Blood Adiponectin Level as a Predictor of Stent Restenosis

Masahiro Yamauchi1, Tomoyuki Kunishima1, Akio Hayashi1, Keisuke Kida1, Eiji Takahashi2, Koji Inoue2, Kensuke Kawasaki1, Nobuyuki Hashimoto2, Haruki Musha1, and Fumihiko Miyake1

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Abstract

Objective: Adiponectin is believed to be a risk factor for the development of coronary artery disease, but the changes of this hormone after percutaneous coronary intervention, particularly after stenting, are unclear. We investigated the relationship between adiponectin and chronic stent restenosis.

Subjects and Methods: The subjects were 32 patients with coronary artery disease who underwent elective coronary stenting of 35 lesions and chronic-phase coronary angiography. Blood levels of adiponectin, various lipids (total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, and triglycerides), and hemoglobin A1c were measured at the time of angiography. Restenosis was defined as ≥50% diameter stenosis, and differences between the restenosis and non-restenosis groups were compared.

Results: Restenosis occurred in 6 of the 32 patients. No differences of blood lipid levels were detected between the two groups. However, the blood level of adiponectin was significantly lower in the restenosis group than in the non-restenosis group (4.7±2.3 versus 8.4±4.4 μg/ml; p<0.05).

Conclusion: Measurement of adiponectin may be useful for predicting restenosis after stenting.

Key words

Percutaneous coronary intervention, stent restenosis, adiponectin

Introduction

Recently, westernization of the lifestyle in Japan has made it necessary to control risk factors for coronary artery disease, including diabetes mellitus (DM), hyperlipidemia (HL), and hypertension (HT)1-3. Metabolic syndrome is a condition that results from the accumulation of various risk factors for arteriosclerosis (increased visceral fat, insulin resistance, decreased High density lipoprotein-cholesterol (HDL-C), hypertriglyceridemia, and HT), and it often leads to the occurrence of cardiac events4. In this syndrome, various adipocytokines (lipid-derived hormones) are produced in addition to excessive accumulation of fat in the adipose tissue. One of these adipocytokines is known as adiponectin, and it has been shown to be useful as a biomarker of metabolic syndrome5, while blood adiponectin levels are low in patients with coronary artery disease6-9.

In animal studies, adiponectin has been observed to accumulate in the vascular endothelium after balloon catheter injury, suggesting a role of this hormone in the process of vascular injury repair10. Adiponectin was also been reported to be a useful predictor of restenosis after percutaneous coronary intervention in patients with ischemic heart disease11. However, the changes of blood

1 Department of Cardiology, St. Marianna University School of Medicine, Yokohama City Seibu Hospital
2 Department of Internal Medicine, Division of Cardiology, St. Marianna University School of Medicine
adiponectin levels from immediately after coronary stenting through the chronic phase have not been clarified. Accordingly, the present study was performed to determine the relationship between adiponectin and chronic stent restenosis.

Subjects and Methods

Subjects
This study was conducted in 32 patients (35 lesions) with coronary artery disease who underwent elective percutaneous coronary intervention and stenting between February 2002 and February 2003, as well as having angiography in the chronic phase (6 months later) at the Department of Cardiology of St. Marianna University School of Medicine. The subjects consisted of 23 men and 9 women with a mean age of 65 ±10.0 years. Nineteen patients had old myocardial infarction. Subjects with acute coronary syndrome were excluded.

Percutaneous coronary intervention
All percutaneous coronary intervention procedures were performed by standard methods via the femoral route using 6 or 7 French guide catheters. After insertion of an arterial sheath, heparin (10,000 IU) was administered, with additional doses being given if needed. Before the procedure, all patients were treated with aspirin (81–200 mg) and ticlopidine (200 mg). Afterwards, oral ticlopidine (200 mg/day) was administered for 2 weeks and aspirin therapy (81–200 mg/day) was continued over the long term.

The stents were selected by the interventionist on the basis of the coronary angiography findings. Each stent was placed to completely cover the lesion detected on angiography. If insufficient dilation was achieved, repeat dilation was done for the stents with a high expansion pressure.

Quantitative coronary angiography
Quantitative coronary angiography (QCA) was performed before and after intervention, as well as at the time of angiography during the chronic phase (about 6 months later), using constant imaging parameters to enable to compare. Analysis was done with a QCA system (CMS Inc., MO, USA). The reference diameter, minimum lesion diameter, and lesion length were measured in each patient to calculate the percent diameter stenosis, acute gain, and late loss. A percent diameter stenosis ≥50% at the time of chronic angiography was defined as stent restenosis and a percent diameter stenosis <50% was defined as the absence of restenosis.

