-C levels should be considered when estimating CVD risk. © 2017 IMSS. Published by Elsevier Inc.

Key Words: Cholesterol LDL, Cholesterol HDL, Coronary artery disease, Vascular calcification, Coronary vessels.

Introduction

Despite substantial efforts, cardiovascular disease (CVD) remains the leading global cause of death, accounting for $>$17.3 million deaths in 2013 (1), and the number of affected individuals is expected to exceed 23.6 million by 2030 (2). In 2010, the estimated global cost of CVD was $863 billion, and it is expected to reach $1.044 trillion by 2030 (3).

Address reprint requests to: Eun-Jung Rhee, Won-Young Lee, Division of Endocrinology and Metabolism, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 29 Saemunan-ro, Jongno-gu, Seoul 03181, South Korea; Phone: (+82) 2-2001-2485; FAX: (+81) 3-5802-7712; E-mail: hongsiri@hanmail.net, drlwy@hanmail.net.

0188-4409/$ - see front matter.
http://dx.doi.org/10.1016/j.arcmed.2017.06.005

High low-density lipoprotein cholesterol (LDL-C) levels are associated with an increased risk for CVD events (4–6). Therefore, current treatment guidelines for dyslipidemia focus on reducing LDL-C levels as the primary goal (7–10). Nonetheless, the 5 year incidence rates of a major CVD event occurring among statin-treated patients with low LDL-C levels in randomized clinical trials were 22% for individuals with prior CVD and 10% for individuals without prior CVD (6,11). One explanation for this 'residual risk' after statin treatment is a low baseline level of high-density lipoprotein cholesterol (HDL-C) (10,12). In the Framingham Heart Study, low HDL-C levels represented a greater risk factor for coronary heart disease than high LDL-C levels (13).

The coronary artery calcium score (CACS) measured using cardiac computed tomography is a linear estimate of the total burden of coronary atherosclerosis, and it is highly correlated with autopsy and intravascular ultrasound assessments (14). CACS provides a better estimate of disease burden than luminal stenosis as determined by angiography (15), as less obstructive plaques give rise to more occlusions than more obstructive plaques because of their greater number (16). The ability of CACS to predict CVD events in asymptomatic individuals has been confirmed in many large clinical trials, and it is superior to traditional risk stratification tools, such as clinical risk factor assessment and carotid intima–media thickness testing (17–21).

Aim

Whereas several studies demonstrated that coronary artery calcification (CAC) is associated with metabolic diseases, few studies examined the relationship between lipid profiles and CAC risk. Therefore, our study aimed to analyze the relationship between incident CAC development and LDL-C levels according to HDL-C levels in Korean men over a period of 4 years.

Materials and Methods

Subjects

We investigated the medical records of adults aged 20 years or older who participated in medical health checkup programs at the Health Promotion Center of Kangbuk Samsung Hospital, Sungkyunkwan University, Seoul, Korea. Most of the examinees were employees and family members of various industrial companies around the country. The purpose of the medical health checkup program is to promote the health of employees through regular health examinations and enhance the early detection of diseases. These medical examinations are largely paid for by the employers, and a considerable proportion of the examinees undergo examinations annually or biannually.

We assessed the eligibility of 2432 men who participated in the program between January and December 2010 and again between January and December 2014. They underwent CACS measurement in both periods. Among them, 300 subjects were excluded because of a history of diabetes, ischemic stroke, or coronary artery disease or because of missing data, especially lipid profile information. Based on the American Diabetes Association criteria (22), diabetes was defined as fasting glucose levels ≥126 mg/dL or glycated hemoglobin (HbA1c) ≥6.5% and/or the current use of anti-hyperglycemic medications. The final analyses included 2132 men.

The subjects provided written informed consent for the use of their health screening data in the research. This study was reviewed and approved by the Institutional Review Board of Kangbuk Samsung Hospital (KBS12089) and was conducted in accordance with the 1975 Declaration of Helsinki.

Anthropometric and Laboratory Measurements

Each subject completed a structured questionnaire addressing demographic characteristics at the first visit. Body weight was measured in light clothing without shoes to the nearest 0.1 kg using a digital scale. Height was measured to the nearest 0.1 cm. The body mass index (BMI) of subjects was calculated as the weight in kilograms divided by the square of height in meters. Blood pressure (BP) was measured using a standardized sphygmomanometer after 5 min of rest. Trained nurses measured sitting BP using standard mercury sphygmomanometers. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or the current use of antihypertensive medications according to criteria recommended by the seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high BP (23).

Venous blood samples were collected in the morning (8–9 am) after an overnight fast of at least 8 h. The hexokinase method was used to test fasting plasma glucose (FPG) concentrations (Hitachi Modular D2400; Roche, Tokyo, Japan). An enzymatic calorimetric test was used to measure total cholesterol (TC) and triglyceride (TG) concentrations. The selective inhibition method was used to measure HDL-C levels, and a homogeneous enzymatic calorimetric test was used to measure LDL-C levels. FPG, TC, TG, HDL-C, and LDL-C levels were measured as integer range. HbA1c was measured via an immunoturbidimetric assay using a Cobra Integra 800 automatic analyzer (Roche Diagnostics, Basel, Switzerland) with a reference value of 4.4–6.4%. The methodology aligned with Diabetes Control and Complications Trial and National Glycohemoglobin Standardization Program (NGSP) (24) standards. The intra-assay coefficient of variation (CV) was 2.3%, and the inter-assay CV was 2.4%. Both values were within the NGSP acceptable limits (25). Serum high-sensitivity C-reactive protein (hsCRP) concentrations were measured using a nephelometric assay and a