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Original Article

Association Between Lipoprotein (a) Levels and Coronary Artery Disease (CAD) Among Patients With or Without CAD Family History

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ABSTRACT

Objective: Lipoprotein (a) (Lp[a]), which is a highly heritable trait, is associated with coronary artery disease (CAD). However, the insight into whether the association between Lp(a) and CAD differs according to the family history of CAD remains unclear.
Methods: We investigated clinical data of 4,512 participants who underwent serum Lp(a) level measurement at Kanazawa University Hospital between 2008 and 2016. The association between Lp(a) and CAD according to CAD family history was investigated through logistic regression analyses.
Results: CAD family history and Lp(a) levels were significantly associated with CAD development (odds ratio [OR], 1.32; 95% confidence interval [CI], 1.12–1.52; $p<0.001$ and OR, 1.13; 95% CI, 1.03–1.23; $p<0.001$ per 10 mg/dL, respectively). In patients without CAD family history, those with Lp(a) levels ≥30 mg/dL had higher CAD risk than those with Lp(a) levels <30 mg/dL (reference) (OR, 1.33; 95% CI, 1.05–1.61; $p<0.001$). In patients with CAD family history, those who had Lp(a) levels <30 and ≥30 mg/dL were both highly at risk for CAD (OR, 1.24; 95% CI, 1.04–1.44; $p<0.001$ and OR, 1.68; 95% CI, 1.34–2.02; $p<0.001$, respectively). Adding CAD family history and Lp(a) information to other conventional risk factors enhanced CAD risk discrimination (C-statistics: 0.744 [0.704–0.784] to 0.768 [0.730–0.806], and 0.791 [0.751–0.831], respectively; $p<0.05$ for both).
Conclusion: Lp(a) level was associated with CAD development regardless of CAD family history status.

Keywords: Lipoprotein(a); Lipoprotein; Medical family history; Coronary artery disease

INTRODUCTION

Lipoprotein (a) (Lp[a]) is a lipoprotein consisting of a particle resembling a low-density lipoprotein (LDL), and this is one of the crucial residual risk factors of CAD.[1,2] In fact, Lp(a) level appears to be quite useful in CAD risk discrimination on top of classical risk scores, especially when it is elevated.[3] International clinical guidelines now recommend assessing Lp(a) levels in several situations, including, at least once in a lifetime (Europe and Canada),[4-6] when additional risk discrimination would be needed (US and Europe),[5,7] statin intolerance

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Conflict of Interest

The authors have no conflicts of interest to declare.

Data Availability Statement

The datasets generated and analyzed during the study are not publicly available due to the terms to which the participants agreed. However, the datasets generated and/or analyzed during the current study are available upon request from the corresponding author.

Author Contributions

Conceptualization: Tada H, Kawashiri MA; Data curation: Tada H, Kojima N, Yamagami K, Takeji Y, Sakata K, Usui S, Kawashiri MA, Takamura M; Formal analysis: Tada H, Kojima N, Yamagami K, Takeji Y, Sakata K, Usui S, Kawashiri MA, Takamura M; Funding acquisition: Tada H; Supervision: Takamura M; Writing - original draft: Tada H, Kojima N, Yamagami K, Takeji Y, Sakata K, Usui S, Kawashiri MA, Takamura M.

(US),[8] and a family history of premature CAD (US, Europe, and Canada).[5,6,8] Among these situations, a family history of premature CAD is the most adopted because Lp(a) level is determined mostly by genetic factors.[9] CAD is a heritable trait; thus, CAD family history, especially premature CAD family history, has long been considered as an important element of risk discrimination.[10] Considering these facts, most of us would wonder 1) if a part of association between CAD family history and CAD may be explained by the Lp(a) level, and 2) if the association between Lp(a) and CAD differs according to CAD family history. Given that newer agents that can substantially reduce Lp(a) levels will be available very soon,[11-13] this study aimed to investigate the association between Lp(a) and CAD according to the presence or absence of CAD family history.

