Lipoprotein(a) Levels and Apolipoprotein(a) Isoforms Related to Life Style Risk Factors

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Lipoprotein(a) [Lp(a)] has been considered to be a predictor of premature coronary heart disease and other cardiovascular diseases. Lp(a) levels are largely genetically determined, but the detailed mechanism of Lp(a) elevation is uncertain.

We examined the association between Lp(a) levels and apolipoprotein(a) [apo(a)] phenotypes as well as that of Lp(a) level and other various conditions. The subjects were 280 healthy Japanese (102 males and 178 females) aged 39 to 70 years who were living in a rural community in 1992. We obtained apo(a) phenotypes determined by SDS-PAGE as well as Lp(a) levels and other cardiovascular risk factors. We combined apo(a) phenotypes form 4 groups according to molecular weights (from high apo(a) molecular weight to low: I, II, III and IV).

Lp(a) levels were associated with apo(a) phenotype-groups, that is, they were inversely associated with apo(a) molecular weight. Small apo(a) phenotypes were less frequent than large ones. The median Lp(a) level was higher in smoking (29.2 mg/dL) than in non-smoking subjects (18.5 mg/dL) in phenotype-group III. Adjusted means of total cholesterol and fibrinogen levels in apo(a) phenotype-group IV were the highest of all phenotype-groups. Age, apo(a) phenotype, smoking status, total cholesterol and fibrinogen were positively correlated with Lp(a) levels by multiple regression analysis.

Lp(a) levels were found to be mainly associated with apo(a) phenotype, but varied broadly within the same apo(a) phenotype at various conditions, such as smoking status and high total cholesterol. J Epidemiol, 1999 ; 9 : 32-39

Lp(a) is a macromolecular complex in human plasma that assembled from a low density lipoprotein (LDL) and a high molecular weight Lp(a) glycoprotein or apolipoprotein(a) [apo(a)]. Since Berg first described Lipoprotein(a) [Lp(a)], many studies have examined the association between Lp(a) concentrations and cardiovascular diseases (CVD) 1 2 3 4 5. Although some prospective studies have reported negative result 4 6 7, the association between Lp(a) levels and coronary heart disease has been recently confirmed 8 9 10 11.

Unlike other lipoproteins, it has been reported that Lp(a) levels are mainly determined genetically 11 and are not markedly influenced by other factors, such as sex, age and food 12 13. Increased levels of Lp(a) are associated with various conditions, including myocardial infarction 3 12, cerebral infarction 14, peripheral vascular diseases 15, diabetes mellitus 16, renal failure 17, menopausal status 18 19, smoking, aging 19 20 21, and heredity 22.

Utermann et al. established the conception regarding Lp(a) isoforms and apo(a) phenotypes, that serum Lp(a) levels are largely determined by Lp(a) isoforms, but within the same type of Lp(a) isoform, serum Lp(a) levels vary broadly 23 24. It is unclear to what extent Lp(a) levels are determined genetically.

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and environmentally. Abe et al. reported Lp(a) levels and distribution of apo(a) phenotypes in healthy Japanese subjects, but we cannot find the studies to investigate the relationship of Lp(a) levels and apo(a) phenotypes with other risk factors in Japanese. This is the first study, to our knowledge, to clarify not only the distribution of apo(a) phenotypes, but the association between apo(a) phenotypes and other risk factors such as smoking and drinking habits, blood pressure and other serum lipids in a rural district in Japan as a part of the JMS Cohort Study.4,21,26,27

METHODS AND MATERIALS

The subjects were 280 healthy Japanese (men: 102 and women: 178) aged 39 to 70 years in Akaike town, Fukuoka, Japan, obtained by mass screening examination in November, 1992. All subjects had no past histories of CVD such as myocardial infarction or apoplexy. The subjects were included as a part of the JMS Cohort Study.19

Systolic and diastolic blood pressures (BP) were measured with a fully automated sphygmomanometer, BP203RV-II (Nippon Colin, Kornaki, Japan), placed on the right arm of the subjects who had been in the sitting position for 5 minutes before the measurement.

