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The role of insulin resistance and metabolic risk factors on culprit coronary plaque

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ABSTRACT

Background: Detailed relationships between insulin resistance (IR) and vulnerable plaque are not clear, therefore, we sought the role of IR and metabolic risk factors on culprit coronary plaque.
Methods: Plaque components at a region of interest (ROI, 10 mm) were analyzed by virtual histology intravascular ultrasound. IR was defined as quantitative insulin sensitivity check index (QUICKI) ≤0.33. Seven metabolic risk factors (5 risk factors for metabolic syndrome defined by ATP III, history of smoking, and hsCRP) for IR were determined.
Results: The data for 150 (males 104) patients were analyzed. Patients with IR (n = 69) had greater necrotic core (NC) at the ROI (21.2 ± 15.8 mm^3 vs 15.7 ± 11.9 mm^3, p = 0.02) than in patients without IR (n = 81). The NC at the ROI was correlated with QUICKI (r = −0.16, p = 0.05), HbA1c (r = 0.24, p < 0.01), body mass index (r = 0.17, p = 0.04), presence of diabetes mellitus (r = 0.29, p < 0.001), hsCRP (r = 0.17, p = 0.04) and the numbers of risk factors for IR (r = 0.41, p < 0.001). The multivariate analysis revealed that the numbers of risk factors for IR was an independent factor for the NC at the ROI (beta coefficient = 0.44, p = 0.003), but QUICKI was not (beta coefficient = −0.01, p = 0.94).
Conclusions: Instead of a single measurement of IR index or each metabolic risk factor, clustering of risk factors for IR plays an important role on plaque vulnerability.
Condensed abstract: We investigated the role of insulin resistance (IR) on culprit coronary plaque. Patients with IR had a greater amount of necrotic core in culprit coronary lesions than in patients without IR. Rather than a single measurement of IR index or each metabolic risk factor, clustering of metabolic risk factors for IR plays an important role in plaque vulnerability in patients with coronary artery disease. Our study demonstrates the role of IR on culprit coronary plaque and highlights the importance of the clustering of metabolic risk factors for IR in vulnerable plaque pathogenesis.

1. Introduction

Vulnerable plaques are high-risk atherosclerotic lesions and complications of these plaques such as plaque rupture, luminal and mural thrombosis, intraplaque hemorrhage, rapid progression in stenosis severity and spasm lead to acute coronary syndrome [1]. Recently, spectral analysis of virtual histology intravascular ultrasound (VH-IVUS) radiofrequency data has demonstrated potential to provide detailed quantitative information on plaque morphology and component: fibrous, fibro-fatty, dense calcium and lipid-rich necrotic core (NC) and has been validated in studies of explanted human coronary segments [2]. Unstable, lipid-rich plaques are believed to play a key role in these events and to quantify the amount of NC in lesions could be a potential measure for plaque vulnerability and further risk stratification [3].

Insulin resistance (IR) plays a major pathophysiological role in atherosclerotic cardiovascular diseases and is related to adverse cardiovascular outcome [4–10]. It has been reported that metabolic syndrome was associated with the lipid-rich plaque in non-culprit coronary lesions and lesions in pre-intervention on three coronary vessels [11,12] and hyperinsulinemia and abnormal glucose regulation were associated with lipid rich coronary plaque by intracoronary imaging methods [10,13]. However, there is no data for the independent role of IR index and detailed relationships between IR including metabolic risk factors and plaque vulnerability in culprit coronary lesions. In the present

Abbreviations: BMI, body mass index; CAD, coronary artery disease; CSA, cross sectional area; DC, dense calcium; EEM, external elastic membrane; FBS, fasting blood sugar; FF, fibro-fatty; HbA1c, glycated hemoglobin; hsCRP, high sensitivity C-reactive protein; IFG, impaired fasting glucose; IR, insulin resistance; IVUS, intravascular ultrasound; MI, myocardial infarction; NC, necrotic core; QUICKI, using quantitative insulin sensitivity check index; ROI, region of interest; TCFA, thin cap fibroatheroma; VH-IVUS, virtual histology intravascular ultrasound.

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study, we compared the plaque characteristics between patients with IR and without IR and sought the role of IR including metabolic risk factors on culprit coronary plaque.

2. Patients and methods

2.1. Patients and study design

This study was a cross sectional study which used the data from the registry in patients with coronary artery disease (diameter stenosis > 50%) who underwent VH-IVUS before percutaneous coronary intervention by operators' discretion. Between August 2008 and September 2011, 258 consecutive patients were enrolled. We excluded patients with previous coronary stent insertion, manual pullback of IVUS catheter, coronary artery bypass graft failure, and patients with inadequate IVUS images. Also patients with a left ventricular ejection fraction of less than 35% and severe hepatic and renal disease were excluded. To avoid the effects of insulin on insulin sensitivity index, diabetic patients who required insulin treatment were also excluded. In patients who underwent multi-vessel VH-IVUS, the lesion with the worst diameter stenosis and more complex morphology was selected for VH-IVUS analysis. Finally, 150 patients with analyzable IVUS images of native coronary vessels, pullback length greater than 10 mm, and with complete clinical and laboratory value, were enrolled to this analysis. Hospital records of patients were reviewed to obtain information on clinical demographics. The local Institutional Review Board approved this study, and written informed consents were obtained from all patients.

