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High-sensitivity C-reactive protein in the low- and intermediate-Framingham risk score groups: Analysis with ^{18}F-fluorodeoxyglucose positron emission tomography

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ABSTRACT

Objectives: To evaluate vascular inflammation according to high-sensitivity C-reactive protein (hsCRP) levels in the low- (<10%) and intermediate- (10%–20%) Framingham risk score (FRS) groups using ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT, which reflects vascular inflammation and vulnerable atherosclerotic plaque.
Methods: We measured hsCRP levels and traditional cardiovascular risk factors in 142 non-diabetic subjects without history of cardiovascular disease. To assess the vascular influence of hsCRP on each FRS category, we compared carotid intima-media thickness (CIMT), brachial-ankle pulse wave velocity (baPWV), and vascular inflammation, which was represented as the target-to-background ratio (TBR) measured using FDG-PET/CT.
Results: In both low- and intermediate-FRS categories, mean TBR values in subjects with higher hsCRP levels (≥2 mg/L) were significantly increased compared to those with lower hsCRP levels (<2 mg/L) ($P = 0.001$, $P<0.001$, respectively). However, baPWV and CIMT values did not significantly differ according to hsCRP levels in the same FRS categories. Mean TBR levels positively correlated with FRS, body mass index (BMI), whereas negatively correlated with HDL-cholesterol. Multiple stepwise regression analyses showed that hsCRP, LDL-cholesterol, BMI, and insulin resistance were independently associated with mean TBR values ($R^2 = 0.414$).
Conclusions: In both intermediate and low FRS risk groups, vascular inflammation measured using FDG-PET/CT was increased in individuals with higher hsCRP levels compared to those with lower hsCRP. (Clinicaltrials.gov: NCT01022684).

1. Introduction

Major cardiovascular and cerebrovascular events, including myocardial infarction and stroke, often occur in individuals without known preexisting cardiovascular disease (CVD). Thus, assessing the risk for developing coronary heart disease (CHD) in asymptomatic individuals has been a pivotal challenge for clinicians. Framingham risk score (FRS) is a standard clinical tool for assessing global 10-year CHD risk in this population. However, only a small proportion of asymptomatic US adults (<1% of women and approximately 5% of men) are classified as "high risk" for CVD by their FRS, and they are currently the primary candidates for intensive intervention [1]. Therefore, there is critical need for additional risk assessment methods, especially in individuals that are not classified in the FRS high risk group.

High-sensitivity C-reactive protein (hsCRP) is a candidate biomarker for CHD prediction as well as a marker of systemic inflammation. hsCRP has been found in atherosclerotic plaques [2] and is associated with most of the risk factors for CHD. Furthermore, more than 20 prospective studies have demonstrated that increased hsCRP levels are associated with an increased risk of cardiovascular (CV) events, even after multivariate adjustment for traditional risk factors [1]. When hsCRP is added to standard risk assessment such as FRS, many patients with intermediate risk can be more accurately reclassified into either the low- or high-risk groups [3].

The inflammatory state and biological composition of an atherosclerotic plaque, rather than the degree of stenosis, are known to be the major determinants of acute cardiovascular events [4]. Recently, positron emission tomography (PET) with ^{18}F-fluoro-deoxyglucose (FDG) has emerged as a novel imaging technique to identify vascular inflammation [5]. Tawakol et al. reported significant correlation between the PET signal from carotid plaques and macrophage staining

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from the corresponding histological sections ($r = 0.70$; $P < 0.0001$) [6]. Rudd et al. demonstrated that atherosclerotic plaque inflammation can be imaged with FDG-PET/CT, and that symptomatic, unstable plaques accumulate more ^{18}FDG than asymptomatic lesions [7]. It has also been reported that the FDG uptake in carotid atherosclerosis measured by FDG-PET/CT is positively associated with cardiovascular risk factors, including the components of the metabolic syndrome [8]. Therefore, FDG-PET/CT has been recognized as an advanced imaging approach that evaluates atherosclerotic vascular disease and vulnerable plaques [9].

