

Lipoprotein(a) in Cerebrovascular and Coronary Atherosclerosis

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ABSTRACT

Serum lipoprotein(a) [Lp(a)] was determined in 85 healthy controls (control group), in 49 patients with cerebrovascular disease (CVD group), and in 87 patients with acute myocardial infarction (AMI group). Lp(a) concentration was measured using a single radial immunodiffusion method. Because Lp(a) showed a skewed distribution, Lp(a) was plotted in each group on a box plot and analyzed using non-parametric methods. The following results were obtained:

1) Lp(a) levels were significantly higher in both the AMI and CVD groups than in the control group.

2) The CVD group was divided into 4 groups: [1] cerebral hemorrhage (HEM); [2] cardioembolic infarction (EMB); [3] lacunar infarction (LAC); and [4] atherothrombotic infarction (THR). In the THR group, Lp(a) concentration was higher than those in the control and LAC groups.

3) In the CVD group, patients with an elevated Lp(a) value showed severe lesions in the major cerebral arteries evaluated by cerebral arteriograms.

4) In the AMI patients who underwent coronary angiography, the Lp(a) level showed a marked increase with an increase in the number of affected vessels. The correlation between coronary index (CI) and Lp(a) was also investigated. The lesion severity of coronary arteries was correlated with serum Lp(a) concentration.

These results suggest that a high Lp(a) value is linked to atherosclerosis of the cerebral and coronary arteries, and influences its severity.

Key words: *Lipoprotein(a), Atherosclerosis, Angiography, Box plot*

Lipoprotein(a) [Lp(a)] is a serum lipoprotein first reported by Berg in 1963⁴. It is similar to low density lipoprotein (LDL) in lipid composition and the presence of apolipoprotein B-100 (apo B-100). However, in addition to apo B-100, Lp(a) contains a highly glycosylated protein called apolipoprotein (a) [apo(a)], which is associated with apo B-100 via a disulfide link^{1,12,29}. Since the study of Dahlen et al in 1972, Lp(a) has attracted the attention of many researchers because a high Lp(a) level is associated with coronary atherosclerosis^{6,15,23}. In addition to coronary disease, evidence is accumulating that Lp(a) may be of importance in cerebrovascular disease^{20,30,32}. Furthermore, the cDNA sequence of apo(a) has been determined and shows a remarkable homology with human plasminogen^{9,19}. This finding may provide a direct link between thrombogenesis and progressive atherosclerosis^{5,25}.

In ischemic heart disease, some reports suggest that high levels of serum Lp(a) are related to the significantly greater severity of lesions quantified by coronary angiography^{7,11}. However, there are few reports on the association between Lp(a) con-

centration and lesion severity, evaluated by angiography, in cerebrovascular disease.

In our department, Ohtsuki studied the correlation between serum Lp(a) level and the stenosis of coronary lesions by angiography, and Konemori examined Lp(a) level in cerebral infarction, diagnosed by brain magnetic resonance imaging (MRI)^{14,22}. Their analyses differ from those of others in using box-and-whisker plots (box plots)²⁸. This method is useful in analyzing data which is not of normal distribution, such as Lp(a) concentration. In the present study, the author investigated the association between the Lp(a) level and angiographically assessed atherosclerosis in cerebrovascular disease and coronary artery disease, using box plots.

MATERIALS AND METHODS

Subjects.

All the subjects were males under 80 years of age. Serum lipid and Lp(a) concentrations were determined in 49 consecutive patients with cerebrovascular disease (CVD group) admitted to the Stroke Care Unit (SCU) of the National Cardio-

vascular Center (NCVC), and in 87 consecutive patients with acute myocardial infarction (AMI group) admitted to the Coronary Care Unit (CCU) of NCVC. The CVD patients were diagnosed by angiography as well as by brain computed tomography (CT) and magnetic resonance imaging (MRI). They were divided into 4 subgroups: 1) cerebral hemorrhage (HEM); 2) cardioembolic infarction (EMB); 3) lacunar infarction (LAC); and 4) atherothrombotic infarction (THR), according to the 1990 Classification of Cerebrovascular Diseases III developed by the Ad Hoc Committee of the National Institute of Neurological Disorders and Stroke (NINDS)²¹. The AMI subjects were diagnosed by electrocardiography, serum CPK level, echocardiography, and angiography. A total of 85 apparently healthy individuals examined for a medical check up were used as controls (control group). No patients received any drugs affecting the serum Lp(a) value, such as nicotinic acid.

