THE RELATIONSHIP BETWEEN SERUM LIPOPROTEIN(a) AND RESTENOSIS AFTER INITIAL ELECTIVE PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

Kohji Tenda, M.D., Tetsunori Saikawa, M.D., Toshihiro Maeda, M.D., Yasufumi Sato, M.D., Hiroko Niwa, M.D.*, Takeshi Inoue, M.D.*
Hidetoshi Yonemochi, M.D., Tohru Maruyama, M.D.**
Nobuo Shimoyama, M.D., Satoshi Aragaki, M.D.
Masahide Hara, M.D. and Ryosaburo Takaki, M.D.

The purpose of this study was to elucidate the possible link between lipoprotein(a) (Lp(a)) and the occurrence of restenosis after initial elective percutaneous transluminal coronary angioplasty (PTCA). Serum lipids, including Lp(a), total cholesterol, triglyceride, HDL-cholesterol, LDL-cholesterol, apolipoprotein A-I (Apo A-I), and apolipoprotein B (Apo B), and the Apo B/Apo A-I ratio were examined in 63 consecutive patients (41 men and 22 women, average age 63 ± 8 years) who underwent initial elective PTCA in our department. Forty two target lesions were in left anterior descending, 10 were in left circumflex and 11 were in right coronary branches. Restenosis was observed in 22 patients (35%) 6.4 ± 2.6 months after PTCA.
The serum Lp(a) level was significantly higher in the restenosis group than in the non-restenosis group (38.0 vs 19.9 mg/dl, p<0.05). A significant correlation was observed between serum Lp(a) levels and the degree of % restenosis after PTCA (r=0.557, p<0.001). However, other lipids showed no significant relationship to restenosis. In addition, the % stenosis before PTCA was found to be related to the occurrence of restenosis after successful PTCA.
We conclude that the serum Lp(a) level has a close correlation with the degree of % restenosis after PTCA, and may be a useful index for predicting the possibility of restenosis after PTCA, especially in patients with an Lp(a) level above 30 mg/dl. (Jpn Circ J 1993; 57: 789—795)

TREMENDOUS progress has been made in recent years in the treatment of ischemic heart disease. Percutaneous transluminal coronary angioplasty (PTCA) has become the established treatment among currently available options for patients with angina pectoris and myocardial infarction. However, one problem with this treatment is a considerably high incidence of restenosis1—5 Many studies and clinical trials have failed to elucidate the mechanism of, and methods to prevent, restenosis6—9 Diabetes mellitus and high serum cholesterol seem to be possible risk factors of restenosis in the United States and Europe9 However, this has not yet been demonstrated in Japan.
The role of lipoprotein(a) (LP(a))10—15 in coronary atherosclerosis and myocardial

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Department of Medicine, Oita Medical University, Oita 879-55, Japan
*Department of Medicine, Oita National Hospital, Oita 870, Japan
**First Department of Internal Medicine, Kyushu University, Fukuoka, Japan
Mailing address: Dr. T. Saikawa, Department of Medicine, Oita Medical University, Oita 879-55, Japan

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infarction has recently caught the attention of cardiologists. Lp(a) consists of a low density lipoprotein (LDL) and apolipoprotein(a), a protein with a structure similar to that of plasminogen, which is responsible for fibrinolysis. Lp(a) is known to localize in human atherosclerotic plaques\textsuperscript{16,17} and correlates with coronary heart disease. Lp(a) has also been shown to predict vein graft stenosis after coronary bypass surgery\textsuperscript{18}. These various results inspired us to study the relationship between Lp(a) and restenosis after successful PTCA, since the factors involved in restenosis after PTCA may involve a pathophysiologic process similar to that of graft stenosis and coronary arteriosclerosis, with such as the proliferation of vascular smooth muscle cells.

METHODS

Patients and protocol

Eighty consecutive patients who underwent initial elective PTCA in our department (55 males and 25 females) were enrolled as the subjects of the present study performed from April 1989 to April 1991. Among these patients, 17 patients with distinct dissection or intimal flap at the target lesion immediately after the elective PTCA were excluded from the present study, and the data obtained from the remaining 63 patients were analyzed.

The mean age of the 63 patients was 63±8 years. PTCA was performed on patients with more than 90% stenosis, according to the AHA classification, in the main branches of right and left coronary arteries. Follow-up arteriography was performed at a mean of 6.8±2.6 months (2.7–12.0 months) after the initial elective PTCA. Percent stenosis was calculated by measuring the diameter of the involved lesion with a hand-held caliper using a catheter as a scaling device. Restenosis was defined as either (1) progression of stenosis to more than 50% of the dilation gained immediately after PTCA, or (2) the presence of stenosis to more than 60% of the diameter of the involved lesion after PTCA. The degree of % restenosis was calculated as the difference between the % stenosis immediately after PTCA and % stenosis at the follow-up arteriogram. To avoid variation in the measurements of the degree of coronary artery stenosis, the measurements were taken by three cardiologists who were not informed of the Lp(a) level, and the mean of the three measurements was adopted for the following analyses.