In the present study, we examined the impact of increased hsCRP on atherosclerosis, stratified by FRS categories, in subjects without histories of CVD. Atherosclerosis risk was measured by examining carotid intima-media thickness (CIMT), brachial-ankle pulse wave velocity (baPWV), and target-to-background ratios (TBR) measured using FDG-PET/CT, which indicate atherosclerotic burden, arterial stiffness, and vascular inflammation, respectively.

2. Materials and methods

2.1. Study design and subjects

We used predefined inclusion and exclusion criteria to consecutively enroll 142 apparently healthy participants who underwent a medical check-up in the health promotion center of the Korea University Guro Hospital. All participants had no history of cardiovascular disease (myocardial infarction, unstable angina, stroke, peripheral artery disease, or cardiovascular revascularization), diabetes, stage 2 hypertension (resting blood pressure ≥160/100 mm Hg), malignancy, or severe renal or hepatic disease. Participants were free of any lipid-lowering therapies and postmenopausal hormone replacement therapy for at least the 6-month period prior to enrollment. We also excluded subjects with a history of inflammatory conditions or those taking medications that might affect inflammatory status within 6 months. Finally, we excluded subjects who had ≥20% of FRS in this study. All participants provided written informed consent and the Korea University Institutional Review Board, in accordance with the Declaration of Helsinki of the World Medical Association, approved this study protocol.

2.2. Anthropometric and laboratory measurements

The body mass index (BMI) was calculated as weight/height^2 (kg/m^2) and waist circumference was measured at the midpoint between the lower border of the rib cage and iliac crest. All blood samples were obtained in the morning after a 12-hour overnight fast, and were immediately stored at −80 °C for subsequent assays. Serum triglycerides and HDL cholesterol were determined enzymatically using a chemistry analyzer (Hitachi 747, Tokyo, Japan). The LDL cholesterol concentration was estimated using the Friedewald formula [10]. A glucose oxidase method was employed to measure plasma glucose. High-sensitivity C-reactive protein (hsCRP) levels were checked by a chemiluminescence immunoassay (Beckman, Coulter, USA).

2.3. Measurement of carotid intima-media thickness (CIMT) and pulse wave velocity (PWV)

The IMT of the common carotid artery was determined using high-resolution B-mode ultrasonography (EnVisor, Philips Medical Systems, Andover, MA, USA) with a 5–12 MHz transducer. Measurements of carotid IMT were made using the IMT measurement software Intimascope (Media Cross Co., Tokyo, Japan) at 3 levels of the lateral and medial walls, 1 cm to 3 cm proximal to the carotid bifurcation. Mean IMT was the average value of 99 computer-based points in the region, and maximal IMT was the IMT value at a maximal point of the region. Using a Colin Waveform Analyzer (model BP-203RPE II; Colin, Komaki, Japan), baPWV was measured. Extremity blood pressure was measured using an oscillometric method, and ankle-brachial pressure index (ABI) was automatically calculated. Right brachial-ankle PWV (rt. baPWV: right upper arm-right ankle), left brachial-ankle PWV (lt. baPWV: right upper arm-left ankle) and mean brachial-ankle PWV (baPWV) were also measured and calculated. The reproducibility of this method was reported previously [11]. All measurements were recorded by a single trained technician who was blinded to the subject's anthropometric and laboratory data.

