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Relation between Plasma Adiponectin, High-Sensitivity C-Reactive Protein, and Coronary Plaque Components in Patients With Acute Coronary Syndrome

Running title: Coronary Plaque Components in ACS Patients

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Abstract

The present study investigated the relation between plasma high-sensitivity C-reactive protein (hs-CRP) and adiponectin levels, and coronary plaque components in patients with acute coronary syndrome (ACS). Previous studies demonstrated a pivotal role of inflammation in the progression of atherosclerosis and the prognostic values of several biomarkers, however the relationship among inflammatory biomarkers and plaque characteristics remains unknown. We analyzed 93 culprit plaques (ACS: n=50, non-ACS: n=43) and 56 non-culprit plaques (ACS: n=28, non-ACS: n=28) using intravascular ultrasound virtual histology (IVUS-VH) to examine the relationship among plasma hs-CRP levels, adiponectin levels, and the ratio of each coronary plaque component. Plasma adiponectin levels were significantly lower and plasma hs-CRP levels were significantly higher in patients with ACS than those in patients with non-ACS. Culprit plaques in patients with ACS had greater amounts of necrotic core plaque than those in patients with non-ACS. There was an inverse relationship between serum hs-CRP and adiponectin levels with regard to the necrotic core ratio, both in culprit and non-culprit lesions in patients with ACS, but not non-ACS. In conclusion, increased plasma hs-CRP and hypo-adiponectinemia might be related to the progression of ACS.

Key words: vulnerable plaque, plaque character, adiponectin, hs-CRP
Introduction

Adiponectin is an adipocyte-derived protein with anti-atherogenic and anti-inflammatory properties (1,2). Several studies have demonstrated an inverse relationship between serum C-reactive protein (CRP) and adiponectin levels (3,4). We hypothesized that CRP and adiponectin affect coronary plaque properties, especially in acute coronary syndrome (ACS) patients, in whom disease progression are strongly affected by inflammation. Several studies showed that CRP (5) and adiponectin (6) are related to lesion complexity, however, the qualitative assessment was not performed. Therefore, we investigated the relation among serum high-sensitivity CRP (hs-CRP) and adiponectin levels, and plaque components using Spectral analysis of intravascular ultrasound (IVUS) radiofrequency technology (Virtual Histology™ IVUS technology: VH-IVUS) (7).

Method

Between April 2005 and January 2006, 63 consecutive patients with ACS that underwent coronary intervention were enrolled in the study. As a control group, we examined 43 consecutive chronic stable angina patients with VH-IVUS imaging. The ACS group consisted of patients with recent myocardial infarction and unstable angina pectoris, whereas the non-ACS group consisted of patients with stable angina. Unstable angina was defined as new-onset severe angina, accelerated angina, or rest angina, and recent myocardial infarction was defined as an
occurrence within the preceding 4 weeks. Stable angina was defined as no change in frequency, duration, or intensity of symptoms within 4 weeks. Culprit lesions were identified by analyzing pre-crisis and inter-crisis electrocardiograms (ECG), left ventricular wall motion abnormalities, and angiographic lesion appearance.

Patients with active inflammatory disorders, chronic total occlusions, and severe angulations or calcification in a major epicardial artery were excluded. The local research ethics committee approved the study protocol, and all patients provided written informed consent.

Cineangiograms were analyzed with a computer-assisted, automated edge detection algorithm (CMS, MEDIS, Leesburg, VA) using standard protocols (8). All parameters were calculated for both culprit lesions and non-culprit lesions. Because some non-culprit plaques were completely undetectable by angiogram, information from the IVUS study was necessary to identify the plaque location.