Laboratory tests
Blood was collected through the arterial sheath before heparin administration at the time of stenting and immediately before chronic-phase angiography. Total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), HDL-C, triglycerides (TG), hemoglobin A1c (HbA1c), and adiponectin were measured.

Ethics
The study protocol was approved by the Bioethics Committee of St. Marianna University School of Medicine (Approval No. 586), and all patients gave written informed consent.

Statistical analysis
Results are shown as the mean ± SD. Data were compared between the two groups by using the Mann-Whitney U test or the chi-squared test as appropriate, with p<0.05 being considered to indicate statistical significance.

Results

Clinical characteristics
Table 1 shows the clinical characteristics of the patients stratified according to the presence or absence of chronic stent restenosis. Of the 35 lesions in 32 patients, 7 lesions (20%) in 6 patients developed restenosis. None of the patients suffered from...
any cardiovascular events (including death) during their hospital stay or during follow-up for approximately 6 months until chronic angiography. There were no significant differences between the restenosis and non-restenosis groups with regard to age, sex, left heart function on left ventriculography, and target lesion morphology classified according to the ACC/AHA classification. However, all of the patients in the restenosis group had DM, a coronary risk factor. In the non-restenosis group, 13 patients (14 lesions) had diabetes and 13 did not. There were no significant differences between the restenosis and non-restenosis groups with regard to Body mass index (BMI). But in restenosis group, BMI was significantly higher than in the diabetic subgroup of the non-restenosis group, 27.5 ± 6.2 kg/m² vs 23.9 ± 3.3 kg/m²; p < 0.05. There were no significant differences of age, sex, left heart function, and lesion morphology between the restenosis and non-restenosis groups.

Quantitative coronary angiography
Table 2 shows lesion morphology determined by QCA before percutaneous coronary intervention, as well as the stent size, stent design, and maximum dilatation pressure. There were no significant differences between the restenosis group and the non-restenosis group (including subgroups with or without diabetes).

Table 3 summarizes the findings of QCA immediately after percutaneous intervention. In the restenosis group, the minimum lesion diameter (MLD) increased from 0.7 ± 0.5 mm to 2.6 ± 0.3 mm and the percent diameter stenosis (%DS) decreased from 71.4 ± 21.4% to 12.4 ± 8.5%. In the non-restenosis group, the MLD increased from 0.8 ± 0.5 mm to 2.9 ± 0.5 mm and %DS decreased from 70.9 ± 17.2% to 11.4 ± 9.2%. Satisfactory dilation was obtained in both groups at the time of stenting. The acute gain was 1.9 ± 0.3 mm in the restenosis group and 2.1 ± 0.7 mm in the non-restenosis group. Satisfactory dilation was also achieved in the diabetic subgroup of the non-restenosis group.

Chronic angiography was performed about 6 months after stenting and the results are displayed in Table 4. In the restenosis group, the MLD was 1.0 ± 0.2 mm, %DS was 58.5 ± 6.8%, and the late loss was 1.6 ± 0.3 mm. In the non-restenosis group, the MLD was 2.3 ± 0.6 mm, the %DS was 24.7 ± 12.4%, and the late loss was 0.6 ± 0.4 mm. The differences of these parameters between the two groups were significant. In the diabetic subgroup of the non-restenosis group, the MLD was 1.8 ± 0.5 mm, %DS was 27.2 ± 12.1%, and the late loss was 0.6 ± 0.5, with these parameters all being significantly better compared with those of the restenosis group.

Laboratory data
Table 5 shows the results obtained immediately before chronic angiography. There were no significant differences of TC, LDL-C, HDL-C, and TG between the restenosis and non-restenosis groups. The Hb A1c level was 6.4 ± 0.4% in the restenosis group and 5.6 ± 0.8% in the non-restenosis group, showing a significant difference. The Hb A1c level in the diabetic subgroup of the non-restenosis group was 6.2 ± 0.9%, which was not significantly different from that of the restenosis group.