2.4. FDG-PET/CT imaging

FDG-PET/CT was performed using the Gemini TF 16 Slice PET/CT scanner (Philips Medical Systems, Cleveland, USA). This TF scanner is a new high-performance, time-of-flight (TOF) capable, fully 3-dimensional (3D) PET scanner using lutetium-yttrium oxyorthosilicate (LYSO) crystals. After at least 12 h of fasting, ^{18}F-FDG (370–550 MBq) was injected intravenously, and patients rested in a quiet room for 60 min. Whole body PET image (below cerebellum to inguinal) was acquired for 10 min (1 min per bed). PET image analysis was performed on a dedicated workstation (Extended Brilliance Workspace 3.5 with PET/CT viewer for automated image registration, Philips). Right carotid FDG uptake was measured along the length of the right carotid vessel, starting at the bifurcation and extending inferiorly and superiorly every 4 mm. Arterial FDG uptake was quantified by defining a region of interest (ROI) around each artery on every slice of the coregistered transaxial PET/CT images. The ROI was fitted to the artery wall on each axial slice, and coronal and sagittal views were used to ensure that the FDG uptake was from the artery. The standardized uptake value (SUV) is the decay-corrected tissue concentration of FDG (in kBq/mL) divided by the injected dose per body weight (kBq/g). The arterial SUV value was normalized to the blood pool SUV value measured from the jugular vein (standardized circular ROIs; the right carotid artery, area = 77.9 ± 3.42 mm^2, 9 pixels and the right jugular vein, area = 95.0 ± 12.7 mm^2, 9 pixels). Afterward, the target-to-background ratio (TBR) was calculated as the right carotid vessel wall SUV divided by venous blood SUV, and a mean and maximum value of TBR was calculated for each patient. To determine the variability of the mean and maximum TBR measurements, images from 20 subjects were twice analyzed, several weeks apart, by two readers who were blinded to the subject's clinical history. The intra- and inter-observer correlation coefficient values of mean and maximum TBR measurements were greater than 0.8.

2.5. Statistical analysis

Data are expressed as mean ± SD. Differences between groups were tested using the independent two-sample *t*-test, Mann–Whitney *U* test, or χ^2 test. Spearman rank correlation tests were performed to determine the relations between mean TBR, FRS, hsCRP, PWV, CIMT values and other cardiovascular risk variables. Multiple regression analysis was conducted using TBR as a dependent variable. Age, gender, BMI, waist circumference, systolic blood pressure, diastolic blood pressure, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglyceride, HOMA-IR and hsCRP levels were adopted as independent variables. Data were analyzed using SPSS for Windows (version 12.0; SPSS Inc., Chicago, IL, USA). A P value <0.05 was accepted as indicating statistical significance.

3. Results

3.1. Patient characteristics

Clinical and biochemical characteristics of the study subjects are shown in Table 1. In the low-risk group (FRS <10%), subjects with higher hsCRP levels (≥2 mg/L) had increased BMI, waist circumference, blood pressure, triglyceride, glucose, and HOMA-IR compared to those with lower hsCRP levels (<2 mg/L). However, there was no significant difference in anthropometric or laboratory parameters according to hsCRP levels in the intermediate-risk group (10% ≤ FRS < 20%).

3.2. Imaging and clinical parameters

By Spearman correlation analysis, mean TBR levels were positively correlated with FRS, BMI, waist circumference, LDL-cholesterol, triglyceride, creatinine, glucose, and hsCRP, whereas negatively correlated with HDL-cholesterol. Although baPWV levels positively correlated with mean TBR values, CIMT levels did not (Table 2).

Importantly, mean TBR values were significantly higher in subjects with higher hsCRP in both the low- and intermediate-risk FRS groups (1.13 ± 0.12 vs. 1.41 ± 0.23, $P < 0.001$; 1.15 ± 0.08 vs. 1.42 ± 0.16, $P = 0.001$, respectively), compared to those with lower hsCRP in the same risk group. However, CIMT and baPWV values did not significantly differ according to hsCRP in both the low- and intermediate-risk groups, although they showed increased tendency.

In multiple stepwise regression analyses, performed using mean TBR as a dependent variable, hsCRP ($P < 0.001$), LDL-cholesterol ($P < 0.001$), BMI ($P = 0.002$), and HOMA-IR ($P = 0.014$) were significantly associated with mean TBR values ($R^2 = 0.414$) (Table 3).

4. Discussion

This study showed for the first time that, within the low- and intermediate-FRS group, vascular inflammation measured using FDG-PET/CT is increased in individuals with higher hsCRP levels compared to those with lower hsCRP levels. These results suggest that hsCRP may be useful as an influential supplement factor for cardiovascular risk stratification.