Percutaneous intracoronary thrombectomy was performed using a thrombectomy catheter (Thrombuster; Kaneka Medix Corp, Japan) for all ACS cases before IVUS-VH imaging to avoid mischaracterizing afforded by thrombus. Several aspirations at the occlusion site were performed until a flexible, soft thrombectomy catheter could be smoothly introduced and advanced. The ECG-gated IVUS-VH examinations were performed in percutaneous coronary intervention target plaque and non-target plaque in the following manner. After intracoronary administration
of 0.2 mg nitroglycerin, the IVUS catheter (Eagle Eye Gold™, Volcano Therapeutics, Inc., Rancho Cordova, CA) was positioned sufficiently distal (>10 mm distal) to the percutaneous coronary intervention site. Pullback and IVUS-VH data acquisition were performed automatically at 0.5 mm/s using an automated pullback device, with a dedicated IVUS-VH console (Volcano Therapeutics) before intervention.

After successful pre-interventional imaging and treatment for the culprit lesion, IVUS examinations of the remaining non-culprit lesions with mild to moderate stenosis within the same vessel were performed if the patient had such lesions. The identification of two separate plaques in the same artery (i.e., culprit versus non-culprit plaques) required a greater than 5-mm reference segment between them; otherwise, they were considered to be part of one long culprit lesion. Quantitative IVUS analysis was performed with computerized planimetry, both at the culprit and non-culprit lesions. Using a Netra 3D IVUS system (ScImage, Los Altos, CA), percent plaque volume (%PV) was defined as: vessel volume minus lumen volume/vessel volume×100. Remodeling index was defined as the lesion external elastic membrane (EEM) divided by the mean reference EEM CSA. Quantitative analysis was performed by an independent experienced IVUS investigator blinded to patient groups and to angiographic results.

The IVUS-VH analyses were performed with the investigator blinded with regard to the
Venous blood was drawn from all patients and control subjects just before the procedure. The hs-CRP levels were determined using an ultrasensitive CRP test with a coefficient of variation less than 5% (N Latex CRP; Dade Behring Co Ltd, West Sacramento, CA). The adiponectin concentrations were determined by enzyme linked immunosorbent assay (ELISA) with a coefficient of variation below 5% (Otsuka Pharmaceutical Co Ltd, Japan). Low density lipoprotein cholesterol was determined by a homogeneous direct method from Genzyme Corp (Cambridge, MA). Serum total cholesterol and triglyceride concentrations were determined by an enzymatic method. High-density lipoprotein cholesterol was also measured by an enzymatic method after heparin and calcium precipitation. Plasma glucose was measured by a glucose
oxidase method. The value of hemoglobin A1c was determined by high-performance liquid chromatography. Insulin resistance was assessed by homeostasis model assessment (insulin resistance index = [fasting glucose (mmol/l) × fasting insulin (U/ml)]/22.5(9).

Statistical analysis was conducted with a commercially available software package (StatView ver.5.0, SAS Institute Inc., Cary, NC). For continuous variables, results are presented as mean ± SD. Differences in continuous parameters between the two groups were calculated using an unpaired t-test. Categorical variables were presented using frequency counts, and intergroup comparisons were analyzed by chi square test. Simple correlations between plasma concentrations of adiponectin and the-values of other parameters were examined by Pearson’s coefficient of correlation. P values of 0.05 or less were considered to be statistically significant.

**Results**

Two experienced cardiologists independently reviewed all clinical and angiographic data to determine angina status and culprit lesions. There was no disagreement on angina status or culprit lesion assignment. Among 63 ACS patients, 7 patients with chronic inflammatory disease, 3 patients with severe tortuous lesions, and 3 patients with poor IVUS images were excluded from the final analysis. As a control group, we included 43 consecutive chronic stable angina patients. Thus, 50 ACS patients and 43 non-ACS patients aged 44 to 88 years (mean age: 66) constituted the final-study population.
The plaques were divided as follows: culprit lesions of ACS patients (n=50), nonculprit lesions of ACS patients (n=28), culprit lesions of non-ACS patients (n=43), and non-culprit lesions of non-ACS patients (n=28).

Baseline patient characteristics are listed in Table 1. There were no significant differences in the patient characteristics between the ACS and non-ACS groups, except for the use of angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor (AT1) blockade.

