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ORIGINAL ARTICLE

# Significance of changes in plasma adiponectin concentration after the implantation of stents in patients with stable angina

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**KEYWORDS**
Coronary artery disease;
Stent;
Adiponectin;
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**Summary**
*Objective:* Although plasma adiponectin levels may be a marker for the severity of coronary artery disease (CAD) and can help to predict future cardiovascular events in patients with CAD, the significance of changes in plasma adiponectin levels after the implantation of stents in patients with stable angina is unclear.
*Methods:* The subjects included 32 consecutive patients with stable angina who had undergone successful coronary stenting [bare metal stent (BMS, $n = 16$) or sirolimus-eluting stent (SES, $n = 16$)]. Blood sampling was performed at baseline, and at 24 h, 48 h, 14 days and 6 months after stenting.
*Results:* Plasma high-sensitivity C-reactive protein (hs-CRP) levels at baseline ($0.16 \pm 0.15$ mg/dl) were significantly increased at 24 h ($0.36 \pm 0.45$ mg/dl, $p = 0.011$) and 48 h ($1.01 \pm 1.01$ mg/dl, $p < 0.001$), and plasma adiponectin levels at baseline ($6.7 \pm 4.2$ μg/ml) were significantly decreased at 24 h ($6.1 \pm 4.2$ μg/ml, $p = 0.019$) and 48 h ($6.2 \pm 4.9$ μg/ml, $p = 0.010$) in all subjects. Although there were no significant differences in changes in plasma hs-CRP and adiponectin levels between BMS and SES groups during the study period, BMS group ($6.5 \pm 0.9$ μg/ml at baseline) showed a significant reduction of plasma adiponectin at 48 h ($5.8 \pm 1.1$ μg/ml, $p = 0.022$) and 6 months after stenting ($4.7 \pm 2.3$ μg/ml, $p = 0.011$). Percent diameter stenosis (%DS) at 6 months after stenting was negatively correlated with changes in the plasma adiponectin levels within 6 months [Δadiponectin (6 months − baseline)]. In addition, multiple logistic regression analysis revealed that the %DS at 6 months after stenting was most closely correlated with Δadiponectin (6 months − baseline) after adjusting for age, sex and body mass index.

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*Conclusions:* Coronary stenting may decrease circulating adiponectin in association with an inflammatory response. The changes in plasma levels of adiponectin after stenting may also be a predictor of coronary restenosis in patients with CAD.


## Introduction

Adiponectin is an adipokine that is predominantly synthesized in adipose tissue [1]. It is paradoxically reduced in obesity and has been found to be a major modulator of insulin resistance and to be related to metabolic syndrome.

Metabolic syndrome, which consists of a clustering of cardiovascular risk factors, such as abdominal obesity, insulin resistance, dyslipidemia and hypertension, is associated with increased cardiovascular morbidity and mortality [2]. Since plasma levels of adiponectin are significantly decreased in patients with coronary artery disease (CAD) [3], hypoadiponectinemia is also considered to be an independent risk factor for CAD. Furthermore, plasma concentrations of adiponectin in patients with acute coronary syndrome (ACS) were significantly lower than those in patients with stable angina pectoris and in the control group [4]. Plasma adiponectin levels are significantly associated with coronary lesion complexity in men with CAD, and low adiponectin levels may also contribute to coronary plaque vulnerability [5]. Although these numerous reports indicate that plasma adiponectin levels are a marker for the severity of CAD and can predict future cardiovascular events in patients with CAD, the significance of changes in plasma adiponectin levels after the implantation of stents in patients with CAD is unclear. In addition, Kochiadakis et al. reported that there were differences in inflammatory activation between the implantation of a bare metal stent (BMS) and sirolimus-eluting stent (SES) [6]. It is possible that the time course of plasma levels of adiponectin is also different between BMS and SES.