Lipid and lipoprotein determinations.

Blood samples were drawn from the fasting patients early in the morning following hospital admission. The serum was isolated by low-speed centrifugation. Very low density lipoprotein (VLDL) was separated after ultracentrifugation for 18 hours at 40,000 rpm at a solvent density of 1.006 g/ml, as described previously³¹. The levels of cholesterol (Ch) and triglycerides (TG) in the serum and the VLDL fraction were determined by the enzymatic method. High density lipoprotein (HDL) cholesterol was measured by a precipitation method. The low density lipoprotein (LDL) cholesterol level was calculated as the serum cholesterol concentration minus the sum of VLDL-Ch and HDL-Ch levels.

Quantitation of Lp(a) concentration.

Serum Lp(a) levels were measured using a single radial immunodiffusion (SRID) technique with a mono-specific antibody against human Lp(a). This antibody was kindly provided by Dr. S. N. Pokrovsky (Institute of Experimental Cardiology, Cardiology Research Center, Moscow, Russia). The gel, at a volume of 6 ml per plate, consisted of 0.05M barbital buffer containing 1% (W/V) agarose and 120 μ l of antibody against Lp(a) (2 mg/dl). Wells of 2.5 mm diameter were punched out, and 4 μ l of standard or sample was added to each well. After 72 hours, the ring-shaped immuno-precipitates were measured in a tenth of a millimeter. The relationship between the Lp(a) level and the squared diameter of the precipitate ring was linear in the range of 2.5-32.0 mg/dl. Samples exceeding this range were diluted with 0.15 M NaCl.

Angiography.

A total of 42 CVD patients underwent four-vessel cerebral angiography. The cerebral arteries were divided into extracranial and intracranial arteries as described by Mathew et al¹⁸. In this study, the evaluation of atherosclerotic lesions was restricted to the extracranial arteries and major intracranial arteries.

In 76 AMI patients, coronary angiography was performed using the Judkins or Sones technique^{13,26}. The angiographic findings were evaluated by two different methods: 1) Patients were subdivided into groups with one-, two-, and three-vessel disease based on 75% or greater narrowing of the transluminal diameter of the left anterior descending artery, the left circumflex artery, and the right coronary artery. 2) Coronary arteries were divided into segments according to the American Heart Association Committee Report². In each segment, the extent of stenosis was evaluated and the coronary index (CI) was calculated by modified Balcon's method³. In CI, the lower the score, the greater the severity of the lesions.

Data analysis.

Lp(a) was plotted in each group on a box plot, as reported by Ohtsuki²² and Konemori¹⁴. With the box plot method, a box is formed by the 25th percentile and 75th percentile values that enclose the median. The distribution is expressed by widening the box to 1.5 times the 25th percentile and 75th percentile values, respectively. Comparison of the distribution of Lp(a) and other lipids between the two groups was performed by the Mann-Whitney test, and among the three groups the Kruskal-Wallis test was applied. The relation between Lp(a) level and the coronary index

Table 1. Characteristics of the subjects

Variable	control (n=85)	AMI (n=87)	CVD (n=49)
Age (yr)	48 (42-53)	61* (52-68)	59* (55-63)
Cholesterol	191 (172-212)	188 (162-216)	187 (154-201)
Triglyceride	115 (74-163)	106 (74-162)	124 (96-188)
HDL-Ch	45 (38-53)	34* (31-43)	35* (30-42)

AMI, acute myocardial infarction group;

CVD, cerebrovascular disease group;

Ch, cholesterol; n=number of subjects.

