Lipoprotein(a) and the Risk of Chronic Kidney Disease in Hospitalized Japanese Patients

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Abstract:
Objective Lipoprotein(a), or Lp(a), has been shown to be associated with the development of chronic kidney disease (CKD) in populations of various ethnicities. This study aimed to investigate the association between serum Lp(a) and CKD in Japanese patients.
Methods A total of 6,130 subjects who underwent a serum Lp(a) level assessment for any reason (e.g. any type of surgery requiring prolonged bed rest or risk factors for atherosclerosis, such as hypertension or diabetes) were retrospectively investigated at Kanazawa University Hospital from April 2004 to March 2014. Of these, 1,895 subjects were excluded because of the lack of clinical data. Subjects were assessed for Lp(a), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, hypertension, diabetes, smoking, body mass index (BMI), coronary artery disease (CAD), and CKD (stage 3).
Results When the study subjects were divided into quartiles of Lp(a) levels, significant trends were observed with regard to the presence of CKD (p = 2.7×10^{-13}). A multiple regression analysis showed that Lp(a) was significantly associated with CKD [odds ratio (OR), 1.12; 95% confidence interval (CI), 1.08-1.17; p = 1.3×10^{-7}, per 10 mg/dL], independent of other classical risk factors, including age, gender, BMI, hypertension, diabetes, smoking, LDL cholesterol, and triglycerides. Under these conditions, Lp(a) was significantly associated with CAD (OR = 1.11, 95% CI = 1.06-1.16; p = 1.7×10^{-6}, per 10 mg/dL), independent of other risk factors.
Conclusion Serum Lp(a) was associated with CKD, independent of other classical risk factors in a Japanese population.

Key words: Lipoprotein(a), lipoprotein, chronic kidney disease, coronary artery disease

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Introduction
Chronic kidney disease (CKD), which is typically caused by diabetes, high blood pressure, glomerulonephritis, and polycystic kidney disease, is characterized by a gradual loss of the kidney function over a prolonged period (1). The prevalence of CKD is currently estimated to be approximately 10% (1, 2) and is expected to increase with the aging population. CKD has been shown to be associated with high morbidity and mortality (3). CKD progression must be prevented because patients with end-stage kidney disease exhibit extremely high mortality rates and a decreased quality of life, requiring dialysis and/or transplantation that results in a substantial socioeconomic burden (4). Current CKD management guidelines recommend using angiotensin-converting enzyme inhibitors (ACEis) or angiotensin II receptor blockers (ARBs) (5, 6). These medications have been shown to reduce albuminuria and slow CKD progression (7-9). However, further treatment targets are warranted to fully control the development of this condition.

Lipoprotein(a), or Lp(a), is a low-density lipoprotein (LDL)-like particle consisting of an apolipoprotein B100 (Apo B) molecule linked to a very large glycoprotein known as apolipoprotein(a), or apo(a) (10-12). Serum Lp(a) levels have been shown to be associated with CKD in populations...
of most ethnicities (13-15) along with coronary artery disease (CAD) (16-18). In addition, a recent Mendelian randomization trial suggested an etiological association between serum Lp(a) levels and CKD (19). Furthermore, Lp(a) appears to be a residual risk factor for cardiovascular disease in the statin era (20). The recent treatment option offered by proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors has been shown to reduce Lp(a) by up to 30%, although the mechanism underlying this effect remains unclear (21).

However, few data exist regarding this issue in the Japanese population. Therefore, this study aimed to investigate the association between serum Lp(a) and CKD in Japanese patients.

### Materials and Methods

#### Study population

A total of 6,130 subjects who underwent serum Lp(a) level assessment were retrospectively investigated at Kanazawa University Hospital from April 2004 to March 2014. Of these, 1,895 subjects were excluded because of the lack of clinical data. Thus, the remaining 4,235 subjects [2,270 men (53.6%), mean age = 59 years, CAD = 818 (19.3%), CKD = 653 (15.4%)] were analyzed. The baseline examination findings were reviewed, including the medical history, physical examination findings, and blood sampling results. Most study subjects were inpatients referred to the hospital, enabling the assessment of fasted blood samples. The characteristics of the study subjects are listed in Table 1.

#### Ethical considerations

This study was approved by the Ethics Committee of Kanazawa University. All procedures were in accordance with the ethical standards of the institutional and national committees on human experimentation and complied with the 1975 Declaration of Helsinki, as revised in 2008.