MATERIALS AND METHODS

1. Study population

This study retrospectively investigated 5,437 Japanese participants who underwent serum Lp(a) level assessment at Kanazawa University Hospital between 2008 and March 2016. Among them, 925 participants were excluded because of having no clinical data (**Supplementary Fig. 1**). Thus, the 4,512 remaining participants were analyzed. Baseline data including medical history, physical examination findings, and blood test results were assessed. The cohort commonly included inpatients referred to the hospital for fasting blood sample assessment. **Table 1** shows the participants' characteristics.

2. Biochemical analysis

For biochemical assay, blood samples were collected after overnight fasting. Automated instruments were used for measuring serum creatinine, LDL cholesterol, triglyceride, and high-density lipoprotein (HDL)-cholesterol levels enzymatically. Lp(a) concentrations were determined through the enzyme-linked immunosorbent assay.[14] The coefficient of variation of Lp(a) measurement was <8% within and between assays.[14]

Table 1. Participants' baseline characteristics

Variables	All (n=4,512)	Family history (+) (n=954)	Family history (–) (n=3,558)	*p*-value
Age (yr)	59±16	52±17	60±16	<0.001
Male	2,432 (53.9%)	524 (54.9%)	1,908 (53.6%)	0.5
BMI (kg/m^2)	23.7±4.6	23.5±4.4	23.8±4.6	0.19
Hypertension	2,423 (53.7%)	501 (52.5%)	1,922 (54.0%)	0.43
Diabetes	1,550 (33.9%)	315 (33.0%)	1,235 (34.7%)	0.35
Smoking	1,998 (44.3%)	410 (43.0%)	1,588 (44.6%)	0.38
Total cholesterol (mg/dL)	187 (157–219)	196 (168–224)	182 (153–216)	<0.001
Triglyceride (mg/dL)	105 (73–156)	120 (80–174)	104 (70–152)	<0.001
HDL cholesterol (mg/dL)	49 (39–61)	44 (36–55)	50 (39–61)	<0.001
LDL cholesterol (mg/dL)	107 (85–134)	128 (100–148)	104 (82–130)	<0.001
Lipid-lowering therapy	1,169 (25.9%)	534 (56.0%)	635 (17.8%)	<0.001
Lp(a) (mg/dL)	13.0 (6.7–28.5)	18.9 (8.4–44.2)	12.8 (6.4–27.0)	<0.001
CAD	885 (19.6%)	344 (36.1%)	541 (15.2%)	<0.001

Categorical variables, expressed as percentages and continuous variables with a normal distribution are presented as the mean ± standard deviation, whereas those without a normal distribution are presented as the median and interquartile range.
BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein (a); CAD, coronary artery disease.

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3. Clinical evaluation

Patients were considered having a family history of CAD if at least one of their first-degree relatives was diagnosed with CAD. Those with a systolic blood pressure of at least 140 mmHg, a diastolic blood pressure of at least 90 mmHg, or antihypertensive medication were regarded as hypertensive. Furthermore, patients were considered diabetic if they met the diabetes description of the Japan Diabetes Society[15] or if they were under diabetes medication. Body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared. Smoking was defined as any smoking habit. We also assessed data on the participants' baseline medications, including lipid-lowering, antihypertensive, antidiabetic, and antithrombotic drugs. Finally, CAD was defined as the presence of angina pectoris, myocardial infarction, or severe stenotic region(s) in the coronary artery identified via angiogram or computed tomography scan.

4. Ethical considerations

This study obtained approval from the Ethics Committee of Kanazawa University (IRB No. 1737). All procedures conformed to the ethical standards of the responsible committee on human experimentation (institutional and national); the 1975 Declaration of Helsinki, as revised in 2008; the Ethical Guidelines for Medical and Health Research Involving Human Subjects; and all other associated laws and guidelines in Japan.

5. Statistical analysis

Categorical variables, expressed as percentages, were analyzed using the Fisher's exact test or the χ^2 test, as applicable. Continuous variables with a normal distribution are presented as the mean ± standard deviation, whereas those without a normal distribution are presented as the median and interquartile range. The associations between various factors, including age, sex, BMI, hypertension, diabetes, smoking, LDL cholesterol, triglyceride, HDL cholesterol, and Lp(a) levels, were assessed using logistic regression analysis. In addition, we conducted receiver operating characteristic curve analysis and calculated the C-statistic value to estimate the predictive performance of the considered parameters. Continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were also calculated. All statistical data were analyzed using the R statistical software. The *p*-values <0.05 were considered statistically significant.