We obtained blood samples before noon after an overnight fast. Lp(a) concentrations were determined by enzyme-linked immunosorbent assay (ELISA) (Immuno AG, Vienna, Austria). Apo(a) isoforms were determined by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) under reducing conditions and the Lp(a) proteins were demonstrated by immunoblotting using polyclonal rabbit anti-apo(a) antibody. The subjects were tested exhibiting single or double band(s). According to their relative mobilities, the Lp(a) patterns were classified into phenotype F (faster than apo B-100), B (identical to apo B-100), S1, S2, S3 and S4 (slower to different degrees than apo B-100), and into the respective double-band phenotypes. Null type had no detectable apo(a) band. We combined the apo(a) phenotypes form 4 groups according to molecular weights, as previously performed by Klausen et al. 26

Plasma fibrinogen levels were determined with a one-stage clotting assay kit (Data-Fi, Dade, Miami, FL, USA). Factor VII coagulant activity (FVIIc) was measured by achromogenic assay using a human FVII-deficient plasma kit (Behringwerke AG, Marburg, Germany), and a chromogenic assay autoanalyzer (Behring chromatimer, Behringwerke, Marburg, Germany). The activity of commercially available pooled plasma (CTS Standard plasma; Behringwerke AG) was considered 100%. Total cholesterol and triglycerides were measured by an enzymatic method (Wako, Osaka, Japan). High density lipoprotein (HDL) cholesterol was measured by the phosphotungstate precipitation method (Wako, Osaka, Japan).

STATISTICAL METHODS

Statistical analysis was performed using the Statistical Analysis System (SAS) 6.12 edition (SAS Institute Inc., Cary, NC, USA). Lp(a) levels were presented as medians (95% confidence intervals). Systolic and diastolic blood pressure, total and HDL-cholesterol, fibrinogen and FVIIc were presented as means (± standard error (SE)). Lp(a) level and triglycerides were used for calculation after logarithmic transformation. Variables classified by apo(a) phenotype-groups were calculated using analysis of variance. The Kruskal-Wallis rank test and Wilcoxon's rank sum test were used for differences among Lp(a) levels. Multiple regression analysis was used to analyze the association between Lp(a) and other variables.

RESULTS

Frequencies of apo(a) phenotypes are shown in Table 1. Large molecular phenotypes of apo(a) were most frequently observed, (S3: 25.4%, S4: 27.1% and S3S4: 11.8%), and null type demonstrated 9.3% a frequency. We combined phenotypes S4 and null as phenotype-group I, phenotypes S3 and S3S4 as phenotype-group II, phenotypes S2, S2S3 and S2S4 as phenotype-group III, and other phenotypes as phenotype-group IV. Lp(a) concentrations increased with the numbers of phenotype-groups in order (I<II<III<IV), and the differences among Lp(a) levels of phenotype-groups were significant in both men and women (p<0.001 for both) (Table 2), which indicating that Lp(a) concentrations were inversely related to the molecular size of apo(a) phenotypes. No differences were seen between Lp(a) levels in men and women in each phenotype-group. Distributions of Lp(a) levels by apo(a) phenotype-groups are shown in Figure 1, each of which was highly skewed and varied broadly. However the modes were shifted to the higher levels of Lp(a) according to apo(a) phenotype-group.

Lp(a) levels were slightly increased with age in both men and women, but no significant differences were found among age groups in both sexes (p=0.515 in men and p=0.156 in women). No differences were seen between Lp(a) levels in men and women in total, in each age group (Table 3).

Total cholesterol levels tended to be higher in phenotype-groups III and IV (p=0.08), and HDL-cholesterol levels of phenotype-group III were higher than those of the other groups in the analysis of variance (p<0.01). Triglycerides levels of phenotype-group II were higher than those of the other groups (p=0.06). Both systolic and diastolic blood pressure, fibrinogen and FVIIc were not significantly different among apo(a) phenotype-groups (Table 4).

Lp(a) levels were not significantly different between hyper-
### Table 1. Distribution of Apo (a) phenotypes.

| Apo (a) Phenotype-group | Apo (a) Phenotype | n  | %   |
|-------------------------|-------------------|----|-----|
| I                       | S4                | 76 | 27.1|
|                         | Null              | 26 | 9.3 |
|                         | Sum               | 102| 36.4|
| II                      | S3                | 71 | 25.4|
|                         | S3, S4            | 33 | 11.8|
|                         | Sum               | 104| 37.2|
| III                     | S2                | 16 | 5.7 |
|                         | S2, S3            | 12 | 4.3 |
|                         | S2, S4            | 9  | 3.2 |
|                         | Sum               | 37 | 13.2|
| IV                      | F                 | 2  | 0.7 |
|                         | F, B              | 1  | 0.4 |
|                         | F, S1             |    |     |
|                         | F, S2             | 1  | 0.4 |
|                         | F, S3             | 1  | 0.4 |
|                         | F, S4             | 4  | 1.4 |
|                         | B                 | 4  | 1.4 |
|                         | B, S1             | 1  | 0.4 |
|                         | B, S2             | 2  | 0.7 |
|                         | B, S3             | 1  | 0.4 |
|                         | B, S4             | 4  | 1.4 |
|                         | S1                | 3  | 1.1 |
|                         | S1, S2            | 2  | 0.7 |
|                         | S1, S3            | 5  | 1.8 |
|                         | S1, S4            | 6  | 2.1 |
|                         | Sum               | 37 | 13.2|

