Serum Lp(a) Lipoprotein Concentrations of Japanese Patients with Coronary Heart Disease

RYUICHI SANO, AKIHISA FUJINO, HIROMICHI SHIMAZU, MASAYOSHI KOBAYASHI, YOSHIKAZU YAHATA, ATSUIRO OGYYU, KATSUNORI SUZUKI, MASAYUKI KITAGAWA, TSUNEYOSHI SAITO and HIROSHI INOKUCHI*

Yonezawa City Hospital, Internal Medicine and Laboratory*, Yonezawa 992

SANO, R., FUJINO, A., SHIMAZU, H., KOBAYASHI, M., YAHATA, Y., OGYYU, A., SUZUKI, K., KITAGAWA, M., SAITO, T. and INOKUCHI, H. Serum Lp(a) Lipoprotein Concentrations of Japanese Patients with Coronary Heart Disease. Tohoku J. Exp. Med., 1990, 162 (3), 261-267 — The serum Lp(a) lipoprotein concentration in 103 healthy control subjects was determined by ELISA (TintElise Lp(a) kit, Biopool, Umea, Sweden). The distribution of Lp(a) in the controls was highly skewed (mean 132, S.D. 109, median 99 mg/liter), which is similar to the results previously reported. Serum Lp(a) level in 104 subjects who underwent coronary angiography was also measured. These subjects were divided into two groups: 59 cases of stenosis(−) and 45 of stenosis(+) groups. Lp(a) level of the stenosis(+) group (mean 235, s.d. 197, median 159 mg/liter) was significantly higher than that of the stenosis(−) group (mean 156, s.d. 133, median 123 mg/liter) and of the controls (Wilcoxon test, p < 0.05 and p < 0.01, respectively). Further, stenosis(+) group was divided into three subgroups: 20 with single vessel disease, 13 with double vessel disease and 12 with triple vessel disease subgroups. Lp(a) level was correlated with the number of stenotic coronary vessels (Spearman’s rank correlation coefficient, p < 0.05). These results suggest that Lp(a) may play an important part as a risk factor for coronary heart disease.

Berg (1963) first described the lipoprotein(a), or Lp(a), as a genetic variant of beta-lipoprotein which was considered a qualitative genetic marker. The lipoprotein was detected in the place of a pre-beta-1 by electrophoresis (Dahlen et al. 1972). “Sinking” pre-beta band (density 1.050-1.080 g/ml) was previously reported by the combination of electrophoresis and ultracentrifugation (Rider et al. 1970). It was known that Lp(a) was a quantitative trait being found in all individuals (Harvie and Schultz 1970). More recently, Lp(a) was reported to be a low density lipoprotein (LDL) that carries a glycoprotein called apolipoprotein(a) (apo) (a), joined to apo B-100 by a disulfide linkage (Brown and Goldstein 1987; Scanu 1988). Apo(a) was demonstrated to have size heter-
ogeneity with apparent Mr in the range 400-700 kDa and a high degree of homology with plasminogen (Eaton et al. 1987). It was suggested that Lp(a) was related with atherosclerosis and thrombosis. Many studies indicate that Lp(a) is regarded as a high risk not only in cardiovascular disease (Kostner et al. 1981; Armstrong et al. 1986; Ghilain et al. 1988) but also in cerebrovascular disease (Murai et al. 1986; Zenker et al. 1986). However, reports on plasma Lp(a) in Japanese people are little known.

In this study, we determined serum Lp(a) levels in the subjects examined by coronary angiography (CAG) as well as in the healthy controls, and investigated the association between Lp(a) and coronary heart disease in Japanese people.

**Subjects and Methods**

Serum was collected from 103 controls (Control) (65 males and 38 females, average 47.1±7.0 (s.D.) years old), who underwent for a medical check up in our hospital and diagnosed as normal according to electrocardiogram and laboratory data. A hundred and four subjects (64 males and 40 females, average 59.9±8.6 years old) were examined CAG by Judkins' method (1967) in our hospital from February, 1987 to December, 1988. They were divided into two groups: stenosis(−) group (Stenosis(−)) and stenosis(+) group (Stenosis(+)). The former group consisted of 59 subjects (30 males and 29 females, mean age 58.6±8.4) with less than 75% stenosis in any vessels evaluated according to AHA Committee Report (1975). The latter group consisted of 45 patients (34 males and 11 females, mean age 61.6±8.8) with over 75% stenosis in one or more vessels. Further, the group of Stenosis(+) was divided into three subgroups: 20 with single vessel disease (1VD), 13 with double vessel disease (2VD) and 12 with triple vessel disease (3VD) subgroups.

The blood sample was drawn from the antecubital veins after an overnight fast. Serum triglycerides (TG), total cholesterol (TC) and high density lipoprotein-cholesterol (HDL-C) were determined by autoanalyzer (CL20, Shimadzu, Kyoto) in all cases. LDL-cholesterol (LDL-C) was calculated by Friedwald’s formula (Friedwald et al. 1972). Serum Lp(a) was examined in all cases by enzyme immunoassay (ELISA) utilized polyclonal antibodies against purified human Lp(a) (TintElize Lp(a) kit; Biopool, Umea, Sweden). Serum apolipoproteins in the subjects who underwent CAG were examined by immunoturbidity methods (Apo A-I, A-II, B, C-II, C-III and E AUTO “DAI-ICHI”, Dai-ichi Pure Chem., Tokyo), and measured by autoanalyzer (COBAS MIRA, Roche, Switzerland).

