Distribution of Lipoprotein (a) and Relationships between its Level and Blood Chemical Findings in a Rural Area in Japan

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To reveal a distribution of lipoprotein (a) (Lp(a)) in Japan and to explore relationships between Lp(a) and conventional cardiovascular risk factors, transaminase (GOT(ALT)), GPT(ALT) and γ-glutamyltranspeptidase (γ-GTP), a cross-sectional study in a healthy population was performed. We measured serum Lp(a) of 497 apparently healthy subjects aged 40-69 years old in a rural area in Japan; 198 males and 299 females. Lp(a) frequency distributions were highly skewed to the low level. Serum Lp(a) level is significantly higher in the females (15.1±1.08 mg/dl) than in the males (12.0±1.01 mg/dl). Among males the median and mean log Lp(a) levels increased according to age. Pearson's correlation analysis showed statistically significant correlations (p<0.05) between Lp(a) and GOT, GPT, γ-GTP, total cholesterol (TCH), triglyceride, but no statistically significant correlations between Lp(a) and body mass index, blood pressure, high-density lipoprotein cholesterol, blood sugar, corrected TCH for males. On the other hand, the same analysis showed no statistically significant correlation among Lp(a) and each item observed for females. We suppose Lp(a) is not related to conventional cardiovascular risk factors. J Epidemiol, 1994; 4 : 163-169.

Lipoprotein (a) (Lp(a)) was discovered in 1963 by Berg¹, a geneticist in Norway, and was reported as a genetic variation of low density lipoprotein cholesterol (LDL cholesterol). Many researchers have reported its clinical meanings since 1972, when Dahlen regarded it as an independent risk factor of arteriosclerotic diseases². When the primary structure of Apoprotein (a), which composes Lp(a), was determined in 1987, it was proved that the structure of Lp(a) was similar to the plasminogen³. After then, the role of Lp(a) in the mechanisms of arteriosclerosis became argued from two view points; atheroscleroses and the thrombogeneses. There are considerable evidences that Lp(a) is a strong independent risk factor for coronary heart disease⁴. Lipoprotein (a) has been studied, however, predominantly in white populations. In this study we revealed the distribution of Lp(a) in Japan, and we explored whether there is an association between Lp(a) and conventional cardiovascular risk factors and whether there is an association between Lp(a) and enzymes as indicators of hepatocellular damage such as transaminase and γ-glutamyltranspeptidase.

MATERIALS AND METHODS

Health screening programs were performed from June 2nd through June 4th, 1992 in T area of Tako-machi, Chiba prefecture. The target population of the programs were those aged 40-69 years. Specimens were collected from 497 persons who came to the programs.

The following data were collected at the screening programs.

- Height (cm), weight (kg), Body Mass Index (BMI), systolic blood pressure (SBP) (mmHg), diastolic blood pressure (DBP) (mmHg), white blood cell count (WBC), red blood cell count (RBC), hematocrit (Ht) (%), hemoglobin (Hb) (g/dl), glutamate oxaloacetate transaminase (GOT) (IU/l), glutamate pyruvate transaminase (GPT) (IU/l), γ-glutamyltransferase (γ-GTP) (IU/l), total cholesterol (TCH) (mg/dl), HDL cholesterol (HDL) (mg/dl),
triglyceride (TG) (mg/dl), blood sugar (BS) (mg/dl), lipoprotein (a) (Lp(a)) (mg/dl)

We analyzed relationships between each of the items and Lp(a). Blood samples were collected without consideration of meal intake.

Because the distribution of Lp(a) has been reported to be very skewed, we observed the Lp(a) value changed into the common logarithm. We used logarithmic values of other findings, such as GOT, GPT, γ-GTP as well, because of the same reason. We used a t-test for approval of the difference of the mean, and Peason's correlation coefficients for observation of the relationships between Lp(a) and the other findings. Since Lp(a) contains cholesterol much, we used the cholesterol value obtained by subtracting the cholesterol contained in Lp(a) from the total cholesterol to observe relationships between Lp(a) and total cholesterol. The formula to estimate cholesterol contained in Lp(a) is (Lp(a) (mg/dl) x 0.3)α. Serum Lp(a) levels were measured by a single lot of an Enzyme-Linked ImmunoSorbent Assay (ELISA) kit of the Biopool company.

RESULTS

1) The numbers of the object persons and the participating persons, and the participating rate by sex and age

The numbers of the object persons and the participants, and the participation rate are shown in Table 1 by sex and age. The participation rate was 34% for males and 47% for females. In terms of age classes, there was no difference of the participation rates between sexes.

