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Low plasma adiponectin levels are associated with presence of thin-cap fibroatheroma in men with stable coronary artery disease

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Abstract

Background: Previous studies demonstrated the inverse association of adiponectin with coronary artery disease (CAD) especially in men with acute coronary syndrome, however their association with in vivo plaque vulnerability in stable CAD, which may be reflected by the thin-cap fibroatheroma (TCFA) prevalence, remains unknown.

Methods: In 50 men with stable CAD, we identified TCFA with multi-vessel examination of combined use of virtual histology intravascular ultrasound (VH-IVUS) and optical coherence tomography (OCT). The definition of TCFA was described as follows; necrotic-core rich lesion (% necrotic-core >10%) without evidence of an overlying fibrous component and % plaque-volume >40% in at least 3 consecutive frames by VH-IVUS, and the thinnest fibrous-cap thickness <65 μm by OCT. The patients were divided into two groups, patients with TCFA and without TCFA, and plasma adiponectin level was compared between the groups.

Results: Among 50 patients, we could observe 116 vessels (2.32±0.47 vessel/patient). At least one TCFA was identified in 20 patients. Patients with TCFA had significantly lower plasma adiponectin levels than patients without TCFA ($P<0.0001$). Furthermore, the plasma adiponectin levels in patients with multi-vessel TCFA were significantly lower than those in patients with single-vessel TCFA ($P=0.049$). Multivariate logistic regression analysis revealed that plasma adiponectin was the strongest predictive factor of the presence of TCFA ($P=0.0007$).

Conclusions: Low plasma adiponectin was associated with the presence of TCFA in men with stable CAD. This finding suggests that, in these subjects, it may be a biomarker that can be used to stratify "vulnerable patients" into risk categories.

Keywords: Thin-cap fibroatheroma; Adiponectin; Optical coherence tomography; Virtual histology intravascular ultrasound

1. Introduction

Lipid and blood sugar profiles [1] and inflammatory markers [2] are thought to be the promising predictors of acute coronary syndrome (ACS). Besides, recent reports revealed that low plasma level of adiponectin, an abundant circulating hormone secreted predominantly from adipocytes [3], is an independent risk factor of coronary artery disease (CAD) [4,5], and is associated with increased risk of future myocardial infarction [6] and cardiac mortality [7] in men. Furthermore, low plasma adiponectin level is associated with angiographic coronary lesion complexity in men with CAD [8] and the necrotic core ratio of atherosclerotic plaque in ACS patients based on VH-IVUS analysis [9]. Thus, adiponectin may have anti-atherogenic properties, and affects plaque components, lesion morphology, and plaque

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vulnerability. These effects seem to be massive in patients with ACS [4–9]. However, the association between adiponectin levels and more detailed intra-coronary plaque vulnerability in stable CAD patients, such as a necrotic core volume, necrotic core distribution and fibrous-cap thickness, which may be reflected by the presence of thin-cap fibroatheroma (TCFA) [10,11], remains to be fully clarified. In the present study, we focused on men because several studies have reported that gender-dependent differences in plasma adiponectin were found and androgen-induced hypoadiponectinemia are related to the high risk of atherosclerosis in men [12]. Thus, we hypothesized that adiponectin affects an intra-coronary plaque vulnerability and is useful for stratifying "vulnerable patients" into risk category in men with stable CAD. To investigate this hypothesis, we identified TCFA by the combined use of VH-IVUS and OCT, that is the optimum method for detecting in vivo TCFA [13], and evaluated the association between plasma adiponectin levels and the presence of TCFA in these subjects.

2. Material and methods

2.1. Study subjects

Between April 2006 and June 2008, 531 patients with CAD underwent coronary angiography in our hospital. The exclusion criteria included women ($n=199$) and patients ($n=114$) with unstable CAD requiring emergency percutaneous coronary intervention (PCI). Therefore, 218 men with stable CAD were enrolled into the study. Stable CAD was defined as a significant coronary stenosis (angiographically >75% stenosis) causing apparent myocardial ischemia or a past history of PCI, and the absence of a change in symptom frequency, duration, or intensity over 4 weeks. To ensure safety during the OCT procedure, we excluded patients ($n=54$) with vessels that had a chronically total occluded lesion, heavily calcified lesion, significant left main artery disease, or severe tortuous lesion that might cause difficulty in advancing the IVUS or OCT catheters. We also excluded patients ($n=53$) with a lesion that required PCI before IVUS or OCT examination because the plaque morphology and fibrous-cap might be affected. Of the remaining 111 patients, 55 patients did not provide consent for an invasive intra-coronary examination, and the remaining 56 patients allowed us to perform the VH-IVUS and OCT examination. Patients ($n=6$) with chronic inflammatory disease (infection, collagen disease, malignancy, etc) or treated with hemodialysis were also excluded to rule out a secondary cause of a change in biomarker levels. Of the remaining 50 men with stable CAD, we were able to obtain multi-vessel imaging with both OCT and VH-IVUS and this group was included in the analyses presented here.