RESULTS

1. Participant characteristics

Table 1 shows the participants' clinical characteristics. Of the 4,512 included patients, almost half (53.9%) were male, and 885 (19.6%) had CAD. Overall, the mean age was 59 years. Patients with CAD family history were significantly younger than those without CAD family history (52 vs. 60 years, $p<0.001$). More than half of the patients (53.6%) had hypertension, approximately one-third (33.9%) had diabetes, and almost half (44.3%) had smoking habits. Their median LDL cholesterol level was 107 mg/dL, and 1,169 (25.9%) participants received lipid-lowering therapies. In group comparison, the median total cholesterol, triglycerides, and LDL cholesterol levels were significantly higher in patients with CAD family history than in those without (196 vs. 182 mg/dL, 120 vs. 104 mg/dL, and 128 vs. 104 mg/dL, respectively; all $p<0.001$). Conversely, the HDL cholesterol level was significantly lower in patients with CAD family history than in those without (44 vs. 50 mg/dL, $p<0.001$). The median Lp(a) level was 13.0 (interquartile range: 6.7–28.5) mg/dL. When comparing the groups, the median

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Lp(a) level was significantly higher in patients with CAD family history than in those without (18.9 vs. 12.8 mg/dL, p<0.001). Patients with CAD family history also had a significantly higher CAD prevalence than those without (36.1% vs. 15.2%, p<0.001).

2. Factors associated with CAD

The factors that are possibly associated with atherosclerotic diseases were assessed. Multivariate logistic regression analysis showed that age (p<0.001), male sex (p<0.001), hypertension (p<0.001), diabetes (p<0.001), smoking (p<0.001), triglycerides (p=0.03), HDL cholesterol (p<0.001), lipid-lowering therapy (p<0.001), family history (p<0.001), and Lp(a) level (p<0.001) were independently associated with CAD (**Table 2**).

3. Odds for CAD development according to CAD family history and Lp(a) levels

In participants without CAD family history, those who had Lp(a) level ≥30 mg/dL exhibited higher odds for CAD development than those who had Lp(a) level <30 mg/dL as a reference (p<0.001; **Fig. 1**). In participants with CAD family history, those who had Lp(a) level <30 mg/

Table 2. Factors associated with CAD

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Age (per year)	1.04 (1.02–1.06)	<0.001	1.04 (1.02–1.06)	<0.001
Male (yes vs. no)	1.55 (1.20–1.90)	<0.001	1.70 (1.18–2.22)	<0.001
BMI (per kg/m^2)	1.10 (1.03–1.17)	0.002	1.04 (0.95–1.15)	0.24
Hypertension (yes vs. no)	4.40 (2.24–6.16)	<0.001	3.10 (2.00–4.20)	<0.001
Diabetes (yes vs. no)	1.44 (1.10–1.78)	<0.001	1.32 (1.06–1.58)	<0.001
Smoking (yes vs. no)	2.44 (1.28–3.60)	<0.001	1.70 (1.20–2.20)	<0.001
LDL cholesterol (per mg/dL)	0.97 (0.95–1.00)	0.12	0.98 (0.96–1.00)	0.12
Triglycerides (per mg/dL)	1.00 (1.00–1.00)	0.01	1.00 (1.00–1.00)	0.03
HDL cholesterol (per mg/dL)	0.98 (0.97–0.99)	<0.001	0.98 (0.97–0.99)	<0.001
Lipid-lowering therapy (yes vs. no)	2.96 (1.80–4.12)	<0.001	2.42 (1.40–3.44)	<0.001
Family history (yes vs. no)	1.56 (1.16–1.96)	<0.001	1.32 (1.12–1.52)	<0.001
Lp(a) (per 10 mg/dL)	1.20 (1.05–1.35)	<0.001	1.13 (1.03–1.23)	<0.001

CAD, coronary artery disease; OR, odds ratio; CI, confidence interval; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; Lp(a), lipoprotein (a).