Table 2. Features of the Target Lesion on Quantitative Coronary Angiography and Stent Characteristics
| PCI: percutaneous coronary intervention, RD: reference diameter, MLD: minimal lumen diameter, DS: diameter stenosis, max pressure: maximum pressure |
|---|---|---|
| Pre-PCI | non-restenosis group | non-restenosis group (diabetic) |
| RD (mm) | 2.4 ± 0.6 | 2.8 ± 0.7 | 2.5 ± 0.6 |
| MLD (mm) | 0.7 ± 0.5 | 0.8 ± 0.5 | 0.8 ± 0.3 |
| %DS (%) | 71.4 ± 21.4 | 70.9 ± 17.2 | 66.4 ± 13.3 |
| Lesion Length (mm) | 11.2 ± 3.3 | 12.0 ± 3.3 | 11.2 ± 4.4 |

Table 3. Post-procedure Quantitative Coronary Angiography Findings
| Post-PCI |
|---|---|---|
| RD (mm) | 2.9 ± 0.4 | 3.2 ± 0.6 | 2.9 ± 0.5 |
| MLD (mm) | 2.8 ± 0.3 | 3.0 ± 0.5 | 2.8 ± 0.5 |
| %DS (%) | 12.4 ± 8.5 | 11.4 ± 9.2 | 10.1 ± 8.6 |
| Acute Gain (mm) | 1.9 ± 0.3 | 2.1 ± 0.7 | 1.8 ± 0.7 |

Table 4. Chronic-phase Quantitative Coronary Angiographic Findings
| Follow-up CD |
|---|---|---|
| PIU [day] (y) | 0.5 ± 0.5 | 0.4 ± 0.3 | 0.5 ± 0.3 |
| RD (mm) | 2.2 ± 0.3 | 3.0 ± 0.5 | 2.7 ± 0.5 |
| M (mm) | 5.0 ± 0.3 | 7.0 ± 0.5 | 5.0 ± 0.3 |
| %DS (%) | 12.4 ± 8.5 | 27.0 ± 17.2 | 12.4 ± 8.5 |
| Late Loss (mm) | 1.0 ± 0.2 | 0.2 ± 0.2 | 0.2 ± 0.2 |
group. The adiponectin level was 4.7 ± 2.3 μg/ml in the restenosis group and 8.4 ± 4.4 μg/ml in the non-restenosis group, showing a significant difference. In the diabetic subgroup of the non-restenosis group, it was 7.8 ± 3.5 μg/ml and was significantly higher than in the restenosis group (Table 5). No significant relationship was detected between hemoglobin A1c and adiponectin in the whole study population or the diabetic patients from each group (Fig. 1).

**Discussion**

The risk factors for coronary artery disease include HT, DM, HL, and cigarette smoking. The Framingham Study indicated that a combination of these risk factors leads to a more rapid increase in the occurrence of heart disease. Among patients with coronary artery disease, those with three or more risk factors have a 10.56-fold higher risk of developing cardiovascular events. In the present study, we investigated the relationship between stent restenosis and adiponectin. The decrease of adiponectin levels in the restenosis group suggested that this hormone might be involved in the process of restenosis. The lack of a correlation between the levels of adiponectin and HbA1c, a marker of diabetes which is a coronary risk factor, suggested that adiponectin might be an independent risk factor for restenosis.

Coronary stenting, unlike balloon angioplasty, supports the treated blood vessel from the inside with a metal coil to create a more stable vascular lumen. Although stenting is able to prevent elastic recoil, which is a cause of acute restenosis, it imposes greater mechanical stress on the vessel walls than balloon angioplasty. As a consequence of damage caused by the stent, neointimal hyperplasia is reported to occur. Smooth muscle cells are directly involved in the process of neointimal hyperplasia, and the differentiation, migration, and proliferation of smooth muscle cells are reported to be stimulated by various factors. These include decreased production of vasodilatory factors (nitric oxide and prostaglandin I2), increased production of growth factors associated with thrombosis (platelet-derived growth factor, transforming growth factor-β, and epidermal growth factor), increased production of angiotensin II, serotonin and endothelin, as well as the involvement of neutrophils and macrophages. Adiponectin regulates the activa-