Lipid values are expressed in mg/dl.

Values are median (25th percentile - 75th percentile).

*p<0.01 (vs. control, Mann-Whitney test)

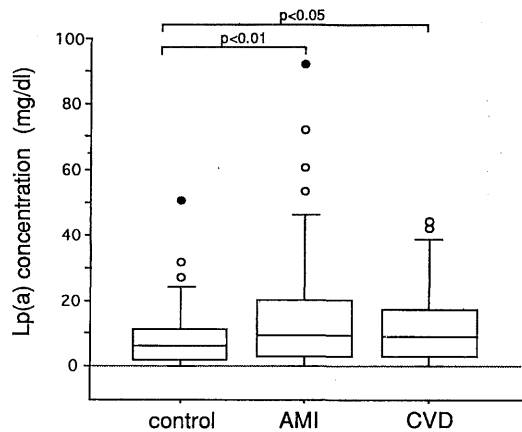


Fig. 1. Distributions of serum Lp(a) concentrations in the control, AMI, and CVD groups. Control, control group; AMI, acute myocardial infarction group; CVD, cerebrovascular disease group.

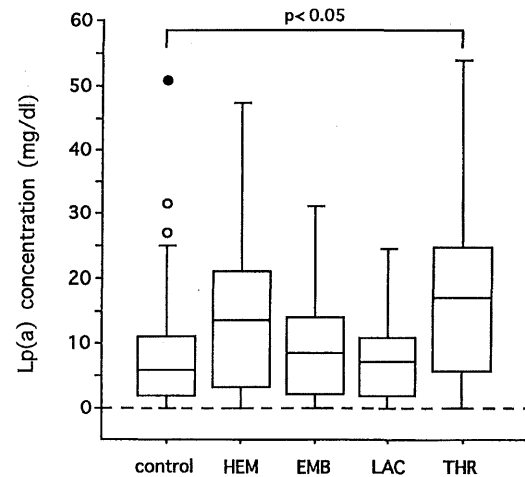


Fig. 2. Distributions of serum Lp(a) levels in the CVD subgroups. HEM, cerebral hemorrhage; EMB, cardioembolic infarction; LAC, lacunar infarction; THR, atherothrombotic infarction.

was investigated by Spearman's rank correlation coefficient. The level of significance was set at 0.05 for all analyses.

RESULTS

The serum lipoprotein profile in each group is shown in Table 1. AMI and CVD groups were older than the control group. HDL-Ch was significantly lower in the AMI and CVD groups compared to that in the control group, whereas there were no differences in the serum cholesterol and triglyceride levels.

The distributions of serum Lp(a) concentration in the three groups are shown by parallel box plot in Fig. 1. In the control group, the 25th percentile value, 50th percentile value and 75th percentile value of serum Lp(a) were 2.0 mg/dl, 6.0 mg/dl, and 11.5 mg/dl, respectively. Lp(a) did not show a normal distribution. The median of Lp(a) in the AMI and CVD groups was 9.3 mg/dl and 9.0 mg/dl, respectively. The serum Lp(a) concentrations were significantly higher in both the AMI and CVD groups than in the control group.

Since the age distribution of the AMI and CVD groups was different from that of the control

group, the subjects in each group were grouped by decade. There was no difference in the Lp(a) level among these 10-year age groups, and the Lp(a) concentration was higher in all the AMI and CVD subgroups compared to the control group (data not shown).

