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High Density Lipoprotein is a Clinical Predictor of Restenosis after Successful Coronary Angioplasty

Yuichi Ishikawa¹, Yoshio Fujioka², Yasuo Kitagawa², Akihiro Takahashi², Akira Nobusawa², Takahiro Taniguchi², Motoshi Takeuchi², and Mitsuhiro Yokoyama².

Percutaneous transluminal coronary angioplasty (PTCA) is an effective and widely applied method of myocardial revascularization. Restenosis after PTCA occurs in approximately 30% of patients within 3 to 6 months. To assess the clinical risk factors in relation to restenosis, statistical analysis for clinical risk factors was carried out for age, sex, diabetes mellitus, hypertension, smoking habits and coronary stenotic scores (Gensini) in patients who underwent a first successful PTCA. There was no significant difference in these factors between restenosis group (RS) and non-restenosis group (NRS). In addition, serum levels of cholesterol (TC), triglyceride (TG), HDL-cholesterol (HDL), apolipoproteins, and lipoprotein (a) [Lp (a)] were measured. Serum levels of TC and TG in RS and NRS were not different statistically. Lp (a) in RS was slightly higher than that in NRS, but there was no significant difference. There were no significant differences in the serum levels of apolipoproteins (A1, AII, B, CII, CIII, E) between RS and NRS. The serum concentration of HDL in RS was significantly lower than that in NRS. (p < 0.025)

Low level of serum HDL can be the risk factor for restenosis after successful PTCA.

Key Words
Percutaneous transluminal coronary angioplasty, clinical risk factor, lipoprotein (a), HDL-cholesterol.

INTRODUCTION

Percutaneous transluminal coronary angioplasty (PTCA) is an effective and widely applied method of myocardial revascularization. Restenosis after PTCA occurs in approximately 30% of patients within 3 to 6 months.¹² The pathophysiology of restenosis is due to vascular injury by the balloon and the process has similarities and distinctions from atherosclerosis.³⁴ Two large studies¹² analyzed clinical data and attempted to correlate demographic and procedural factors with restenosis and showed the factors associated with increased rate of restenosis: male gender, PTCA of bypass graft stenosis, severity of angina or unstable angina before PTCA, no history of myocardial infarction and a large residual stenosis after PTCA. Dyslipidemia has been proposed to be an important coronary risk factor, but only a few studies systematically evaluated a role of dyslipidemia as a risk factor for restenosis after

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PTCA.\textsuperscript{5,6} It is important to clarify the factors for restenosis and to minimize the occurrence of the restenosis. This study was carried out to assess the clinical risk factors and the details of lipid fractions in relation to restenosis after successful PTCA.

SUBJECTS and METHODS.

In follow-up study of PTCA, repeated coronary angiography (CAG) was performed in 171 patients after successful PTCA. These 171 patients with successful PTCA were divided into 2 groups, restenosis group (RS) and non-restenosis group (NRS). The successful PTCA was defined as a residual stenosis less than 50%, and restenosis was defined as more than 50% diameter stenosis observed during follow-up angiography.\textsuperscript{2} Out of the 171 patients, 40 patients in whom complete clinical data of risk factors were available were selected and analyzed.

CAG was performed by Judkins' method. The degree of coronary stenosis was estimated by American Heart Association (AHA) classification. Coronary stenotic score was calculated by Gensini's formula using AHA classification.\textsuperscript{7} Blood was sampled after 12 hour-fasting on day 2 after hospitalization. Total cholesterol (TC) and triglyceride (TG) were measured by enzymatic method. High density lipoprotein cholesterol (HDL) was measured by precipitation method.\textsuperscript{8} Apolipoproteins (A1, AII, B, CII, CIII, E) were measured by turbidometric immunoassay method.\textsuperscript{9} Lecithin-cholesterol acyltransferase (LCAT) was measured by Akanuma's method.\textsuperscript{10} Lipoprotein (a) [Lp (a)] was measured by single radial immunodiffusion method (SRID) using COMB-RID kit (Immuno AG, Vienna).\textsuperscript{11} Low density lipoprotein (LDL) was calculated using the formula of Friedewald.\textsuperscript{12}

Statistical Analysis

The values were registered and analysed using StatView4.1 (ABACUS Inc.). Unpaired Student's t test, Chi-square test, Kruskal-Wallis test, Wilcoxon rank sum test, and Spearman's rank correlation coefficient were used appropriately. Results are expressed as mean ± standard deviation (SD) or ± standard error of mean (SEM) as indicated in tables. Differences were considered significant at a value of p < 0.05 (two sided).