Adiponectin is an anti-inflammatory compound through nuclear factor-κB [7]. It also downregulates adhesion molecule expression on endothelial cells [8] and enhances lipid clearance [9]. Since adhesion molecule expression and the C-reactive protein (CRP) concentration are increased after coronary stenting [6], adiponectin could decrease inflammation and adhesion molecule expression. These rescue mechanisms induced by adiponectin may also protect against coronary restenosis.

Therefore, we analyzed plasma adiponectin levels after the implantation of stents in patients with stable angina and compared the differences between a bare metal stent and sirolimus-eluting stent.

## Materials and methods

### Subjects and design

The subjects included 32 consecutive patients with stable angina who had a *de novo* target lesion that was suitable for implanting (stent diameter is more than 2.5 mm) either a BMS ($n = 16$) or a SES ($n = 16$) by the judgment of the operator. All patients received aspirin (100 mg/day) and ticlopidine (200 mg/day) and showed significant coronary stenosis (>50% luminal narrowing) as determined by coronary angiography. Direct stenting was not allowed. Follow-up coronary angiography was performed at 6 months. After successful predilation of the target lesion, patients underwent implantation of the stent. Procedural success was defined as successful implantation of the study device, a final vessel diameter stenosis <50%, and freedom from in-hospital major adverse cardiac events, defined as death, myocardial infarction, and emergency coronary artery bypass grafting. We assessed the absolute changes in plasma levels of adiponectin, high-sensitivity CRP (hs-CRP) and stenosis as measured by quantitative coronary angiography (QCA) between post-stent and follow-up angiograms at 6 months after stenting. There was no cardiac event in any of the patients throughout the study. The ethics committee of Fukuoka University Hospital approved this study and written informed consent was obtained from each patient.

Patients with vascular disease or hepatic dysfunction were excluded from the study. Patients with total cholesterol (TC) greater than 220 mg/dl or triglyceride (TG) greater than 150 mg/dl were diagnosed as hyperlipidemia (HL). Patients with systolic (diastolic) blood pressure greater than 140 mmHg (90 mmHg) or who were under antihypertensive treatment were considered to have

hypertension (HT). Patients who were being treated for diabetes mellitus (DM) or who had a fasting glucose concentration greater than 126 mg/dl were considered to have DM. Otherwise, the results of a 75-g oral glucose tolerance test were used to diagnose DM. None of the patients was receiving hormone replacement therapy.

### Blood sampling

Blood sampling was performed at five points: at baseline and at 24 h, 48 h, 14 days and 6 months after stenting. Samples were examined with regard to plasma adiponectin, hs-CRP and lipid profile. The concentrations of adiponectin in plasma were determined in duplicate by an adiponectin ELISA kit (Otsuka Pharmaceutical Co. Ltd., Tokushima, Japan) according to the manufacturer's instructions. At our laboratory, the intra- and inter-assay coefficients of variation were each 5%.

### Coronary angiography

Coronary angiograms were divided into 15 segments according to the classification of the American Heart Association Grading Committee. All angiograms were analyzed qualitatively and quantitatively at the angiographic core lab at Fukuoka University Hospital. A lab member carried out the analysis blindly without being informed of the kind of stent. QCA was performed on all qualifying angiograms and was conducted using CME (MEDIS, The Netherlands) at pre (immediately after the procedure) and at the 6-month follow-up. Binary restenosis was defined as >50% diameter stenosis (DS). QCA analysis included stent measurement [minimum lumen diameter (MLD) confirmed within the proximal and distal stent borders] and systematic analysis of the proximal and distal stent edges. The observers at the angiographic core lab were blind to the blood sample data.

### Statistical analysis

Statistical analysis was performed using StatView J-5.0 (SAS Institute Inc., Cary, NC). Data are shown as the mean ± S.D. Categorical and continuous variables in the SES and BMS groups were compared by a chi-square analysis and analysis of variance, respectively. In addition, differences in continuous variables (hs-CRP and adiponectin) between two groups were examined by Mann—Whitney *U*-test. The changes in continuous variables during the study period were examined by Wilcoxon signed-rank test. Relationships between variables were tested by Pearson and Spearman correlations. A value of $p < 0.05$ was considered significant. Multiple logistic regression analysis was performed for independent variables that were related to QCA parameters.