The CVD group was further divided into the following 4 subgroups: 1) 10 patients with cerebral hemorrhage (HEM group); 2) 12 patients with cardioembolic infarction (EMB group); 3) 18 patients with lacunar infarction (LAC group); and 4) 9 patients with atherothrombotic infarction (THR group). The lipid levels in each CVD subgroup were not so different from those of the CVD patients (Table 2). The median of Lp(a) concentration in the HEM, EMB, LAC, and THR groups was 13.5 mg/dl, 8.7 mg/dl, 7.2 mg/dl, and 17.2 mg/dl, respectively. In the THR group, the serum Lp(a) level was significantly higher than those in the control and LAC groups, but Lp(a) levels in both the HEM and EMB groups did not significantly differ from that in the control group (Fig. 2).

Table 2. Serum lipid levels in the CVD subgroups

Variable	HEM (n=10)	EMB (n=12)	LAC (n=18)	THR (n=9)
Age (yr)	59* (52-60)	62* (53-64)	62* (57-63)	57* (52-58)
Cholesterol	194 (178-200)	159** (150-191)	184 (142-200)	197 (174-211)
Triglyceride	107 (70-128)	122 (109-200)	118 (96-140)	184 (110-260)
VLDL-Ch	13 (6-17)	22 (16-25)	18 (13-24)	22 (14-32)
LDL-Ch	135 (117-146)	98 (90-120)	123 (79-145)	136 (122-157)
HDL-Ch	43 (35-56)	33* (25-39)	37* (28-45)	32* (31-34)

Abbreviations are as in Table 1.

* $p < 0.01$, ** $p < 0.05$ (vs. control, Mann-Whitney test)

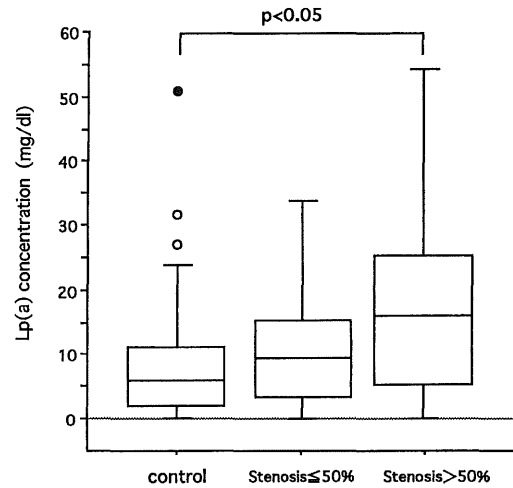
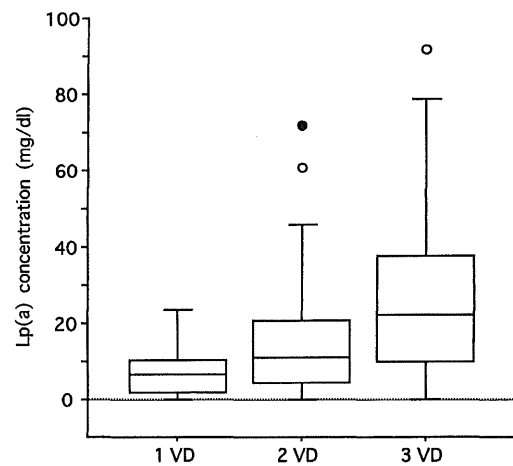
Table 3. Relationship between lipid level and severity of cerebral artery lesions by angiography

Variable	Stenosis \leq 50% (n=31)	Stenosis >50% (n=11)
Age (yr)	59 (56–63)	59 (56–63)
Cholesterol	187 (157–202)	181 (150–199)
Triglyceride	118 (93–151)	177 (106–189)
VLDL-Ch	18 (11–23)	22 (11–30)
LDL-Ch	122 (90–145)	128 (100–147)
HDL-Ch	38 (31–47)	32 (25–35)

Abbreviations are as in Table 1.

In the 42 CVD subjects, four-vessel cerebral angiography was performed and the relationship between serum lipid level and the extent of lesions in the major extracranial and intracranial arteries was investigated. These patients were divided into two groups according to the extent of lesions. Eleven patients had more than 50% stenosis of transluminal diameter (severe stenosis) and 31 patients had mild stenosis (<50%). There was no difference among these subgroups in the lipid and lipoprotein parameters (Table 3). The median of Lp(a) level in patients with mild stenosis and severe stenosis was 9.5 mg/dl, and 16.0 mg/dl, respectively. The Lp(a) value in patients with severe stenosis was significantly higher compared to the control group (Fig. 3).