**Table 5.** Laboratory Data in the Chronic Phase

<table>
<thead>
<tr>
<th></th>
<th>restenosis group</th>
<th>non-restenosis group</th>
<th>diabetic subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>6.4 ± 0.4</td>
<td>5.6 ± 0.8</td>
<td>6.2 ± 0.9</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>175.2 ± 27.3</td>
<td>173.5 ± 24.3</td>
<td>184.2 ± 29.3</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>116.2 ± 15.5</td>
<td>112.6 ± 22.2</td>
<td>99.2 ± 44.5</td>
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<tr>
<td>HDL-C (mg/dL)</td>
<td>51.2 ± 13.2</td>
<td>53.1 ± 13.2</td>
<td>51.1 ± 11.4</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>88.1 ± 12.4</td>
<td>103.5 ± 24.5</td>
<td>58.1 ± 22.2</td>
</tr>
<tr>
<td>adiponectin (μg/ml)</td>
<td>6.7 ± 1.2</td>
<td>8.4 ± 4.4</td>
<td>7.8 ± 3.7</td>
</tr>
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**Figure 1.** Plasma adiponectin versus hemoglobin A1c in different groups. Upper left: Adiponectin versus hemoglobin A1c in all patients. Lower left: Adiponectin versus hemoglobin A1c in the non-restenosis group. Upper right: Adiponectin versus hemoglobin A1c in the restenosis group. Lower right: Adiponectin versus hemoglobin A1c in the diabetic subgroup of the non-restenosis group.
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Restenosis after stenting in the acute period was not a predictor of chronic al hyperplasia be related to an increase of neointimal intervention than nondiabetic patients, and this might evidenced of restenosis after percutaneous coronary intervention. Shimada et al. have reported that the blood level of adiponectin in the acute period was not a predictor of chronic restenosis after stenting. Despite this, it seems feasible that adiponectin may play a role in the regulation of intimal hyperplasia after stenting, and our study also suggested such a possibility.

Relationship between adiponectin and diabetes
Since all of the patients with restenosis had diabetes, we also performed a comparison between the restenosis group and only the diabetic patients from the non-restenosis group. There were significant differences between the two groups with regard to the BMI and the adiponectin level. Adiponectin is known to show a positive correlation with insulin resistance, and a negative correlation with BMI. In addition, low adiponectin level is considered to contribute to the development of both insulin resistance and arteriosclerosis. It has been reported that diabetic patients have a higher incidence of restenosis after percutaneous coronary intervention than nondiabetic patients, and this might be related to an increase of neointimal hyperplasia. However, the present study suggested that adiponectin might be another predictor of neointimal hyperplasia after stenting. Although, insulin resistance was not assessed in this study, the number of patients was small, and the influence of other drugs was not evaluated. Accordingly, it will be necessary to investigate such factors in a larger study in the future.

Conclusion
When the relationship between restenosis after stenting and adiponectin was evaluated, the restenosis group had significantly lower adiponectin levels than the non-restenosis group. Our results suggested that monitoring of adiponectin might be useful for predicting restenosis after stenting.

Acknowledgment
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References
10) Hanke H, Kamenz J, Hassenstein S, Oberhoff


18) Hotta K, Funahashi T, Bodkin NL, Ortmeyer HK, Arita Y, Hansen BC and Matsuzawa Y. Circulating concentrations of the adipocyte protein, adiponectin, are decreased in parallel with reduced insulin sensitivity during the progression to type-2 diabetes in rhesus monkeys. *Diabetes* 2001; 50: 1126-1133.


スチント留置術後の再狭窄予測因子としての
血中アディポネクチン値の有用性について

山内 正博¹ 国島 友之¹ 林 明生¹ 木田 圭亮²
高橋 英二² 井上 康二¹ 川崎 健介¹ 橋本 信行²
武者 春樹¹ 三宅 良彦¹

抄録
目的: アディポネクチンは冠動脈疾患の発症に関与し、危険因子であるとされているが、冠動脈形成術、そのうちスチント留置後に及ぼす影響は明らかではない。今回我々はスチント留置後の慢性期再狭窄とアディポネクチンの関与について検討を行った。

対象: 待機的に冠動脈内にスチント留置を行い、慢性期の冠動脈造影検査を行った32例（35病変）の冠動脈疾患患者で、慢性期冠動脈造影時に血中アディポネクチン、血中脂質（総コレステロール、HDLコレステロール、LDLコレステロール、中性脂肪）、ヘモグロビンA1cを測定した。慢性期冠動脈造影で％diameter stenosisが50％以上を再狭窄として、非再狭窄群と再狭窄群を比較検討した。

結果: 再狭窄は32例中6例で認めた。両群で血中脂質に差は認めなかった。しかし、再狭窄群は非再狭窄群より有意に血中アディポネクチン値が低値であった（4.7±2.3 versus 8.4±4.4μg/ml; p<0.05）。

結論: スチント留置後の再狭窄の予測に慢性期血中アディポネクチンは有用であった。

1 聖マリアンナ医科大学横浜市西部病院 内科学（循環器内科）
2 聖マリアンナ医科大学 内科学（循環器内科）