## Results

### Patient characteristics

Patient characteristics [age, sex, body mass index, the incidences of HT, DM, HL and hyperuricemia (HU) or medications (angiotensin converting enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, β-blocker, etc.)] in all subjects are shown in Table 1. There were no differences in any of the patient characteristics between the BMS and SES groups (data not shown).

**Table 1** Baseline patients characteristics

| Variable | |
|---|---|
| Age (years) | 63.3 ± 11.4 |
| Male, *n* (%) 3 | 29 (90.1) |
| BMI (kg/m$^2$) | 24.2 ± 2.9 |
| History, *n* (%) | |
| HT | 22 (68.8) |
| DM | 18 (56.3) |
| Hyperlipidemia | 18 (56.3) |
| Hyperuricemia | 10 (31.3) |
| Current smoker | 20 (62.5) |
| Preprocedural laboratory | |
| HbAlc (%) | 6.3 ± 1.7 |
| TC (mg/dl) | 180.3 ± 30.3 |
| TG (mg/dl) | 126.7 ± 68.5 |
| HDL-C (mg/dl) | 44.5 ± 11.5 |
| LDL-C (mg/dl) | 110.4 ± 25.0 |
| UA (mg/dl) | 5.4 ± 1.4 |
| Preprocedural medications, *n* (%) | |
| ACEI | 3 (9.4) |
| ARB | 18 (56.3) |
| CCB | 16 (50.0) |
| β-Blocker | 5 (15.6) |
| Diuretics | 6 (18.8) |
| ISDN | 10 (31.3) |
| Statin | 14 (43.8) |

BMI, body mass index; HT, hypertension; DM, diabetes mellitus; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; UA, uric acid; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; ISDN, isosorbide dinitrate.

**Table 2** Angiographic characteristics and quantitative coronary angiographic analysis

| | All | BMS group | SES group |
|---|---|---|---|
| Pre-procedure | | | |
| Number of vessels (*n*) | | | |
| 1VD/2VD/3VD | 19/8/5 | 12/2/2 | 7/6/3 |
| Culprit coronary artery (*n*) | | | |
| RCA/LAD/LCx | 9/14/9 | 5/7/4 | 4/7/5 |
| Lesion type B2/C, *n* (%) | 19 (54) | 7 (44) | 12 (75) |
| Reference (mm) | 3.13 ± 0.12 | 3.26 ± 0.19 | 3.04 ± 0.15 |
| MLD (mm) | 0.92 ± 0.07 | 0.93 ± 0.09 | 0.91 ± 0.11 |
| %DS | 69.9 ± 2.2 | 69.1 ± 2.6 | 63.9 ± 3.9 |
| Final procedure | | | |
| Stent length (mm) | 20 ± 7 | 20 ± 5 | 21 ± 3 |
| Stent diameter (mm) | 3.3 ± 0.7 | 3.4 ± 0.5 | 3.1 ± 0.3 |
| Maximal inflation pressure (atm) | 14 ± 2 | 13 ± 2 | 15 ± 2 |
| Reference (mm) | 3.12 ± 0.09 | 3.20 ± 0.11 | 3.09 ± 0.12 |
| MLD (mm) | 2.14 ± 0.06 | 2.21 ± 0.08 | 2.08 ± 0.10 |
| %DS | 26.0 ± 1.8 | 25.3 ± 2.4 | 26.3 ± 2.7 |
| Acute lumen gain (mm) | 1.22 ± 0.07 | 1.27 ± 0.11 | 1.16 ± 0.08 |
| 6 months follow-up | | | |
| Reference (mm) | 3.19 ± 0.10 | 3.18 ± 0.14 | 3.19 ± 0.14 |
| MDL (mm) | 1.87 ± 0.10 | 1.66 ± 0.15 | 2.26 ± 0.10* |
| %DS | 37.1 ± 2.7 | 44.9 ± 3.4 | 23.1 ± 0.1* |
| In-stent lumen loss (mm) | 0.27 ± 0.10 | 0.55 ± 0.15 | −0.18 ± 0.07* |