The study vessel was the left anterior descending artery in 38 (41%) patients, the left circumflex artery in 26 (28%), and the right coronary artery in 29 (31%). Although there were no significant differences between the two groups in lesion characteristics, the minimum lumen diameter of the ACS group was significantly smaller than that of the non-ACS group (Table 2).

Table 3 shows the baseline data of conventional Gray-scale IVUS analysis of the culprit lesions. Reference vessel parameters were similar between the two groups. The ACS group, however, had a smaller lumen cross-sectional area compared with the non-ACS group (2.7±0.8 mm² vs 3.2±1.1 mm², P=0.04) at a minimum lumen site, and the ACS group tended to have a greater remodeling index than the non-ACS group (1.27±0.46 vs 1.12±0.26, P=0.09). Figure 1 shows the four relative quantifications of the culprit plaque. Necrotic core plaque occupied 17.3±7.3% of the ACS culprit lesion plaque volume and 14.2±6.5% of the non-ACS lesion plaque volume (P =0.03), whereas there were no significant differences between the two groups in the other three
culprit plaque components (Figure 1A). Plasma adiponectin levels were significantly lower and plasma hs-CRP levels were significantly higher in patients with ACS than those in patients with non-ACS (adiponectin: $7.2 \pm 4.0 \mu g/ml$ vs $10.4 \pm 5.2 \mu g/ml$, $P=0.001$, hs-CRP: $3.5 \pm 3.8$ mg/L vs $1.9 \pm 2.5$ mg/L $P=0.03$; Table 1). Other biomarkers were not statistically different between the two groups (Table 1).

The NC component ratio in the culprit plaque was positively correlated with plasma hs-CRP levels only in patients with ACS ($P=0.01$, $r=0.36$ Figure 2D). Also, the NC component ratio in culprit lesions was negatively correlated with plasma adiponectin levels only in patients with ACS ($P=0.04$, $r=-0.29$ Figure 3D). Furthermore, the fibro-fatty ratio positively correlated with the level of adiponectin only in patients with ACS ($P=0.01$, $r=0.34$ Figure 3B). Other culprit plaque components were not significantly correlated with plasma hs-CRP and adiponectin levels. On the other hand, the NC component was not correlated with other biomarkers, such as those listed in Table 1 (data not shown).

There was no significant difference between the two groups in non-culprit lesion characteristics, angiographic analysis, conventional gray-scale IVUS and IVUS-VH data (Fig 1B). There was a positive significant correlation, however, between the hs-CRP level and the NC ratio of non-culprit plaque in patients with ACS ($r=0.39$, $P=0.04$ Fig 4D), but not in non-ACS patients. Furthermore, the adiponectin level positively correlated with the fibro-fatty ratio
(r=0.36 P=0.05 Fig 5B), and it tended to negatively correlate with the NC ratio only in patients with ACS (r=-0.30, P=0.09 Fig 5D). There were no other correlations (Figs. 4 and 5).

**Discussion**

The results of the present study indicated an inverse relation between serum hs-CRP and adiponectin levels in relation to the NC ratio both in culprit and non-culprit lesions of ACS patients. These associations were not observed in non-ACS patients. Furthermore, ACS patients had greater amounts of NC-rich plaque in culprit lesions compared with non-ACS patients. These findings indicate that higher serum hs-CRP and lower adiponectin levels reflect lesion or vessel vulnerability, especially in patients with ACS.

Several recent studies have demonstrated that CRP is synthesized locally in atherosclerotic plaque (10,11) and in higher amounts within unstable plaque compared with stable plaque (12-14). In our study, the serum hs-CRP levels were higher in ACS patients than in non-ACS patients and were positively correlated with NC, not only in culprit plaque, but also in non-culprit plaque in ACS patients. This indicates that serum hs-CRP levels might reflect whole vessel vulnerability, especially in patients with ACS. Previous pathologic studies suggest that the decisive factor determining plaque vulnerability is plaque composition rather than the degree of luminal narrowing (15,16) and that baseline CRP levels predict the risk of cardiovascular events (17,18). Taking these findings into consideration, the positive correlation between hs-CRP and
the NC component ratio in unstable plaque might reflect the degree of inflammation in the process of plaque instability. CRP might be a key functional protein that links inflammation to acute coronary events.