Values are given in terms of mean ± s.d. The statistical evaluation of Lp(a) levels was performed by non-parametric test. The other variables were evaluated by parametric tests.

**Results**

As shown in Table 1, the age of Control was significantly lower in Control than in Stenosis(−) and Stenosis(+) (p < 0.01 and p < 0.01, respectively). The Stenosis(+) had significantly higher male/female ratio than Stenosis(−) (chi-square test, p < 0.05). A significant difference was not recognized in body mass index (BMI), TC, TG and LDL-C levels of these groups. Stenosis(+) had significantly lower HDL-C levels than Control and Stenosis(−) (p < 0.01 and p < 0.01, respectively).

The distribution of serum Lp(a) levels among Control was, as expected,
highly skewed, with a mean (s.d.) of 132 (108) mg/liter and a median of 99 mg/liter (Fig. 1). The distribution among the subjects examined CAG was also highly skewed, with a mean (s.d.) Lp(a) level of 190 (168) mg/liter and a median of 139 mg/liter.

The cumulative frequencies of serum Lp(a) in Stenosis(−) and Stenosis(+)
are shown in Fig. 2. The distribution in Stenosis(+) was shifted to higher values than in Stenosis(−) (p < 0.05). Further, Stenosis(+) was distributed to higher values than Control (p < 0.01). The distributions of Stenosis(−) was not different from that of Control (p > 0.05).

Table 2 shows the relation between serum Lp(a) level and number of stenotic coronary vessels in the subjects examined by CAG. The Lp(a) levels of OVD (=Stenosis(−)), 1VD, 2VD and 3VD subgroups were 156±132, 211±191, 213±169, and 297±237 mg/liter, respectively. Lp(a) had a weak but significant correlation to the number of stenotic vessels (Spearman’s rank correlation coefficient, p < 0.05).

As shown in Table 3, Stenosis(+) has lower levels of serum apoA-I and apoA-II than Stenosis(−) (p < 0.01 and p < 0.05, respectively). There was no difference in other serum apolipoprotein levels in these groups.

**Table 2.** Rank correlation coefficient between serum Lp(a) levels and the number of stenotic coronary vessels

<table>
<thead>
<tr>
<th>Coronary stenosis (number)</th>
<th>Serum Lp(a) levels (mg/liter)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-99</td>
</tr>
<tr>
<td>0VD (59)</td>
<td>22</td>
</tr>
<tr>
<td>1VD (20)</td>
<td>6</td>
</tr>
<tr>
<td>2VD (13)</td>
<td>1</td>
</tr>
<tr>
<td>3VD (12)</td>
<td>3</td>
</tr>
</tbody>
</table>

Spearman’s rank correlation coefficient; rs = 0.22, p < 0.05
We tested univariate correlation between serum Lp(a) and lipid-apolipoprotein variables in the subjects examined by CAG (Table 4). A weak but significant correlation for Lp(a) was only observed in TC, LDL-C and apoB ($p < 0.05$, $p < 0.01$ and $p < 0.05$, respectively).

**DISCUSSION**

The distribution of serum Lp(a) levels among Control, Stenosis(−) and Stenosis(+) groups are highly skewed. This result is similar to the distributions already reported among Caucasian subjects (Dahlen et al. 1986; Rhoads et al. 1986). The distribution of Stenosis(+) is shifted to higher values than Control and Stenosis(−). There is no difference in Lp(a) levels among Control and Stenosis(−).

Utermann and co-workers (1987, 1988) reported that apo(a) is encoded by a single locus with seven alleles ($Lp^5$, $Lp^8$, $Lp^{S1}$, $Lp^{S2}$, $Lp^{S3}$, $Lp^{S4}$ and $Lp^o$), which
produce proteins of different size and categorized into Lp(a) phenotypes (F, B, S1, S2, S3, S4 and null). Moreover, it was shown that there is a highly significant association between Lp(a) phenotypes and its concentrations, phenotypes of B, S1 and S2 with high, S3 and S4 with intermediate, and null with low concentrations (or absent). It is suggested that Stenosis(+) distributed higher values of Lp(a) has many subjects with phenotype B, S1 or S2 rather than Stenosis(-) and Control, and that the Lp(a) phenotype frequency of Stenosis(-) is similar to that of Control.

In this study, there is no difference in serum Lp(a) levels and the other variables between Control and Stenosis(-). Stenosis(+) had significantly higher Lp(a) levels, and had lower HDL-C, apoA-I and apoA-II levels than Stenosis(-). Whereas Lp(a) has a weak but significant correlation to TC, LDL-C and apo B, Stenosis(+) had higher level of only Lp(a), and did not have higher levels of the other variables than Stenosis(-). Further, serum Lp(a) level was correlated to the number of stenotic coronary vessels. These data suggested that increasing Lp(a) concentration, as well as decreasing HDL-C, encourage the risk of coronary artery disease in Japanese population.

Scanu (1989) summarized that Lp(a) may bridge the area of atherosclerosis and thrombosis. For prevention of cardiovascular disease, as progression and attack, it seems important to measure the serum Lp(a) concentrations in individuals, and to decrease its levels. Among drugs that lower LDL levels, only nicotinic acid which also lowers Lp(a) levels (Carlson et al. 1989) can be used in Japan. Further precise research of the clinical role of Lp(a) and treatment for patients with high levels of serum Lp(a) is needed.

Acknowledgments

We thank Professor Takayoshi Toyota, Dr. Shin-ichi Oikawa (The Third Department of Internal Medicine, Tohoku University School of Medicine) and Dr. Ryuzo Abe (Oota Nishinouchi Hospital) for having revised this report.

References