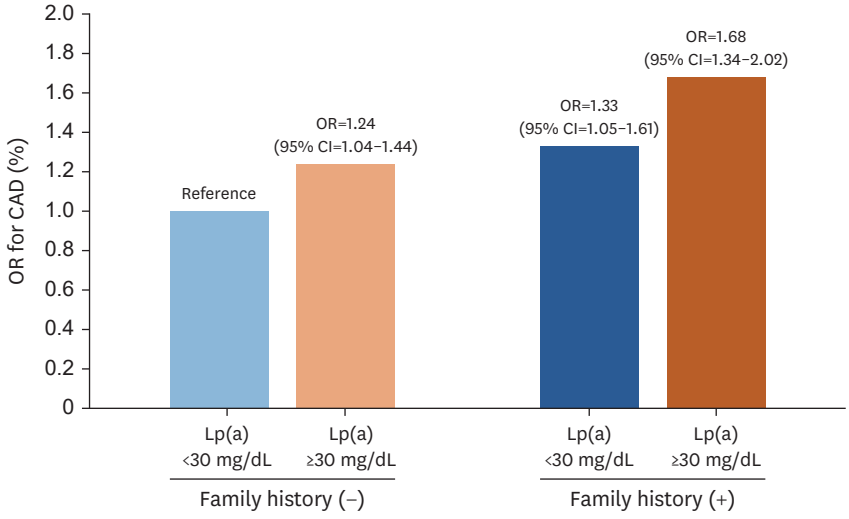

Fig. 1. Lp(a) level, family history, and odds ratios for coronary artery disease.
Light blue and light orange indicate patients without a family history of CAD who had Lp(a) levels of <30 and ≥30 mg/dL, respectively. Dark blue and dark orange indicate patients with a family history of CAD who have Lp(a) levels <30 and ≥30 mg/dL, respectively.
Lp(a), lipoprotein (a); CAD, coronary artery disease; OR, odds ratio; CI, confidence interval.

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Table 3. C-statistic of models for predicting CAD

Models	C-statistics (95% CI)	*p*-value	NRI (95% CI)	*p*-value	IDI (95% CI)	*p*-value
Conventional model	0.744 (0.704–0.784)	reference	reference		reference	
Conventional model + family history	0.768 (0.730–0.806)	0.021	0.116 (0.030–0.192)	0.012	0.034 (0.011–0.045)	0.01
Conventional model + Lp(a)	0.760 (0.724–0.96)	0.033	0.098 (0.021–0.185)	0.022	0.024 (0.010–0.038)	0.03
Conventional model + family history + Lp(a)	0.791 (0.751–0.831)	0.004	0.178 (0.068–0.288)	0.004	0.050 (0.018–0.082)	0.003

CAD, coronary artery disease; CI, confidence interval; NRI, net reclassification improvement; IDI, integrated discrimination improvement; Lp(a), lipoprotein (a).

dL also exhibited higher odds for CAD, and those who had Lp(a) level ≥30 mg/dL exhibited even higher odds for CAD (both $p<0.001$; **Fig. 1**).

4. Risk discrimination for CAD according to lifestyle risk score

We further investigated whether the discrimination ability of a model based on the traditional risk factors associated with CAD (age, sex, hypertension, diabetes, smoking, and LDL cholesterol level) differed from those of models that included CAD family history and Lp(a). Moreover, the C-statistic value of the traditional risk factor model increased from 0.744 to 0.768, and 0.760 after incorporating CAD family history or Lp(a) into the model ($p=0.021$ and $p=0.033$, respectively; **Table 3**). It even further increased to 0.791 after including Lp(a) into the model ($p=0.004$; **Table 3**). We also assessed the continuous NRI and IDI. We found that the addition of family history (continuous NRI, 0.116; 95% CI, 0.030–0.192; $p=0.012$ and IDI, 0.034; 95% CI, 0.011–0.045; $p=0.01$), Lp(a) (continuous NRI, 0.098; 95% CI, 0.021–0.185; $p=0.022$ and IDI, 0.024; 95% CI, 0.010–0.038; $p=0.03$), and both of them (continuous NRI, 0.178, 95% CI, 0.068–0.288; $p=0.004$ and IDI, 0.050; 95% CI, 0.018–0.082; $p=0.003$) to the conventional model improved reclassification (**Table 3**).