These data were shown mean ± S.D. VD, vessel disease; RCA, right coronary artery; LAD, left anterior descending artery; LCx, left circumflex artery; MLD, minimum lumen diameter; DS, diameter stenosis. *$p < 0.01$ versus BMS group.

## Angiographic and stent implantation procedure characteristics and QCA analysis

Angiographic and stent implantation procedure characteristics are shown in Table 2. Sixteen patients (BMS group) received a Multi-link Zeta stent (Abbott Vascular, USA) ($n = 7$), Express 2 stent (Boston Scientific, USA) ($n = 5$), Driver stent (Goodman, USA) ($n = 2$) or Duraflex stent (Medtronic, USA) ($n = 2$), while all 16 patients in the SES group were given a Cypher stent (Johnson & Johnson, USA). Based on QCA results at 6 months (Table 2), %DS and in-stent late lumen loss in the SES group were significantly lower than those in the BMS group. Therefore, MLD at 6 months in the SES group was significantly greater than that in the BMS group. Consequently, the number of patients with in-stent restenosis and target lesion revascularization in the SES group ($n = 1$ and $n = 1$, respectively) were lower than those in the BMS group ($n = 4$ and $n = 2$, respectively).

## Plasma levels of hs-CRP and adiponectin

Time-course changes in plasma levels of hs-CRP and adiponectin after stenting are shown in Fig. 1a and b, respectively. Plasma hs-CRP levels at baseline (0.16 ± 0.15 mg/dl) were significantly increased at 24 h (0.36 ± 0.45 mg/dl, $p = 0.011$) and 48 h (1.01 ± 1.01 mg/dl, $p < 0.001$), and plasma adiponectin levels at baseline (6.7 ± 4.2 μg/ml) were significantly decreased at 24 h (6.1 ± 4.2 μg/ml, $p = 0.019$) and 48 h (6.2 ± 4.9 μg/ml, $p = 0.010$) in all subjects. Although there were no significant differences in changes in plasma hs-CRP and adiponectin levels between BMS and SES groups during the study period, BMS group (6.5 ± 0.9 μg/ml at baseline) showed a significant reduction of plasma adiponectin at 48 h (5.8 ± 1.1 μg/ml, $p = 0.022$) and 6 months after stenting (4.7 ± 2.3 μg/ml, $p = 0.011$).

## Correlation between changes in plasma adiponectin levels and QCA parameters

A correlation analysis showed that plasma levels of adiponectin at 6 months were positively correlated with MLD at 6 months ($n = 32$, $y = 1.59 + 0.05x$, $r = 0.351$, $p = 0.04$) (Fig. 2a), and changes in plasma levels of adiponectin within 6 months were positively correlated with %DS at 6 months ($n = 32$, $y = 33.9 - 2.9x$, $r = 0.411$, $p = 0.02$) (Fig. 2b). To fur-