Total 280 100.0

### Table 2. Median Lp (a) levels with 95% CIs according to the apo (a) phenotype-group.

| Apo (a) Phenotype-group | Men   | Women  |
|-------------------------|-------|--------|
|                         | n   | Lp (a) | n   | Lp (a) |
| I                       | 37  | 4.1 (1.5-6.4) | 65  | 3.6 (2.3-5.2) |
| II                      | 37  | 9.5 (7.1-14.2) | 67  | 10.5 (7.6-14.0) |
| III                     | 12  | 29.2 (11.5-37.7) | 25  | 18.1 (9.4-26.4) |
| IV                      | 16  | 37.1 (23.2-51.5)** | 21  | 50.5 (39.5-67.1)** |

*** p<0.001 : Median Lp (a) levels among apo (a) phenotype-groups, using the Kruskal-Wallis test
Figure 1(a-d). Frequency by Lp (a) levels in apo(a) phenotype-groups.

Table 3. Median Lp (a) levels with 95% CIs according to age.

|        | Men       | Women     |
|--------|-----------|-----------|
|        | n | Lp (a)     | n | Lp (a)     |
| All    | 102 | 9.8 (7.6-14.2) | 178 | 9.3 (7.3-11.8) |
| Age (Years) | | | | |
| 39-49  | 43 | 8.6 (3.8-11.5) | 57 | 6.7 (3.6-12.2) |
| 50-59  | 16 | 11.7 (4.4-31.2) | 50 | 9.9 (6.5-18.1) |
| 60-70  | 43 | 13.8 (7.8-20.5) | 71 | 10.1 (7.3-14.8) |

Using the Kruskal-Wallis test
tensive and normotensive subjects, or between drinking and non-drinking subjects in each phenotype-group in all subjects (Data not shown). Lp(a) levels were also not significantly different between in smoking and non-smoking subjects in each phenotype-group. However the median Lp(a) level in phenotype group III was higher in smoking subjects than in non-smoking subjects in all subjects [Median level of Lp(a); Smoking: 29.2, Non-smoking: 18.5]. A similar tendency was observed between smoking and non-smoking subjects in only men.

By multivariate regression analysis, logarithmic Lp(a) levels were significantly and positively associated with age (p<0.01), apo(a) phenotype-group (p<0.01), smoking status (p=0.03), total cholesterol (p<0.01) and fibrinogen (p<0.01), and negatively associated with logarithmic triglycerides (p<0.01) (multiple correlation coefficient: 0.49) (Table 5).

Table 4. Means of other cardiovascular risk factors stratified by apo (a) phenotype-group adjusted for sex and age.