#### Biochemical analyses

Blood samples for biochemical assays were collected after overnight fasting. Serum creatinine levels were measured enzymatically using automated instrumentation. Serum levels of LDL cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol were determined enzymatically using automated instrumentation based on previously described protocols (22). An enzyme-linked immunosorbent assay was used to determine Lp(a) concentrations (23). The same assay was used during the entire study period. The coefficient of variation (CV) for Lp(a) measurement was shown to be < 8% within and between assays (23).

#### Clinical evaluations

Hypertension was defined as systolic blood pressure of at least 140 mmHg, diastolic blood pressure of at least 90 mmHg, or the use of antihypertensive medication. Diabetes was defined as previously described by the Japan Diabetes Society (24) or the use of diabetes medication. The body mass index (BMI) was defined as the body weight in kilograms divided by the square of the height measured in meters. CKD was defined as an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m², and the eGFR was calculated using the following formulas: eGFR = 194× serum creatinine - 1.094× age - 0.287 (for men) and eGFR = 194× serum creatinine - 1.094× age - 0.287×0.739 (for women) (25). We assessed the subjects’ baseline medications, including lipid-lowering, antihypertensive, antidiabetic, and antithrombotic therapies. Coronary artery disease (CAD) was defined as the presence of angina pectoris, myocardial infarction, or severe stenotic regions in the coronary artery identified either by an angiogram or computed tomography.

### Table 1. Baseline Characteristics of the Study Subjects.

| Characteristic       | All (n=4,235) | Quartile 1 [0.1 ≤ Lp(a) ≤ 6.6 mg/dL] (n=1,068) | Quartile 2 [6.7 ≤ Lp(a) ≤ 12.1 mg/dL] (n=1,056) | Quartile 3 [12.2 ≤ Lp(a) ≤ 29.7 mg/dL] (n=1,056) | Quartile 4 [29.8 ≤ Lp(a) ≤ 169 mg/dL] (n=1,055) | p value (trends) |
|----------------------|--------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------------------------------------|-----------------|
| Age                  | 59±16        | 56±16                                         | 59±16                                         | 61±16                                         | 62±15                                         | 4.2×10⁻¹⁰       |
| Male (%)             | 2,270 (53.6) | 599 (56.1)                                    | 584 (55.3)                                    | 543 (51.4)                                    | 544 (51.6)                                    | 4.8×10⁻⁴        |
| BMI (kg/m²)          | 23.7±4.5     | 24.1±4.6                                      | 23.7±4.4                                      | 23.5±4.6                                      | 23.4±4.3                                      | 8.7×10⁻⁵        |
| Hypertension (%)     | 2,269 (53.6) | 536 (50.2)                                    | 532 (50.4)                                    | 599 (56.7)                                    | 602 (57.1)                                    | 3.9×10⁻⁹        |
| Diabetes (%)         | 1,464 (34.6) | 410 (38.4)                                    | 370 (35.0)                                    | 335 (31.7)                                    | 349 (33.1)                                    | 0.16            |
| Smoking (%)          | 1,830 (43.2) | 453 (42.4)                                    | 470 (44.5)                                    | 451 (42.7)                                    | 456 (43.2)                                    | 0.18            |
| LDL cholesterol (mg/dL) | 115±49   | 102±41                                         | 113±45                                         | 121±55                                         | 125±53                                         | 5.7×10⁻⁶        |
| HDL cholesterol (mg/dL) | 51±17    | 52±19                                         | 50±16                                          | 51±17                                          | 51±18                                          | 0.51            |
| Triglycerides (mg/dL) | 105 [74-156]| 105 [72-163]                                  | 113 [79-170]                                  | 97 [71-141]                                   | 103 [75-151]                                  | 0.29            |
| CAD (%)              | 818 (19.3)   | 165 (15.4)                                    | 174 (16.5)                                    | 217 (20.5)                                    | 262 (24.8)                                    | 1.6×10⁻¹⁵       |
| CKD (%)              | 653 (15.4)   | 121 (11.3)                                    | 129 (12.2)                                    | 183 (17.3)                                    | 220 (20.9)                                    | 2.7×10⁻¹³       |

Lp(a): lipoprotein (a), BMI: body mass index, CAD: coronary artery disease, CKD: chronic kidney disease, HDL: high-density lipoprotein, LDL: low-density lipoprotein.
Cardiovascular diseases include coronary artery disease and heart failure. “Others” includes inflammatory diseases, malignant diseases, metabolic diseases, and trauma.