2) Average of Lp(a) by sex and age

The mean, quartiles, and 2.5 percentile, 97.5 percentile of Lp(a) values, and the mean of Lp(a) values after the logarithmic change were shown in Table 2. Lp(a) was distributed widely in 1.8-64.6 mg/dl for females and 1.1-58.0 mg/dl for males as the lower to upper 2.5 percentile.

The logarithmic means of serum Lp(a) concentrations in females (15.1 mg/dl) were significantly higher than in males (12.0 mg/dl). The medians of Lp(a) values were close to the logarithmic means, which were 12.7 mg/dl in males and 15.1 mg/dl in females. The quartiles, 2.5 percentile and 97.5 percentile values were also higher in females than in males.

In males the logarithmic means of Lp(a) concentration were significantly higher in the age class of 60's than in that of 40's. Lp(a) concentration tended to rise along with aging in males.

Lp(a) was highest in the age class of 50's and lowest in that of 40's in terms of the medians and the logarithmic means for females. Lp(a) in the age class of 60's was higher than in 40's but lower than in 50's.

3) Relative frequency distribution of Lp(a) by sex

The relative frequency distribution of Lp(a) by sex was shown in Figure 1. The Lp(a) frequency distribution was highly skewed toward the low level. The Lp(a) level seemed meaningfully higher in females than in males. In the lowest class of Lp(a) (Lp(a) ≤ 5 mg/dl), the relative

| Table 1. The number of objects and participants of population screening by age and sex. |
|---|---|---|---|---|---|
| Age (yr) | Both sexes | | | | |
| | total | 40-49 | 50-59 | 60-69 | |
| Objects | 1,212 | 316 | 421 | 475 | |
| Participants | 497 | 122 | 184 | 190 | |
| Participation rate (%) | 41 | 39 | 44 | 40 | |
| Males | | | | | |
| Objects | 576 | 170 | 185 | 221 | |
| Participants | 198 | 57 | 63 | 78 | |
| Participation rate (%) | 34 | 34 | 34 | 35 | |
| Females | | | | | |
| Objects | 636 | 146 | 236 | 254 | |
| Participants | 299 | 65 | 121 | 112 | |
| Participation rate (%) | 47 | 45 | 51 | 44 | |

| Table 2. Lp(a) levels in 497 recruited individuals by sex and age. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| sex | age (year) | Number of subjects | Lp(a) mean (mg/dl) | Lp(a) mean (mg/dl) | La(a) percentiles (mg/dl) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Males | all | 198 | 17.5 | 12.0 | 1.1 | 6.4 | 12.7 | 23.6 | 58.0 |
| | 40-49 | 57 | 14.5 | 9.8 | 0.3 | 5.4 | 10.8 | 17.4 | 53.8 |
| | 50-59 | 63 | 17.3 | 11.8 | 1.1 | 6.2 | 12.7 | 23.2 | 58.4 |
| | 60-69 | 78 | 19.8 | 14.1 | 1.5 | 8.2 | 15.5 | 26.2 | 88.1 |
| Females | all | 299 | 20.7 | 15.1 | 1.8 | 8.2 | 15.1 | 26.5 | 64.6 |
| | 40-49 | 65 | 20.0 | 12.6 | 1.5 | 5.8 | 13.1 | 22.4 | 91.4 |
| | 50-59 | 121 | 18.8 | 16.6 | 2.0 | 8.5 | 18.3 | 29.8 | 59.0 |
| | 60-69 | 112 | 22.8 | 15.1 | 1.8 | 8.9 | 14.7 | 25.4 | 67.2 |

* P < 0.05  
† calculated using log transformation
frequency of males (7.8%) was higher than that of females (11.0%).

A cumulative frequency distribution is shown in Figure 2 by sex and age. The older males were, the higher was the Lp(a) frequency in the high level. The distribution of females differed from that of males. For both the age class of 60's and that of 50's, the frequency shifted to the higher level compared with that of 40's with that of 50's being higher than that of 60's.

4) Correlation coefficients between Lp(a) and observed other findings

Pearson's correlation coefficients between the Lp(a) and observed other findings are shown in Table 3. First, in males significant negative correlations (p<0.05) between Lp(a) and GOT, GPT, γ-GTP were observed. In males, there were significant positive correlations of Lp(a) with creatinine (r=0.17) and with total cholesterol (r=0.15). However, when revised total cholesterol was used there was no significant correlation. Significant negative correlations relation of Lp(a) with the triglyceride (r = -0.16) and with blood sugar (r = -0.16) were observed. In females Pearson's correlation analysis revealed no statistically significant correlation of log lipoprotein (a) with BMI, BP, log GPT, log γ-GTP, log TCH, log TG, log HDL, BS.