In the AMI patients who underwent coronary angiography, the association between the number of affected vessels and serum lipid was examined (Table 4 and Fig. 4). Thirty two patients had one-vessel disease, 32 had two-vessel disease, and 12 had three-vessel disease. The median value of Lp(a) was 6.7 mg/dl in the one-vessel disease group, 11.0 mg/dl in the two-vessel disease group, and 22.1 mg/dl in the three-vessel disease group, indicating that the serum Lp(a) concentrations increased with an increase in the number of affected vessels (Fig. 4). On the other hand, no relationship was observed between the number of

**Fig. 3.** Distributions of Lp(a) levels in the CVD subjects with mild and severe stenosis, studied by cerebral angiography.**Fig. 4.** Distributions of Lp(a) levels in the AMI patients with one-, two-, and three-vessel disease. 1VD, one-vessel disease; 2VD, two-vessel disease; 3VD, three-vessel disease.**Table 4.** Relationship between number of affected vessels and serum lipid level

Variable	number of affected vessels		
	1 (n=32)	2 (n=32)	3 (n=12)
Age (yr)	62 (51–68)	59 (52–65)	61 (52–65)
Cholesterol	186 (158–209)	203 (171–241)	193 (177–224)
Triglyceride	123 (72–168)	105 (75–172)	104 (88–119)
VLDL-Ch	16 (7–27)	15 (8–24)	13 (11–18)
LDL-Ch	128 (107–152)	147 (121–178)	138 (126–170)
HDL-Ch	36 (31–44)	33 (31–39)	40 (31–48)

Abbreviations are as in Table 1.

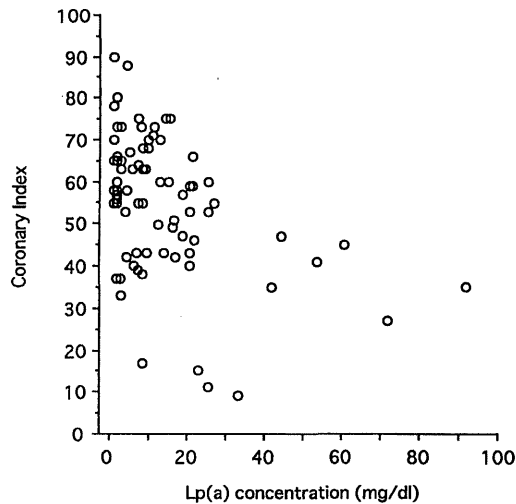


Fig. 5. Correlation between Lp(a) concentration and coronary index in the AMI group.

vessels with stenosis and variables other than Lp(a) (Table 4). Correlation between the coronary index and Lp(a) level was also evaluated in the AMI group (Fig. 5). Lp(a) value was inversely correlated with CI; CI tended to decrease with an increase in the Lp(a) value ($r_s = -0.41$, $p < 0.001$).

DISCUSSION

The distribution of serum Lp(a) concentrations in the control group showed no linearity on the Q-Q plot, and some markedly high values were observed (data not shown). Thus, Lp(a) did not show a normal distribution. This result is consistent with Ohtsuki's report²²). Therefore, it was not appropriate in this analysis to use the moment indicators, such as mean or standard deviation. Other lipids also did not necessarily show normal distributions. The distributions of lipids were therefore assessed using quantile indicators instead of moment indicators.