| Apo (a) phenotype-group | n   | Mean | SE  | p value |
|-------------------------|-----|------|-----|---------|
| Systolic blood pressure |     |      |     |         |
| I                       | 102 | 134.7| 2.0 | 0.66    |
| II                      | 104 | 135.2| 2.0 |         |
| III                     | 37  | 130.6| 3.3 |         |
| IV                      | 37  | 134.5| 3.2 |         |
| Diastolic blood pressure|     |      |     |         |
| I                       | 102 | 82.8 | 1.2 |         |
| II                      | 104 | 81.8 | 1.2 |         |
| III                     | 37  | 79.8 | 1.9 |         |
| IV                      | 37  | 81.5 | 1.9 | 0.60    |
| Total cholesterol       |     |      |     |         |
| I                       | 102 | 199.2| 3.4 |         |
| II                      | 104 | 199.8| 3.4 |         |
| III                     | 37  | 204.5| 5.5 |         |
| IV                      | 37  | 214.9| 5.4 | 0.08    |
| HDL-cholesterol         |     |      |     |         |
| I                       | 102 | 53.1 | 1.5 | <0.01   |
| II                      | 104 | 50.4 | 1.5 |         |
| III                     | 37  | 59.9 | 2.4 |         |
| IV                      | 37  | 53.5 | 2.4 |         |
| Triglycerides#          |     |      |     |         |
| I                       | 102 | 94.5 (93.5-95.6) | |         |
| II                      | 104 | 103.2 (102.2-104.3) | |         |
| III                     | 37  | 81.5 (80.5-82.6) | |         |
| IV                      | 37  | 90.6 (89.6-91.7) | |         |
| Fibrinogen              |     |      |     |         |
| I                       | 102 | 233.1 | 5.5 |         |
| II                      | 104 | 236.5 | 5.5 |         |
| III                     | 37  | 234.3 | 9.0 |         |
| IV                      | 37  | 251.5 | 8.9 | 0.36    |
| Factor VIIc             |     |      |     |         |
| I                       | 102 | 104.3 | 1.6 |         |
| II                      | 104 | 103.8 | 1.6 |         |
| III                     | 37  | 107.3 | 2.6 |         |
| IV                      | 37  | 109.2 | 2.6 | 0.26    |

p value were calculated by analysis of variance
#Geometric mean (±se)
We examined Lp(a) levels and apo(a) phenotypes in a Japanese population using cross-sectional data. Few studies have reported Lp(a) and apo(a) phenotypes in Japanese 25). We studied not only the distribution of apo(a) phenotypes, but the association between apo(a) phenotypes and other risk factors.

Plasma concentrations of Lp(a) are mainly determined by the apo(a) gene locus on chromosome 6 and apo(a) sizes are inversely associated with Lp(a) levels 29,30,31). Apo(a) polymorphism was investigated in various ethnic populations and Lp(a) levels were found to vary between races and ethnic groups 29,32,33). Abe et al. reported that the distribution of Lp(a) and allele frequencies in Japanese were similar to the results for European whites, but they were different from Asian populations, such as Chinese, Indians and Malaysians 34).

Lp(a) has been recognized as an independent risk factor of coronary heart disease (CHD) 6-10). Small apo(a) isoforms (B, S1 and S2) were associated with high Lp(a) levels, as previous studies demonstrated 23), and significantly associated with CHD 28,29, especially in subjects under 60 years of age 26). Small size apo(a) were also associated with premature coronary heart diseases and other cardiovascular diseases 28,29,31,36,37). Rader et al. reported a substantial variation in Lp(a) levels among individuals with the same apo(a) phenotype as determined by the Lp(a) production rate 30). It has been suggested that Lp(a) is initially determined genetically, and is then influenced by various conditions. Higher genetic Lp(a) levels are correlated with CVD. However a surplus of Lp(a), which indicates a difference between the genetic level of Lp(a) and the level after being influenced by environmental factors, may also be associated with CVD.

Subjects with genetically higher levels develop CVD more easily, but subjects with genetically lower levels also may develop CVD, if surplus Lp(a) levels increase. Surplus Lp(a) also acts as a acute phase reacting protein 39). In some situations, such as in end-stage renal failure 17) or after a surgical operation 45), Lp(a) concentrations increase due to the inflammatory state. Cardiovascular events that consist of a long-lasting intravessel change may cause activated coagulating conditions and an elevated Lp(a) level. Therefore high Lp(a) levels are not only risk factors of CVD, but predictors for coagulating conditions.

Sechi et al. reported an association between Lp(a) concentrations and the severity of target-organ damage, and a significantly higher frequency of low-molecular weight apo(a) isoforms with increasing severity of target-organ damage. It has been suggested that Lp(a) concentrations were inversely related to the molecular weight of apo(a), and that a low molecular weight apo(a) was essentially related to CHD or other cardiovascular diseases 37).

In the present study, the median Lp(a) level was higher in smoking (29.2 mg/dL) than in non-smoking subjects (18.5 mg/dL) in phenotype-group III. Adjusted means for sex and age of total cholesterol and fibrinogen levels in apo(a) phenotype-group IV were the highest of all phenotype-groups. By multiple regression analysis Log[Lp(a)] as significantly correlated with apo(a) phenotype-group, age-group, smoking status, total cholesterol, log(triglycerides) and fibrinogen. These results followed the previous studies, in which Lp(a) levels were determined genetically and associated with environmental factors like smoking, age and other cardiovascular risk factors.
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