Two typical scatter diagrams are shown in Figures 3, 4.

Figure 3 is the scatter diagram of γ-GTP against Lp(a) with the largest absolute value of the correlation coefficient. There was a negative correlation.

Figure 4 is the scatter diagram of the triglyceride and Lp(a) for male with the largest absolute value of the correlation coefficient in the observed fats. It was significant but the relation was not so strong (r = -0.16).

**DISCUSSION**

We measured Lp(a) of healthy population in a rural area in Japan using screening programs. Because elevated serum levels of Lp(a) have been shown to be an independent risk factor of the arteriosclerotic disease, it is important to make its distribution clear and define normal ranges for this lipoprotein. We have observed that Lp(a) values do not associated with any risk factor for arteriosclerotic disease measured in the current cross-sectional study.

Although blood samples were collected without consideration of meal intake, it is meaningful to consider relationship between Lp(a) and blood chemical findings, because triglyceride (TG)-rich particles during postprandial lipemia appeared not to be related to the level of Lp(a). The specimens were considered to be made from healthy persons, because the persons visiting hospitals were not recommended to participate in the screening programs. The participation rate for females was higher than for males. However, the difference in participation rates among age classes is small; the averages for each sex observed in this study, thus, would reflect that in the healthy population in a rural area in Japan.

The frequency distribution of Lp(a) was similar to the previous reports for the white and Japanese; the Lp(a) frequency distribution was highly skewed toward the low level. Thus, Lp(a) requires special thought in statistic processing. Because it distributed nearly normal when the logarithmic transformation was performed, we used the value after logarithmic change in statistic processing. Furthermore, we showed quartiles which included a median.
The Lp(a) distribution differed between sexes. The proportions with Lp(a) ≤ 5 mg/dl were 17.8% for males and 11.0% for females. In other words, the proportion of males in this low level class was 1.6 times as large as that of females. This fact caused males and females difference of the mean Lp(a) values. Moreover, the logarithmic means of females was also significantly higher than that of males. Few previous studies showed the sex deference. The reasons why the sex difference has been unclear are small sample sizes and the lack of consideration of highly skewed distribution in previous studies.

The concentration of Lp(a) increased with age in males. This fact was made clear by the medians and the means calculated using logarithmic transformation. Lp(a) value for the age class of 60's was significantly higher than for that of the 40's.

**Figure 2.** Cumulative distribution of Lp(a) concentration by sex and age.
Table 3. Pearson's correlation coefficients between Lp (a) and other findings.

|                  | male     | female  |
|------------------|----------|---------|
| Age              | 0.13     | 0.05    |
| Height           | -0.06    | 0.04    |
| Weight           | -0.09    | 0.10    |
| Body mass index  | -0.07    | -0.10   |
| Systolic blood pressure | -0.13 | 0.08    |
| Diastolic blood pressure | -0.13 | 0.07    |
| White blood cell | -0.01    | -0.05   |
| Red blood cell   | -0.07    | 0.02    |
| Hemoglobin       | -0.09    | 0.03    |
| Hematocrit       | -0.09    | 0.03    |
| GOT\(^a\)        | -0.17\(*\) | -0.04   |
| GPT\(^b\)        | -0.24\(**\) | 0.00    |
| \(\gamma\)-GTP\(^c\) | -0.32\(**\) | -0.03   |
| Creatinine\(^d\) | 0.17\(*\) | -0.02   |
| Total cholesterol\(^e\) | 0.15\(*) | 0.10    |
| Corrected Total cholesterol\(^f\) | 0.02 | -0.03   |
| High density lipoprotein\(^g\) | 0.01 | -0.04   |
| Triglyceride\(^h\) | -0.16\(*\) | 0.05    |
| Blood sugar\(^d\) | -0.16\(*\) | -0.01   |

\(^a\): log transformation was performed
\(^*\) P<0.05  \(^*\) P<0.01
\(^b\) glutamate oxaloate transaminase
\(^c\) glutamate pyruvate transaminase
\(^d\) \(\gamma\)-glutamyl transpeptidase

Figure 3. Relationship between lipoprotein (a) and \(\gamma\)-glutamyltranspeptidase (male).

Figure 4. Relationship between lipoprotein (a) and triglyceride (male).

In females the consecration of Lp(a) was higher in the old age classes, 50's and 60's, than in young age class, 40's, and it was higher in 50's than in 60's. According to a previous report, Lp(a) values were 8% greater in postmenopausal women than in premenopausal ones after controlling for age\(^{14}\). Another paper suggested that in estrogen plus progesterone-treated postmenopausal women, serum Lp(a) concentrations was lowering\(^{15}\). The age difference of Lp(a) values for females in this study might be caused by menstruation. Most of the females in the age classes of 50's and 60's were postmenopausal. Sex hormones may affect the concentration of Lp(a).

