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ORIGINAL ARTICLE

High-sensitivity C-reactive Protein Is Associated with the Presence of Coronary Artery Calcium in Subjects with Normal Blood Pressure but Not in Subjects with Hypertension

Joo-Wook Sung,[a,*] Sung Ho Lee,[a,*] Christopher D. Byrne,[b] Pil-Wook Chung,[c] Yu Sam Won,[d] and Ki-Chul Sung[a]

[a]*Division of Cardiology, Department of Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea*
[b]*Endocrinology and Metabolism Unit, IDS Building, Southampton General Hospital, (University of Southampton) and Southampton National Institute for Health Research Biomedical Research Centre, MP 887, Southampton, UK*
[c]*Neurology,* [d]*Neurosurgery, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea*

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Background and Aims. An association has been described between high sensitivity C-reactive protein (hs-CRP) and cardiovascular disease (CVD) in some studies but not in others. This finding may be explained by a differential impact of inflammation according to the absence or presence of certain co-existing risk factors. Because hypertension may be an effect modifier of inflammation on CVD, our aim was to investigate the relationship between hs-CRP and pre-clinical atherosclerosis in subjects with normal blood pressure and hypertension.

Methods. Data were analyzed from 14,584 Korean subjects. Subjects were stratified according to: a) 6030 (41.3%) patients with normal blood pressure (<120/80 mmHg), b) 5630 (38.6%) patients with pre-hypertension (120–139 mmHg and 80–89 mmHg) and c) 2924 (20.0%) patients with hypertension (≥140/90 mmHg). Prevalence and odds ratio for the association between increased hs-CRP (>2 mg/L) and presence of CAC (coronary artery calcium) were calculated.

Results. In both normal and pre-hypertensive groups, the prevalence of CAC >0 was higher in subjects with increased hs-CRP concentrations (>2 mg/L). Adjusting for age, sex, cerebrovascular accident, coronary heart disease and diabetes mellitus, lifestyle, obesity, fasting glucose, triglyceride, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol concentrations, there was a significant association between higher hs-CRP levels (>2 mg/L) and CAC score in the normal group (OR 1.55, 95% CI 1.11–2.16; $p = 0.010$); a borderline significant association in the pre-hypertensive group (OR 1.33, 95% CI 0.99–1.76; $p = 0.054$); and no association in the hypertensive group (OR 1.01, 95% CI 0.76–1.33; $p = 0.94$).

Conclusions. Higher hs-CRP levels (>2 mg/L) are associated with pre-clinical atherosclerosis in subjects with normal blood pressure but not hypertension.

Key Words: High-sensitivity C-reactive protein, Coronary artery calcium, Hypertension.

Introduction

The inflammatory response plays an important role in the development of atherosclerosis (1). A considerable body of evidence suggests that inflammation plays a major role in the development of atherosclerosis and its clinical manifestations (2,3). Inflammatory markers such

*These authors contributed equally to the work.

Address reprints requests to: Ki-Chul Sung, M.D., Ph.D., Division of Cardiology, Kangbuk Samsung; Hospital, Sungkyunkwan University School of Medicine, #108, Pyung Dong, Jongro-Ku, Seoul 110-746, Republic of Korea; Phone: 82-2-2001-2401; FAX: 82-2-2001-2400; E-mail: kcmd.sung@samsung.com

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as high-sensitivity C-reactive protein (hs-CRP) may be useful biomarkers that could be used in combination with measurements of low-density lipoprotein cholesterol (LDL-C) levels to assist risk stratification of selected patients for prevention of cardiovascular disease (CVD) (4). Although hs-CRP is increased in subjects with overt CVD or who have evidence of subclinical atherosclerosis (3,5−7) hs-CRP concentrations are also increased in subjects with many established risk factors such as hypertension, dyslipidemia, cigarette smoking, diabetes and obesity (6,8−12). Inconsistent association between hs-CRP and atherosclerotic coronary artery disease (3,13−20) may be explained by a differential effect of inflammation in some subjects, but not in others, who are at risk of vascular disease.