Lp(a) was plotted in three groups on parallel box plots (Fig. 1). The median of Lp(a) in the control, AMI, and CVD groups was 6.0 mg/dl, 9.3 mg/dl, and 9.0 mg/dl, respectively. Lp(a) level was higher in the AMI and CVD groups than in the control group. This is consistent with other reports^{15,23,32}). Although the serum Lp(a) concentration has been shown to increase gradually after the acute episode of myocardial infarction, reaching a maximum at 11 days, the Lp(a) level within 24 hours after the onset of the event changes little from the initial value¹⁷). Therefore, subjects in this study were limited to patients admitted ≤ 24 hours after onset, and samples were collected from the fasting patients in the morning following admission. Moreover, our results seem to be unaffected by age differences among the control, AMI, and CVD groups, because no relationship could be demonstrated between Lp(a) level and age^{8,16,24}).

Since cerebrovascular disease is caused by several different etiologies, the CVD individuals were divided into 4 subgroups: HEM group; EMB group; LAC group; and THR group. The categorization was based on the Classification of Cerebrovascular Diseases III developed by the National Institute of Neurological Disorders and Stroke (NINDS-III) of the National Institutes of Health (NIH)²¹). In this classification, lacunar infarction is treated as an independent category of cerebral infarction for the first time. Atherothrombotic infarction is mainly caused by atherosclerotic lesions, which are found in extracranial and major intracranial arteries, whereas lacunar infarction is small infarct mainly caused by lipohyalinosis and microatheroma of penetrating arteries^{10,27}). In our study, the Lp(a) concentration was higher in the THR group than in the control group and LAC group. These data are consistent with the reports of Murai et al and Woo et al^{20,30}). However, Konemori reported that, by multiple logistic regression analysis, Lp(a) did not show a significant odds ratio in cerebral infarction¹⁴). Konemori diagnosed cerebral infarction by MRI, whereas in the present study, cerebral angiography as well as MRI was applied for the diagnosis of the CVD patients, and the atherosclerosis of the large cerebral arteries was investigated in the atherothrombotic infarction. Therefore, the discrepancy seems to be not only due to the difference in the method of analysis but also due to the size and the portion of analyzed vessels.

Zenker et al performed B-mode and Doppler ultrasonography to examine the vascular stenosis of extracranial cerebral arteries, and showed that Lp(a) correlated with the score of lesion severity in cerebrovascular disease³²). However, there are few reports on the association between the Lp(a) level and the lesion severity quantified by cerebral arteriography. In this study, the stenosis of extracranial arteries and major intracranial arteries was evaluated by angiography in 42 CVD patients, and the relationship between Lp(a) value and the extent of lesions was investigated. The Lp(a) level in subjects with severe stenosis was significantly higher than that of the control group. Thus, patients with a high Lp(a) concentration had severe stenosis of the large cerebral arteries, and this result is similar to Zenker's report where the evaluation was made by ultrasonography.

In the AMI group, the association between Lp(a) concentration and angiographically assessed coronary artery stenosis was also studied. Two different approaches were used to investigate the coronary artery stenosis. In the first approach, patients were divided into groups based on the number of arteries with 75% or greater stenosis. The serum Lp(a) concentration

increased with an increase in the number of vessels with stenosis. On the other hand, there was no relationship between the severity of lesions and other lipid levels. These are the same as Ohtsuki's results in our department²². This approach is usually used in the evaluation of lesion severity of coronary arteries. However, it is not possible to assess the atherosclerosis in multiple small lesions by this method. Therefore, in the second approach, the stenosis of each segment was determined, and each score was summed as the coronary index. There are some papers on Lp(a) in which the severity of lesions was scored^{7,11}. However, the method used in the present study was different from theirs. The size of the vessel in the analysis of lesions was also considered, because the weighting of atherosclerosis in large vessels is not similar to that in small vessels. The severity of coronary artery disease appeared to correlate well with the Lp(a) level.

In this study, the author determined Lp(a) concentrations in the CVD and AMI groups and evaluated the relationship between atherosclerosis and Lp(a) levels by cerebral and coronary angiography. The observations suggest that Lp(a) is not only a risk factor for coronary and cerebral atherosclerosis but may also be related to the progression of atherosclerosis.

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