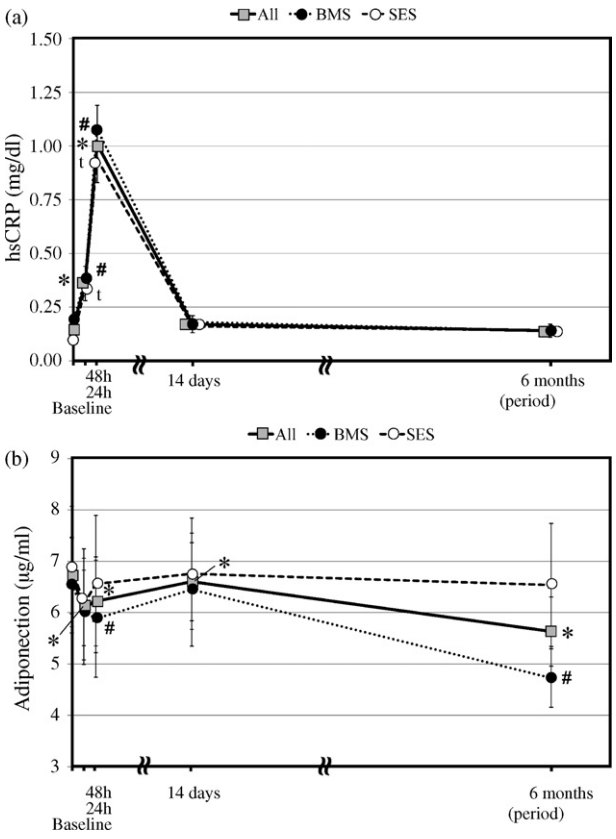


**Figure 1** (a) Time course of hs-CRP in all subjects (gray square), and in the BMS (closed circle) and SES (open circle) groups. $^{*}p < 0.05$ versus at baseline in all subjects. $^{\#}p < 0.05$ versus at baseline in the BMS group. $^{t}p < 0.05$ versus at baseline in the SES group. (b) Time course of plasma adiponectin in all subjects (gray square), and in the BMS (closed circle) and SES (open circle) groups. $^{*}p < 0.05$ versus at baseline in all subjects. $^{\#}p < 0.05$ versus at baseline in the BMS group.

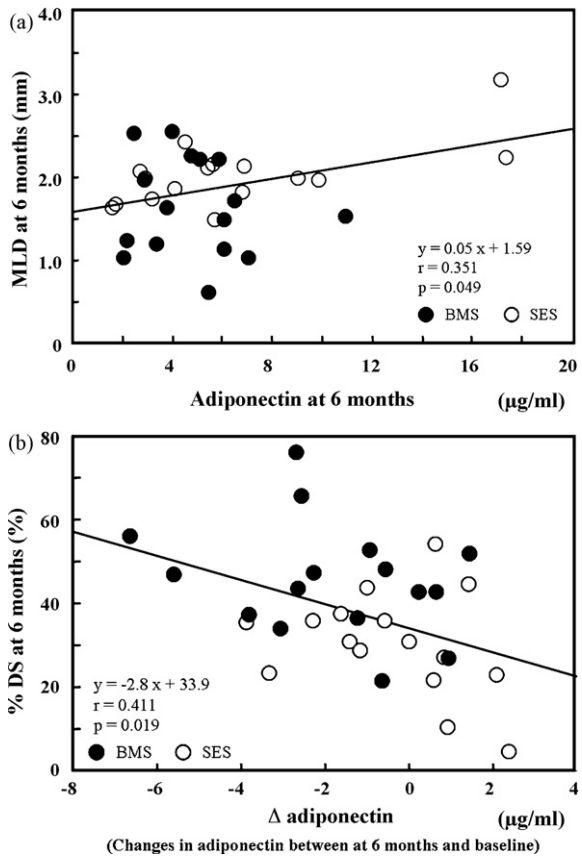


**Figure 2** (a) Correlation between plasma adiponectin at 6 months after stenting and MLD at 6 months. $n = 32$, $y = 0.05x + 1.59$, $r = 0.351$, $p = 0.04$. Open and closed circles indicate BMS and DES groups, respectively. (b) Correlation between changes in plasma adiponectin between baseline and at 6 months after stenting ($\Delta$adiponectin) and %DS at 6 months. $n = 32$, $y = -2.9x + 33.9$, $r = 0.411$, $p = 0.02$. Open and closed circles indicate BMS and DES groups, respectively.

ther analyze the significance of plasma levels of adiponectin after stenting, multiple logistic regression analysis was performed for the independent variables (changes in plasma levels of adiponectin and hs-CRP within 24 h, 48 h, 14 days and 6 months after stenting) that were related to %DS at 6 months. The analysis revealed that %DS at 6 months was most closely correlated with changes in plasma levels of adiponectin within 6 months (standard regression coefficient = −0.484, $p = 0.031$) after adjusting for age, sex and BMI.