PTCA was performed from a femoral approach. Intravenous heparin (10,000 units) was administered at the initiation of PTCA. Intracoronary isosorbide dinitrate (5 mg) was given simultaneously to exclude the possible interaction of vasospasm. The PTCA balloon size was determined according to the diameter of the stenotic segment from the pre-PTCA arteriogram so as to produce a ratio between the size of the inflated balloon and the coronary artery diameter of 1.0. The procedure was terminated when optimal angiographic results were obtained. Dipyridamole (10 mg) and low molecular dextran were administered 24 h prior to PTCA. The usual medication was continued, including aspirin (162 mg/day).

Lipid measurements

Serum Lp(a) was measured either before PTCA (5±1.5 days, range 3–8 days) or within 1–2 months (1.5–2.3 months, mean; 1.2±0.5 months) after PTCA by ELISA. Total cholesterol (T-Chol), triglyceride (TGL), and high density lipoprotein-cholesterol (HDL-C) levels were also measured before PTCA. LDL-cholesterol (LDL-C) was calculated using the Friedewald formula. Apolipoprotein A-I (Apo A-I), apolipoprotein B (Apo B) and the Apo B/Apo A-I ratio were also measured simultaneously. The reference level of Lp(a) in healthy subjects using this method was 15.5±11.4 mg/dl.

Statistical analysis

The data are presented as the mean±SD, except in the case of Lp(a), where the data are presented as the mean±SE. Statistical analysis was performed using paired and nonpaired t-test. Nonparametric analysis was also used. The age and sex-adjusted odds ratio and the 95% confidence interval were also defined.

RESULTS

Among the 63 patients studied, restenosis was observed in 22 patients (35%; restenosis
TABLE I PROFILES OF PATIENTS WITH AND WITHOUT RESTENOSIS

<table>
<thead>
<tr>
<th></th>
<th>Restenosis Group</th>
<th>Non Restenosis Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>number of patients</td>
<td>22</td>
<td>41</td>
</tr>
<tr>
<td>mean age (ys)</td>
<td>64.0 ± 9.5</td>
<td>62.8 ± 7.4</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>16/6</td>
<td>28/15</td>
</tr>
<tr>
<td>Target lesion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>14</td>
<td>25</td>
</tr>
<tr>
<td>RCA</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>CX</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>number of vessels’ disease</td>
<td>2.1 ± 0.3</td>
<td>2.2 ± 0.5</td>
</tr>
<tr>
<td>% stenosis preangioplasty (%)</td>
<td>79 ± 16</td>
<td>71 ± 12</td>
</tr>
<tr>
<td>% stenosis postangioplasty (%)</td>
<td>40 ± 15</td>
<td>38 ± 12</td>
</tr>
</tbody>
</table>

LAD: left anterior descending artery.  RCA: right coronary artery.  LCX: left circumflex artery.

Fig.1. Comparison of total cholesterol, triglyceride, HDL-Cholesterol and LDL-cholesterol in the non-restenosis and restenosis groups. No significant differences were observed between the two groups. Restenosis (+): The patient group with restenosis. Restenosis (−): The patient group without restenosis. These symbols are also used in Fig. 2 and 3.

group) and not observed in the remaining 41 patients (65%; non-restenosis group), according to the criteria described above. The profiles of both groups are shown in Table I. No significant difference was observed between the two groups with regard to age, sex, target lesions, number of stenotic branches, stenosis before PTCA, and % stenosis after PTCA.

The serum levels of T-Chol, TGL, HDL-C and LDL-C in the restenosis group and non-restenosis group were compared. As shown in Fig. 1, the mean serum T-Chol value was 193.8 ± 33.1 mg/dl in the restenosis group and 204.5 ± 40.8 mg/dl in the non-restenosis group. The TGL, HDL-C and LDL-C were 105.2 ± 32.0 mg/dl, 45.5 ± 18.5 mg/dl and 130.8 ± 29.4 mg/dl in the restenosis group and 126.3 ± 49.6 mg/dl, 37.4 ± 10.4 mg/dl and 141.9 ± 40.7 mg/dl in the non-restenosis group.
Fig. 2. Serum apolipoprotein A-I, apolipoprotein B and the ratio of Apo A-I/Apo B in the two patient groups. No significant difference was observed between the 2 groups.

Fig. 3. The level of serum lipoprotein(a) in the non-restenotic and restenotic groups. A significant difference was observed between the mean level of serum lipoprotein(a) in the restenotic group (38.0 ± 6.6, mean ± SE) and that in the non-restenotic group (19.9 ± 2.4 mg/dl).

Fig. 4. The relationship between the level of serum lipoprotein(a) and the degree of % restenosis in 63 patients. Note the significant correlation between the two indices, $r = 0.557$ (p < 0.001).