In these patients, we analyzed the vessels with lesions that were angiographically stenotic by more than 25% by both VH-IVUS and OCT. We did not image angiographically normal vessels because of the low probability of finding plaque. We also did not image small and large vessels (reference diameter either <1.5 mm or >4.0 mm) because we assumed that the IVUS and OCT occlusion catheters could not be inserted in the small vessels and that the OCT occlusion catheter could not occlude the coronary flow in the large vessels.

We assessed patient characteristics, including age, body mass index, presence of coronary risk factors (hypertension, hyperlipidemia, diabetes mellitus, smoking), and medication. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive drugs. Hyperlipidemia was defined as a present or past history of LDL cholesterol level ≥140 mg/dl, or use of statin. Diabetes mellitus was defined as a fasting blood sugar >126 mg/dl and hemoglobinA1c ≥6.4%, or use of antidiabetic medications (insulin or oral hypoglycemics).

All patients provided written informed consent for their participation in the study. This study was approved by the Ethics Committee of Kobe University.

2.2. Angiographic analysis

Cineangiograms were analyzed with a computer-assisted, automated edge detection algorithm (CMS-Medis Medical Imaging Systems, Leiden, the Netherlands). The outer diameter of the contrast-filled catheter was used for calibration and the minimal lumen diameter was obtained from the single worst view. The traditional lesion type was assessed according to the AHA/ACC classification [14] and the plaque location was mapped (proximal, mid, or distal from vessel).

2.3. Image acquisition

All imaging procedures were performed after the administration of intracoronary nitrates (250 μg). First, a 2.9Fr 20-MHz IVUS catheter (EagleEye™; Volcano Therapeutics, Inc., Rancho Cordova, CA) was introduced into the distal coronary artery. Using a motorized pullback device, the IVUS transducer was withdrawn at a rate of 0.5 mm/s until the coronary ostium was observed. Gray-scale IVUS and VH-IVUS data were stored on a CD-ROM/DVD for off-line analysis.

Then, a 0.016-inch OCT wire (ImageWire™, LightLab Imaging Inc) was advanced to the distal end of the coronary artery through an over-the-wire type 3.0Fr occlusion balloon catheter (Helios™, LightLab Imaging Inc, Westford, MA). To clear blood from the imaging site, the occlusion balloon was inflated to 0.5 atm in the vicinity of each coronary artery ostium (except for the left main branch) and Lactated Ringer's solution was infused at 0.5 ml/s. The entire length of the vessel was imaged with an automatic pullback device at 1 mm/s and OCT data were also recorded on a CD-ROM for off-line analysis.

2.4. Image analysis

In this study, we identified plaques based on the gray-scale IVUS findings, and then analyzed each plaque using both VH-IVUS and OCT. A single plaque was defined as a lesion spanning from one normal reference site, which had no evidence of intimal thickening by gray-scale IVUS examination, to the next normal reference site.

A 3D-reconstruction of volumetric IVUS data was performed using a semi-automated quantitative coronary ultrasound cardiovascular measurement system (CMS-Medis Medical Imaging Systems). After counter-detection of both the lumen and vessel interface in each cross-sectional frame, lesion length, lumen volume, vessel volume, and plaque volume (vessel volume – lumen volume) were calculated. Vessel volume and plaque volume were expressed as volume per unit length (mm^3/cm). We then used these data to calculate the % plaque-volume (plaque volume/vessel volume), and remodeling-index (vessel cross sectional area of minimum lumen site/averaged reference vessel cross sectional area). Using version 2.0 VH software, raw radio frequency plaque data were classified as fibrotic, fibro-fatty, dense calcium, and necrotic core components. Plaque components were represented as the ratio of plaque volume (% fibrous, % fibro-fatty, % dense-calcium, % necrotic-core), and also volume of each component (fibrous volume, fibro-fatty volume, dense-calcium volume, necrotic-core volume) was expressed as volume per unit length (mm^3/cm).

OCT images of a signal poor lesion with an unclear border was diagnosed as a lipid core and a signal rich homogenous lesion overlying the lipid content was diagnosed as a fibrous-cap [15]. The thinnest part of the fibrous-cap was measured 3 times and the average value calculated.

According to previous pathologic reports, TCFA are unlikely to be present in segments with less than 40% occlusive lesion and nearly 90% of ruptured plaques had a greater than 10% necrotic core in the plaque area [10] and 95% of ruptured sites have a fibrous-cap thickness of less than 65 μm