RESULTS

Characteristics of clinical variables

In follow-up study of 171 patients, 83 patients were restenosed (48.5%). There was no differences on clinical variables for predictors of restenosis between the numbers of male sex, diabetics, smokers, and hypertension (Table 1). Body Mass Index (BMI) was not also different. The mean age in RS group was slightly higher than that in NRS group, but there is no statistical difference. The number of patients with diabetes mellitus was slightly larger in RS group, but also there is no statistical difference. Table 2 shows the characteristics of angiographic variables in 171 patients. By the quantitative analy-
Table HDL is a clinical predictor of restenosis after PTCA.

### Table 1. Characteristics of Clinical Variables

<table>
<thead>
<tr>
<th></th>
<th>Restenosis (n=83)</th>
<th>Non-restenosis (n=88)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.6±7.8</td>
<td>59.9±8.7</td>
<td>ns</td>
</tr>
<tr>
<td>Male sex</td>
<td>67(80.7%)</td>
<td>67(76.1%)</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetes</td>
<td>32 (38.6%)</td>
<td>24 (27.3%)</td>
<td>ns</td>
</tr>
<tr>
<td>Smokers</td>
<td>52 (62.7%)</td>
<td>57 (64.8%)</td>
<td>ns</td>
</tr>
<tr>
<td>Hypertension</td>
<td>48 (57.8%)</td>
<td>40 (45.5%)</td>
<td>ns</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>23.3±2.8</td>
<td>23.4±2.9</td>
<td>ns</td>
</tr>
</tbody>
</table>

*mean±SD  ns: not significant*

sis of coronary stenosis score by Gensini's method, there was no difference in the severity of coronary stenosis between RS and NRS group. The number of vessels involved was not different between two groups. The mean follow-up period was 4.7 months in RS group and was not different significantly compared to that in NRS group.

### Table 2. Characteristics of Angiographic Variables

<table>
<thead>
<tr>
<th></th>
<th>Restenosis (n=83)</th>
<th>Non-restenosis (n=88)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary stenotic scores (Gensini)</td>
<td>43.4±26.8</td>
<td>46.5±26.9</td>
<td>ns</td>
</tr>
<tr>
<td>Number of diseased vessels</td>
<td>1.7±0.8</td>
<td>1.6±0.8</td>
<td>ns</td>
</tr>
<tr>
<td>Follow up period (month)</td>
<td>4.7±3.3</td>
<td>4.3±1.9</td>
<td>ns</td>
</tr>
</tbody>
</table>

*mean±SD  ns: not significant*

Characteristics of blood chemical variables.

In 40 patients whose clinical blood chemical data were available (Table 3), the serum levels of TC and LDL in NRS group were slightly higher
than those in RS group, but there were no significant differences between two groups. The mean value of TG in RS group was slightly higher than that of NRS group.

The mean value of HDL was significantly lower in RS group, compared to NRS group (p < 0.025) (Figure 1). The incidence of restenosis in patients with low HDL level less than 40 mg/dl was 48% and that with higher level of HDL was 27%. But there was no statistical difference (Figure 2). The level of Lp(a) was slightly higher in RS group but there was no statistical difference.

The analysis of apolipoproteins revealed that the apolipoprotein AI in RS group was slightly lower than that in NRS group, but there was no significant difference. Also, there was no statistical difference in apoprotein B/Al ratio between two groups (Table 4).

**Discussion**

In this study, we indicated that the low level of HDL is a strong predictor for restenosis after successful PTCA. This is a similar result of Shah et al.\(^5\) They studied 68 patients with coronary artery disease who underwent a successful PTCA and showed that the mean HDL level was 33 ± 12 mg/dl in 28 patients with RS and that in 40 patients with NRS was 45 ± 12 mg/dl and indicated that a low HDL level was independently and strongly related to the risk of RS (p < 0.001). The low level of HDL is known to be a strong risk factor for coronary artery disease.\(^{13}\) HDL is a key lipoprotein in reverse cholesterol transport from peripheral tissues such as coronary artery to liver.\(^{14}\) In the lesions after PTCA, HDL may have favorable effects to prevent the stenosis. In our study, the incidence of restenosis in patients with low HDL level lower than 40 mg/dl was 48% and that in higher level of HDL was 27%. But there was no statistical difference (Figure 2).

Other factors related to the reverse cholesterol transport such as cholesterol ester transfer protein and
HDL is a clinical predictor of restenosis after PTCA.