The levels of apolipoprotein in each of the groups were also compared (Fig. 2). In the restenosis group, the levels of apolipoprotein A-I (Apo A-I), apolipoprotein B (Apo-B) and the ratio of Apo B/Apo A-I were 108.0 ± 18.1 mg/dl, 100.4 ± 24.1 mg/dl and 1.0 ± 0.3, while those in the non-restenosis group were 103.9 ± 21.2 mg/dl, 105.9 ± 21.2 mg/dl and 1.1 ± 0.3, respectively. Again, no significant differences were observed between the two groups (Fig. 2).

Serum Lp(a) level was measured in all of the patients tested. The mean level of serum Lp(a) was 38.0 ± 6.6 mg/dl in the restenosis group and 19.9 ± 2.4 mg/dl in the non-restenosis group (Fig. 3). Therefore, the serum level of Lp(a) was significantly higher (p < 0.005) in restenotic patients than in non-restenotic patients (Fig. 3).

In addition to determining whether or not a patient showed restenosis, we also evaluated the extent of % restenosis, as described above. The level of Lp(a) is plotted against the extent of % restenosis in Fig. 4. Serum
level of Lp(a) and the extent of % restenosis exhibited a significant correlation (r = 0.557; p < 0.001), indicating that as the serum Lp(a) level increased, the extent of % restenosis also increased. According to the chi square test, the rate of restenosis was significantly greater among patients with an Lp(a) level above 30 mg/dl than in those with a lower level of Lp(a). The age and sex-adjusted odds ratio was 3.869, with a 95% confidence interval between 1.237 and 12.106. The critical level of 30 mg/dl roughly agreed with that in previous reports.

Multiple logistic regression analysis for risk factors of % restenosis after successful PTCA was performed using age, coronary score, % stenosis before PTCA, % dilatation, Lp(a), total cholesterol, triglyceride and HDL-cholesterol (Table II). The analysis revealed that both % stenosis before PTCA and Lp(a) showed a significant association. The other variables did not show such an association.

DISCUSSION

Since the first description of Lp(a) by Berg19 the pathophysiological role of Lp(a) has been actively investigated. The role of Lp(a) in atherosclerosis has come under scrutiny since Dahlen et al13 reported a possible relationship between Lp(a) and coronary atherosclerosis. Since then, many studies have demonstrated a close correla-

**TABLE II MULTIPLE LOGISTIC REGRESSION ANALYSIS FOR RISK FACTORS OF % RESTENOSIS AFTER PTCA**

<table>
<thead>
<tr>
<th>Variable</th>
<th>( \beta )</th>
<th>S. E.</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.116</td>
<td>0.263</td>
<td>0.625</td>
</tr>
<tr>
<td>Coronary Score</td>
<td>0.030</td>
<td>0.020</td>
<td>0.151</td>
</tr>
<tr>
<td>Pre % stenosis</td>
<td>0.400</td>
<td>0.149</td>
<td>0.009</td>
</tr>
<tr>
<td>% dilatation</td>
<td>0.050</td>
<td>0.135</td>
<td>0.716</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>0.274</td>
<td>0.090</td>
<td>0.002</td>
</tr>
<tr>
<td>TC</td>
<td>0.005</td>
<td>0.050</td>
<td>0.909</td>
</tr>
<tr>
<td>TG</td>
<td>-0.050</td>
<td>0.040</td>
<td>0.225</td>
</tr>
<tr>
<td>HDL-C</td>
<td>-0.179</td>
<td>0.182</td>
<td>0.331</td>
</tr>
</tbody>
</table>


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after PTCA.
Since the present study was a clinical survey, little information was available about the possible role of Lp(a) in the restenosis process after successful PTCA. In addition, the mechanism of restenosis after PTCA is still under investigation and no definite theory has yet been established. However, endothelial injuries in the chronic restenosis lesions were observed which could lead to platelet aggregation, as well as activation of macrophages and proliferation of smooth muscle cells (SMCs).

Recently, Kojima et al. reported that Lp(a) could inhibit the generation of transforming growth factor-β (TGF-β), which is an endogenous inhibitor of SMC migration. Therefore, a high level of serum and/or tissue Lp(a) may well decrease TGF-β production. The decrease of TGF-β would restore SMC migration from media to neointima. In other words, Lp(a) may accelerate SMC migration by reducing TGF-β production, which would favor the development of restenosis lesions. Further study is necessary to elucidate the role of Lp(a) in the pathophysiological process of restenosis.

STUDY LIMITATIONS

In the present study, the coronary artery diameter was measured with a hand-held caliper. Although we tried our best to minimize measurement errors a different technique, such as computer assisted measurement, might be more desirable.

Measuring Lp(a) levels during the various stages after successful PTCA may provide more useful information regarding the possible role of Lp(a) in the pathophysiological mechanism of restenosis. This may be done in a future study.

Previous reports have noted that the restenosis process seemed to be complete within about three months, at which time it plateaued. Since the present study was performed 6.8 ± 2.6 months after PTCA, the restenosis process seemed to be complete. However, a more detailed and scheduled analysis might be desirable.

Acknowledgment

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