## Discussion

In this study, we demonstrated that the changes in plasma levels of adiponectin between baseline and 6 months (late stage) after stenting may predict coronary restenosis in patients with CAD. Coronary stenting may decrease circulating adiponectin at 24—48 h (early stage) after stenting and might be associated with a stenting-induced inflammatory response.

Although it has been reported that the reduction of plasma adiponectin during the time course of myocardial infarction was significantly correlated with the plasma CRP concentration immediately after the onset of AMI [10], this study is the first to show the time course of the plasma adiponectin concentration after stenting in patients with CAD. Kojima et al. suggested that strong inflammatory activity in vulnerable coronary plaque may induce a reduction of plasma adiponectin for up to 72 h [10]. A decrease in the plasma adiponectin concentration will accelerate the inflammatory process. Although our results also indicate that a stenting-induced inflammatory response may decrease plasma adiponectin at an early stage after

stenting, the plasma levels do not predict coronary restenosis at a late stage after stenting. Changes in plasma levels of adiponectin within 6 months after stenting may be a predictor in the severity of coronary restenosis in patients with CAD.

Another issue in this study is that the BMS group, but not SES group, showed a significant reduction of plasma adiponectin at 48 h after stenting. Although rapamycin is known to attenuate vascular wall inflammation at 21 days after angioplasty in a human organ culture model [11], it has been unclear whether SES implantation can induce an anti-inflammatory response at 48 h as in this study. While our experiments were in progress, Kochiadakis et al. reported that SES implantation was associated with a lower CRP elevation than that with BMS implantation [9]. In this study, there were no differences in the elevation of CRP levels at an early stage between the SES and BMS groups. Although the cause of this discrepancy is unclear, the more consumption of circulating adiponectin may have been necessary to induce anti-inflammation in a BMS group based on our observation. However, further studies are required to determine the exact mechanism of the combined effects of adiponectin and rapamycin.

The BMS group also showed a significant reduction of plasma adiponectin at 6 months after stenting. %DS in the BMS group was significantly greater than that in the SES group because SES itself could prevent restenosis, since rapamycin inhibits the proliferation of both smooth muscle cells and endothelial cells and has anti-inflammatory and anti-thrombotic effects [12]. In the case of BMS implantation, the consumption of circulating adiponectin may be needed to prevent coronary restenosis to induce a reduction in adhesion molecule expression because these molecules have been shown to be related to the development of CAD [13], including myocardial infarction [14] and post-angioplasty restenosis [15].

Plasma adiponectin concentration is regulated by many metabolic factors. Low plasma adiponectin concentration is found in patients with metabolic syndrome including obesity and DM [16]. Adiponectin may also be involved in the progression of HT. In addition, ACS patients showed low plasma adiponectin concentration [4]. There were no difference in BMI before and after 6 months, and no adverse cardiac events occurred throughout the study. Although statin [17], angiotensin receptor blocker [18], glitazone [19] and fibrate [20] significantly increased in plasma adiponectin concentration in humans, no patients changed the medications throughout the study.

## Study limitations

Our study is based on cardiac catheterization at a single center and thus is limited by a small sample size. In addition, since we used angiographic determination to estimate the progression of coronary restenosis, some of the patients who were considered to have no progression may actually have had some atherosclerotic progression, but were not recognized. Nonetheless, we believe that our study should contribute to understanding the value of measuring plasma adiponectin in patients with CAD.

## Conclusions

Coronary stenting decreased circulating adiponectin in association with an inflammatory response. The changes in plasma levels of adiponectin after stenting within 6 months may also predict coronary restenosis in patients with CAD.

## Acknowledgment

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