2.2. IVUS procedure and analysis

Before the performance of gray-scale and VH-IVUS examination, patients were administered an intracoronary 0.2 mg of nitroglycerin to prevent coronary spasm. A 20-MHz, 2.9 F IVUS imaging catheter (Eagle Eye, Volcano Corp., Rancho Cordova, CA, USA) was advanced more than 10 mm beyond the lesion; and automated pull-back was performed to a point more than 10 mm proximal to the lesion at a speed of 0.5 mm/s.

Quantitative volumetric gray-scale and VH-IVUS analyses were performed across the entire lesion segment, and cross-sectional analysis was performed at the region of interest (ROI) and at the minimal lumen site. The IVUS region of interest (ROI) was the most diseased 10 mm segment, identified by summarizing plaque volume in contiguous cross sections over an axial distance of 10 mm. Therefore, the segment with the greatest plaque volume constituted the most diseased 10 mm.

Conventional quantitative volumetric gray-scale IVUS analysis was performed according to the American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies [14]. External elastic membrane (EEM) and lumen cross-sectional areas (CSAs) were identified using automatic edge detection and manually corrected when necessary. Plaque plus media CSA was calculated as EEM minus lumen CSA; and plaque burden was calculated as plaque plus media divided by EEM CSA.

The IVUS-VH data were stored on a CD-ROM for offline analysis. Subsequently, VH-IVUS analysis classified the color-coded tissue into four major components: (fibrous [F, labeled green], fibro-fatty [FF, labeled greenish-yellow], dense calcium [DC, labeled white] and necrotic core [NC, labeled red]) [3]. VH-IVUS analysis was reported as absolute plaque amounts and as percentages (relative amounts). Thin-cap fibroatheroma (TCFA) was defined as focal, NC-rich (≥10% of the CSA) plaques being in contact with the lumen in a plaque burden ≥ 40% over three consecutive frames. Analyses were conducted by 2 independent investigators unaware of the clinical data and the mean value was calculated. Inter-observer correlations was excellent, with correlation coefficients (r) being ≥0.90.

2.3. Coronary risk factors and lipids, metabolic parameters

Diabetes mellitus was defined as fasting glucose ≥ 126 mg/dL or 2 h postprandial glucose ≥ 200 mg/dl or glycated hemoglobin (HbA1c) ≥ 6.5%, or if they were already being treated for this condition. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg, or if they were already being treated for this condition. Body mass index (BMI) was calculated as body weight in kilograms divided by the square of height in meters (kg/m^2).

Blood samples for laboratory assays were obtained at the time of coronary angiography following overnight fasting for at least 8 h. Total cholesterol and triglycerides were analyzed with enzymatic methods (Shinyang Chemical, Seoul, Korea), and high density lipoprotein (HDL) cholesterol by a direct immunoinhibition method (Wako Pure Chemical, Osaka, Japan). LDL cholesterol was calculated using the Friedewald equation [15]. Fasting blood sugar (FBS) was determined by the hexokinase method (Shinyang Chemical, Seoul, Korea) using a Hitachi 7600-110. Assays for plasma insulin levels were performed by immunoradiometric assay (INSULIN-RIABEAD® II, TFB, Inc., Tokyo, Japan). Assays for glycated hemoglobin (HgA1c) were measured by high performance liquid chromatography assay (VARIANT II TUR BO®, BIORAD, Inc., Hercules, California). High sensitivity C-reactive protein (hsCRP) levels were determined with a turbidimetric assay (Denka Seiken, Tokyo, Japan) using the Hitachi 7600-110. History of smoking was obtained from all patients.

2.4. Insulin resistance (IR) index, numbers of risk factors for IR

IR index was determined from plasma glucose and insulin concentrations, using quantitative insulin sensitivity check index (QUICKI) and calculated by using the formula; 1 / (log insulin (μU/ml) + log glucose (mg/dL)) [16]. Patients with IR was defined as QUICKI ≤ 0.33 by the previous studies [17,18].

Numbers of risk factors for IR (0–7) were derived from the sum of risk factors which were related with IR from the previous reports [19–24]. These include 1) high BMI > 25 (kg/m^2), 2) impaired fasting glucose (IFG, FBS ≥ 110 mg/dL) or diabetes mellitus, 3) hypertension, 4) hypertriglyceridemia (triglyceride ≥ 150 mg/dL), 5) low HDL cholesterol (male < 40 mg/dL, female < 50 mg/dL), 6) history of smoking, and 7) high hsCRP > 1.0 mg/L. The diagnosis for metabolic syndrome was made by patients who had more than 3 risk factors among 1–5) risk factors for IR. Each criterion for metabolic syndrome was slightly modified for this study.

2.5. Cardiovascular diagnosis

Acute coronary syndromes included unstable angina, non-ST elevation myocardial infarction (MI), or ST elevation MI according to American College of Cardiology/American Heart Association guidelines [25]. The diagnosis of acute MI was based on elevation of at least 1 positive biomarker (creatine kinase, creatine kinase-MB, or troponin T), characteristic electrocardiogram changes, and a history of prolonged acute chest pain. Unstable angina pectoris was defined as either angina with a progressive crescendo pattern or angina that occurred at rest. Stable angina pectoris was defined as no change in the frequency, duration, or intensity of symptoms within 4 weeks before the intervention.

2.6. Data analysis

Patients were divided into two groups according to the presence of IR. Variables were analyzed to compare the characteristics of patients with or without IR. Continuous variables were expressed as