Slunga et al, reported the mean of the Lp(a) for males and females elevated significantly with age as well\(^{16}\). The statistically significant difference among age classes would have been admitted because their sample size was as large as approximately 700. The sample size in this study is also comparatively large with approximately 200 males and about 300 females. However, in many previous studies\(^{9-13}\), it is supposed not to be significant relation between age and Lp(a). Like the sex difference, the age difference has been unclear because the mean was not proper as the measure of central location and the sample size was too small.

Lp(a) was related to the liver functions, such as \(\gamma\)-GTP, GPT, and GOT, with the negative correlation in males in this study. It was reported that Lp(a) decreased in various hepatic injuries, especially in obstructive jaundice\(^{13}\). The
fact of Lp(a)'s lowering with hepatopathy supports the hypothesis that the liver synthesizes Lp(a)\(^{16,17}\).

There is no report which is decisive in the relationship between cholesterol and Lp(a) so far. The relation between Lp(a) and cholesterol is arguable; two studies supposed to be positive straight relation\(^{18,19}\) and others showed no significant relation\(^{20,21}\). It is to be noticed that Slunga et al, used TCH which was revised with Lp(a)\(^{22}\). They subtracted the cholesterol which is contained in Lp(a) from TCH to observe the relation between the cholesterol and Lp(a). The total cholesterol and Lp(a) before the revision showed significant relation. After the revision, however, they supposed that there was not significant relation. We used the same revision formula. In this study before the revision, there was a significant positive relation between TCH and Lp(a) in males; after the revision, however, there was no significant relation.

Blood lipids such as cholesterol and TG are transported in lipoproteins. Lipoproteins consist of lipids and apoproteins. An apoprotein is considered to be a transporter of lipids. Lp(a) contains apoprotein B100 which is the same as LDL cholesterol, so Lp(a) is the cholesterol-rich lipoprotein like LDL. Therefore, Lp(a) level affects TCH level. To examine the relation between Lp(a) and cholesterol, the revision of subtracting the cholesterol which is contained in Lp(a) from TCH is necessary.

Between Lp(a) and triglyceride, there was a negative correlation in males. It has been reported that there were significant negative correlations between Lp(a) and triglyceride, and activities of lipoprotein lipase\(^{21}\). These facts suggest a relationship between the metabolism of triglycerides-rich-lipoproteins and Lp(a).

Between Lp(a) and blood sugar, there was a negative correlation in males and no significant correlation in females. Some case-control studies\(^{22,23}\) have indicated a rise of Lp(a) in insulin dependent diabetes mellitus. On the other hand another study has indicated that Lp(a) levels were not increased in non-insulin dependent diabetes mellitus and non diabetic subjects\(^{24}\). No significant correlation between log-transformed plasma Lp(a) levels and fasting plasma glucose level has been reported as well\(^{25}\). It is likely that there is weak or no association of serum Lp(a) value with blood glucose; thus Lp(a) is an independent risk factor of arteriosclerotic diseases in diabetic subjects.

Diabetic subjects have been reported to have both increased Lp(a) concentrations and an increased risk of renal failure\(^{26}\). Thereby the Lp(a)-renal failure association has been supposed. In this study, positive correlation between Lp(a) and creatinine in males was observed. Few studies have explored the relationship of renal function to lipoprotein Lp(a) concentrations in large population. A case-control study has been reported that Lp(a) was elevated in subjects with chronic renal failure, but that Lp(a) levels were not correlated with the level of creatinine\(^{27}\).

We suppose that there is a weak or no association between Lp(a) concentrations and serum creatinine or renal function. However, the role of Lp(a) in renal failure is not denied. For example, Lp(a) may play a role of promoter in an early stage of renal failure progression.

In conclusion, the current study has made distribution of Lp(a) in the healthy population clear. Lp(a) showed the skewed distribution toward to the low level. Serum log Lp(a) level is significantly higher in females than in males. In males, the median and mean log lipoprotein(a) levels were higher in old subjects than in young subjects. In males, Pearson's correlation analysis revealed statistically significant correlation of log lipoprotein (a) with log GOT, log GPT, log y-GTP, log TCH, log TG, but there was no statistically significant correlation of Lp(a) with BMI, BP, HDL, BS, corrected TCH. In females, Pearson's correlation analysis revealed no statistically significant correlation of log lipoprotein (a) with BMI, BP, log GPT, log y-GTP, log TCH, log TG, log HDL, BS. We suppose Lp(a) is not related to conventional cardiovascular risk factors.

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