DISCUSSION

This study aimed to investigate the association between Lp(a) and CAD according to presence or absence of CAD family history. Results revealed that 1) patients with CAD family history exhibited significantly higher Lp(a) levels, 2) both CAD family history and Lp(a) were independently associated with CAD development, and 3) both CAD family history and Lp(a) independently add risk discrimination information for CAD. Therefore, Lp(a) levels should be assessed regardless of their CAD family history status, although a part of their CAD family history may be explained by their Lp(a) level.

A family history of CAD has been one of the most important data obtained from patients at their initial visit to our clinic because of the fact that CAD is a heritable trait. CAD family history information also adds a predictive value for CAD development.[16,17] Given that this information can be assessed noninvasively without any costs, obtaining it at our clinic is reasonable. However, factors contributing to CAD remain unclear; consequently, the treatment strategy also remains uncertain.

Lp(a) is quite a unique molecule in several aspects. First, its serum level is highly heritable. Approximately 90% of their variability appears to be determined by genetics; thus, we need to conduct cascade screening when we encounter a patient with elevated Lp(a) levels.[18] Second, Lp(a) appears to be causally associated with CAD on the basis of epidemiological studies and Mendelian randomization studies.[5] Importantly, several different oligonucleotide therapeutics are currently being used in randomized clinical trials to investigate whether lowering the Lp(a) levels actually reduces CAD events. Third, its serum level appears to quite vary among different

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ethnicities.[19] Under these circumstances, measuring serum Lp(a) is now recommended by clinical guidelines in patients with premature CAD, owing to the assumption that a part of the association between CAD family history and CAD can be explained by the serum Lp(a) level. The present study verified this fact and showed that Lp(a) levels were associated with CAD regardless of the CAD family history status. Accordingly, we now understand that Lp(a) should be measured in patients with a family history of CAD and that additional intervention should be considered in patients with elevated Lp(a) levels regardless of the presence or absence of CAD family history. Regarding "additional intervention," LDL-lowering therapies and healthy lifestyle appear to be quite beneficial for patients with high Lp(a) levels, although they are not directly associated with Lp(a) reduction.[20] In addition, newer agents that can substantially reduce Lp(a) levels will soon be available.

In this study, we chose to use the cut-off value as 30 mg/dL, because of the fact that reference value among Japanese has been <30 mg/dL for a long time. This is rather lower than other ethnicities; however, it could be justified based on the highly skewed distribution of Lp(a) level among this study subjects (**Supplementary Fig. 2**) as observed in Korean and Chinese populations.[21,22]

This study has some limitations. First, it conducted a retrospective, cross-sectional, and observational analysis. In fact, we observed a reverse causal relationship between lipid-lowering therapy and CAD, and null association between LDL cholesterol and CAD probably because of this study design. Second, it investigated participants who underwent serum Lp(a) level assessment for any reason, possibly resulting in some bias. At our institution, patients who underwent any surgery type requiring prolonged bed rest and those with any risk factors for systemic atherosclerosis commonly underwent routine serum Lp(a) level assessment. Third, the number of Kringle IV domains might affect the assay in this study to some extent.[23] Therefore, an assay that is not sensitive to apolipoprotein (a) isoform size heterogeneity should be used in future studies involving the Japanese population. Fourth, some individuals received lipid-lowering therapies. However, the current therapies have minimal effects on Lp(a) levels. Fifth, we did not assess non-genetic factors that can potentially affect Lp(a) level, such as diet, exercise, menopause hormone replacement therapy, renal function, and liver function. However, it has been shown that up to 90% of the variability of Lp(a) level can be attributed to genetic backgrounds.[24] So, impact of these non-genetic factors could be minimal.

In conclusion, Lp(a) levels were associated with CAD regardless of the presence or absence of CAD family history.

SUPPLEMENTARY MATERIALS

Supplementary Fig. 1
Study flowchart.

Supplementary Fig. 2
Distribution of Lp(a).

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