Coronary artery calcium (CAC) scores with cardiac computed tomography (CT) is a sensitive method to demonstrate the presence of pre-clinical atherosclerosis and the use of CAC scores may also be useful in identifying individuals at increased risk of CVD (21,22). The amount of CAC is correlated with the burden of atherosclerosis detected by coronary angiography or autopsy (23). Takashi Kubo et al. found that increased hs-CRP was related to the amount of the necrotic core in the culprit lesion in subjects with stable angina pectoris. However, in that study intravascular ultrasound, and not a measurement of CAC, was used (14). Many studies have now examined the association between hs-CRP and CAC (13,24−27). In some studies, hs-CRP was not correlated with CAC (13,27,28), whereas in others there was a weak association between hs-CRP and CAC (25,28,29).

Because an association between hs-CRP and CAC has been described in some studies but not in others, we tested the hypothesis that there was a different association between hs-CRP and the presence of CAC according to the presence (or absence) of hypertension. Because hypertension may be an effect modifier in the relationship between hs-CRP and CAC, our aim was to investigate the relationship between hs-CRP and CAC as a marker of pre-clinical atherosclerosis in subjects with normal blood pressure (BP), prehypertension and hypertension.

Subjects and Methods

The study population consisted of individuals who had a comprehensive health examination in 2010 at Kangbuk Samsung Hospital, College of Medicine, Sungkyunkwan University in South Korea. Initially, 14912 participants underwent coronary CT scanning to establish CAC scores and individuals were excluded from the current analyses if data were missing for the following variables: alcohol consumption (n = 116), smoking (n = 143), exercise (n = 111), body mass index (BMI) (n = 12), waist circumference (n = 12), and hs-CRP (n = 168), lipoprotein (a) (n = 157) and past medical history of cerebrovascular accident (CVA) and coronary heart disease (CHD) and diabetes mellitus (DM) (n = 69). Therefore, 14,584 participants were included in this cross-sectional analysis. The CAC score is offered as part of the health check-up program and therefore there is no medical indication for performing the test. Consequently, there are no specific inclusion or exclusion criteria as this is a health check-up and participants are not required to provide consent for research because they are undergoing a health check-up. The Institutional Review Board at Kangbuk Samsung Hospital has ruled that because our study is an analysis of routine data, there is no need for specific informed personal consent to be given because we are not accessing personal identifying information.

Waist circumference was measured at the narrowest point below the ribs or halfway between the lowest ribs and iliac crest. BMI was calculated as weight in kilograms divided by height in meters squared. Questionnaires were used to ascertain information regarding alcohol consumption (glass/day), smoking (never, ex-smoker, current smoker), and frequency of moderate activity each week. Moderate activity was defined as more than 30 min activity per day that induced slight breathlessness. Past medical history of CVA was defined as focal neurological deficits of presumed cerebrovascular origin from ischemic or hemorrhagic stroke events. Past medical history of CHD included a history of angina pectoris, acute coronary syndrome. Each patient was administered a questionnaire that included prior history of CVA and CHD. Diabetes mellitus was defined as a random blood glucose concentration of 200 mg/dL or a fasting blood glucose concentration of 126 mg/dL or use of insulin or an oral hypoglycemic agent at the current examination.

Blood samples for laboratory tests were collected after an overnight fast. Fasting plasma glucose, total cholesterol, triglyceride, LDL-C and HDL-C (high-density lipoprotein cholesterol) concentrations were estimated by the Bayer Reagent Packs on an automated chemistry analyzer (Advia 1650 Autoanalyzer; Bayer Diagnostics, Leverkusen, Germany). Concentrations of serum ferritin were measured by an electrochemiluminescence immunoassay using the Modular E170 analyzer (Roche Diagnostics, Indianapolis, IN). hs-CRP was analyzed by particle-enhanced immunonephelometry with the BNII System (Dade Behring, Marburg, Germany) using a lower detection limit of 0.175 mg/L.

All computed tomography scans were obtained with a Lightspeed VCT XTe-64 slice MDCT scanner (GE Healthcare, Tokyo, Japan) with the same standard scanning protocol using 40×2.5 mm section collimation, 400 msec rotation time, 120 kV tube voltage, and 124 mAS (310 mA*0.4 second) tube current under electrocardiographic-gated dose modulation. The quantitative CAC scores were calculated according to the method described by Agatston et al. (30) The presence of pre-clinical coronary artery calcium was defined by CAC scores >0.