LCAT could be related to the levels of HDL, but in this study there was no statistical difference in the level of LCAT. Lp (a) has been investigated as the risk factor of coronary atherosclerosis. In our previous study, Lp (a) was a significant and independent risk factor for coronary artery disease, but Lp (a) was not

Table 3. Characteristics of Biochemical Variables (I)

<table>
<thead>
<tr>
<th></th>
<th>Restenosis n=16</th>
<th>Non-restenosis n=24</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>192.5 ± 7.3</td>
<td>212.1 ± 8.9</td>
<td>ns</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>169.6 ± 15.9</td>
<td>144.1 ± 18.0</td>
<td>ns</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>32.3 ± 1.7</td>
<td>40.0 ± 2.5</td>
<td>0.025</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>126.3 ± 33.5</td>
<td>143.3 ± 43.6</td>
<td>ns</td>
</tr>
<tr>
<td>Lipoprotein(a) (mg/dl)</td>
<td>28.5 ± 5.6</td>
<td>21.1 ± 4.5</td>
<td>ns *</td>
</tr>
<tr>
<td>LDL/HDL</td>
<td>4.2 ± 1.7</td>
<td>3.9 ± 1.8</td>
<td>ns</td>
</tr>
<tr>
<td>LCAT</td>
<td>80.3 ± 18.2</td>
<td>83.5 ± 17.9</td>
<td>ns</td>
</tr>
</tbody>
</table>

HDL: High Density Lipoprotein
LDL: Low Density Lipoprotein
LCAT: Lecithin:Cholesterol acyltransferase

Table 4. Characteristics of Biochemical Variables (II)

<table>
<thead>
<tr>
<th></th>
<th>Restenosis n=16</th>
<th>Non-restenosis n=24</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apolipoprotein AI</td>
<td>96.1 ± 14.2</td>
<td>103.0 ± 23.4</td>
<td>ns</td>
</tr>
<tr>
<td>Apolipoprotein AII</td>
<td>23.0 ± 5.4</td>
<td>23.6 ± 4.3</td>
<td>ns</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>109.0 ± 23.6</td>
<td>118.2 ± 26.7</td>
<td>ns</td>
</tr>
<tr>
<td>Apolipoprotein C-II</td>
<td>4.1 ± 1.7</td>
<td>3.6 ± 1.7</td>
<td>ns</td>
</tr>
<tr>
<td>Apolipoprotein C-III</td>
<td>9.5 ± 3.8</td>
<td>10.1 ± 4.5</td>
<td>ns</td>
</tr>
<tr>
<td>Apolipoprotein E</td>
<td>5.1 ± 1.4</td>
<td>5.1 ± 1.6</td>
<td>ns</td>
</tr>
<tr>
<td>Apolipoprotein B/AI</td>
<td>1.17 ± 0.34</td>
<td>1.21 ± 0.40</td>
<td>ns</td>
</tr>
</tbody>
</table>

mean ± SEM * Wilcoxon rank-sum test ns: not significant

mean ± SD ns: not significant
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a good predictor for restenosis in this study and in our previous study on the restenosis in elderly.17) The incidence of restenosis in patients with high Lp (a) level more than 20 mg/dl was slightly higher than those with low levels of Lp (a) without statistical difference (data not shown). Miyata et al.18) reported that Lp (a) level is a risk factor for restenosis after PTCA. Our study included the patients with multivessel disease but their study only included patients with single-vessel disease. This may change the results. Desmarais et al.19) also indicated that elevated serum Lp (a) is a risk factor for clinical recurrence after PTCA. They emphasized the method of store of blood samples and showed that Lp (a) decreased over time when serum was frozen and stored for a prolonged period. In our study, some blood samples were frozen for a few weeks at maximum. The negative results may have been influenced by an artifactual decrease in measured Lp (a) concentrations after storage and also by a small sample size (n=40).

It is reported that non-modifiable risk factors such as age, gender, and history of myocardial infarction 1,20,21) and modifiable risk factors such as hyperlipidemia, hypertension, diabetes mellitus, smoking are possible risk factors for restenosis after PTCA6,22,23,25). In patients with diabetes mellitus, the rate of restenosis was reported to be higher than that in non-diabetic patients.26) In diabetic patients, lipid profile showed the low level of HDL and high level of TG, and these profile could explain the high incidence of restenosis in diabetics.

Among the angiographical and procedure-related factors, large residual stenosis after PTCA is known to be a risk factor for restenosis.27) In our study, there were no statistical differences in angiographic variables. In necropsy study 28), it is reported that the ideal coronary artery for PTCA was to be a small (< 3.3mm in internal diameter) artery in which the plaque contained relatively little calcium and lipid. This study suggested the importance of lipid deposition in the outcome of PTCA and also serum lipid profile. Recently pharmacological interventions to prevent restenosis have been carried out extensively using drugs such as aspirin, calcium channel blocker, ACE-inhibitor, thrombin antagonist, cholesterol lowering agents. But so far the results are equivocal and unsatisfactory.29) Further investigations to elucidate the mechanisms of restenosis30,31) and to establish the procedure to prevent the restenosis are mandatory.

REFERENCES

HDL is a clinical predictor of restenosis after PTCA.


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