Adipose tissue secretes a variety of bioactive molecules that directly contribute to the development of cardiovascular disease (19). Adiponectin is an adipose-specific plasma protein and low plasma adiponectin concentrations are observed in patients with coronary artery disease (2). Okamoto et al. demonstrated that adiponectin overexpression reduces atherosclerosis by attenuating the endothelial inflammatory response and macrophage-to-foam cell transformation in vivo (20). Therefore, adiponectin has anti-atherogenic properties through anti-inflammatory effects and the inflammatory process might thus be accelerated in patients with low plasma concentrations of adiponectin. Actually, in a clinical study, high plasma adiponectin concentrations are associated with lower risk of myocardial infarction in men (21). In our study, serum adiponectin levels were significantly lower in the ACS group than in the non-ACS group, and the negative correlation between adiponectin level and NC ratio in both culprit and non-culprit plaque was observed only in patients with ACS. The findings of the present study suggest that adiponectin affects the plaque components and low plasma concentrations of adiponectin, a well-known independent risk factor for coronary artery disease, might enhance the vulnerability of atherosclerotic plaques and vessels, which could lead to ACS.
Hypoadiponectinemia is often observed in obesity-linked diseases (22). Visser et al. measured serum hs-CRP levels and reported that a low-level chronic inflammatory state is highly associated with obesity (23). In addition, plasma hs-CRP levels were positively associated with total body fat mass (24) and decreased during weight reduction (25). In a recent study, Ouchi et al. reported that human adipose tissue expresses CRP, and there is an inverse relationship between CRP and adiponectin in both plasma and adipose tissue (26). These results suggest that adipose tissue acts as an important factor in modulating circulating hs-CRP levels with secretion of adiponectin. Among adipocytokines, CRP and adiponectin have opposite properties against insulin resistance and atherosclerosis. Therefore, a dysregulated elevation of CRP and reduction of adiponectin in the plasma might contribute to the development of atherosclerosis, leading to ACS.

There are a few limitations to our study. First of all, we didn’t perform three-vessel IVUS in the study. Therefore, the selection of the non-culprit plaques might include some bias. Second, there are no classifications for thrombus on VH-IVUS. Therefore thrombus might be assigned to 1 of the current 4 plaque classifications, even though we carefully performed intracoronary thrombectomy before IVUS-VH imaging. However, on the other hand, this procedure might inflict some degree of trauma to the plaque and lead to some change in the plaque morphology. Third, adiponectin exists three major oligomeric forms: trimers, hexamers, and a high-molecular
weight form. Although each form might have different biologic effects, the ELISA we used in this study did not distinguish the three forms. A new ELISA for the measurement of the high-molecular-weight fraction was recently proposed, but requires further validation (27). Future studies, using such novel assays that enable the various forms to be distinguished should help to determine whether there is a specific association between particular forms of adiponectin and plaque components. Finally, **larger number of study subjects which enable to analyze risk factors with multivariate analysis will be required**.


17. Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin,


Figure Legends

**Figure 1.** Virtual histology plaque component analyses across the entire culprit (A) and non-culprit lesion (B) segment. Black bars = acute coronary syndrome (ACS), White bars = non-ACS patients.

**Figure 2.** The relation between plasma hs-CRP level and the ratio of each plaque component of culprit plaque.

**Figure 3.** The relation between plasma adiponectin level and the ratio of each plaque component of culprit plaque.

**Figure 4.** The relation between plasma hs-CRP level and the ratio of each plaque component of non-culprit plaque.

**Figure 5.** The relation between plasma adiponectin level and the ratio of each plaque component of non-culprit plaque.
A (\%)  

\[ P = 0.66 \]

\[ P = 0.17 \]

\[ P = 0.03 \]

Fibrous  
Fibro-fatty  
Dence-calc  
Necrotic core