**Statistical analyses**

Categorical variables were expressed as percentages. Fisher’s exact or chi-square test was used as applicable. Continuous variables with normal distribution were shown as the mean ± standard deviation (SD). For values without a normal distribution, the median and interquartile range (IQR) were reported. A multivariate analysis including factors with a p value <0.10 in the univariate analyses was conducted to assess the association of the factors with CAD and CKD. A receiver operating characteristic analysis was performed, and the C-statistic was calculated to estimate the predictive performance of the considered parameters. All statistical analyses were conducted using the R statistical software program. All p values <0.05 were considered statistically significant.

**Results**

**Characteristics of study subjects**

The clinical characteristics of the study subjects are shown in Table 1. The median Lp(a) level was 12.1 mg/dL (IQR: 6.6-29.7). When divided into quartiles of Lp(a) levels, significant trends were observed with regard to the age, gender, BMI, hypertension, LDL cholesterol, CAD, and CKD. The main causes of referral to our hospital are shown in Table 2. In addition to subjects with cardiovascular diseases, diabetes, and hypertension, we included many subjects admitted to our hospital due to operation and delivery. Medications for metabolic disorders are shown in Table 3. A total of 949 (22.4%) of the study subjects were taking lipid-lowering agents.

**Factors associated with CKD**

To clarify the factors associated with CKD, factors potentially associated with atherosclerotic diseases were assessed. A multivariate analysis that included factors with a p value <0.10 in the univariate analyses showed that an older age [odds ratio (OR) = 1.03, 95% confidence interval (CI) = 1.02-1.04; p = 3.3×10^-7], male gender (OR = 1.54, 95% CI = 1.72-1.96; p = 8.4×10^-16), hypertension (OR = 5.58, 95% CI = 4.18-7.57; p <2.0×10^-16), diabetes (OR = 1.32, 95% CI = 1.09-1.61; p = 0.0053), and high triglyceride (OR = 1.00, 95% CI = 1.00-1.00; p = 0.005) and Lp(a) levels (OR = 1.12, 95% CI = 1.08-1.17; p = 1.3×10^-4), per 10 mg/dL were independently associated with the presence of CKD (Table 4). This trend in Lp(a) was unchanged even after accounting for CAD (OR = 1.10, 95% CI = 1.03-1.24; p = 2.9×10^-4), per 10 mg/dL, in model 2).

**Factors associated with CAD**

To clarify the factors associated with CAD, factors potentially associated with atherosclerotic diseases were assessed. A multivariate analysis that included factors with a p value <0.10 in the univariate analyses showed that an older age (OR = 1.04, 95% CI = 1.03-1.05; p <2.0×10^-16), male gender (OR = 1.52, 95% CI = 1.21-1.92; p = 3.8×10^-7), hypertension (OR = 3.71, 95% CI = 2.89-4.80; p <2.0×10^-4), smoking (OR = 3.32, 95% CI = 2.65-4.18; p <2.0×10^-4), and high levels of Lp(a) (OR = 1.11, 95% CI = 1.06-1.16; p = 1.7×10^-4), per 10 mg/dL were independently associated with the presence of CAD (Table 5). This trend in Lp(a) was unchanged even after accounting for CKD (OR = 1.09, 95% CI = 1.04-1.14; p = 6.8×10^-5), per 10 mg/dL, in model 2).

**Risk discrimination for CKD by Lp(a)**

The present study further investigated whether or not the discrimination ability of a model based on traditional risk factors associated with CKD in this study (age, gender, hypertension, diabetes, and triglycerides) differed from that of a model that included Lp(a). The C-statistic for the traditional risk factor model was 0.775 (95% CI = 0.759-0.792),
which increased to 0.781 (95% CI = 0.764-0.797; Figure, p = 0.00733) after incorporating Lp(a) into the model.

Discussion

In the present study, the association between the Lp(a) levels and CKD in hospitalized Japanese patients was retrospectively investigated. Lp(a) was found to be significantly associated with CKD in this Japanese population, independent of other traditional risk factors, along with CAD.

**Lp(a) and development of CKD**

Since the discovery of Lp(a) in 1963 (26), studies have reported the association between elevated Lp(a) levels and CKD in populations of different ethnicities (13, 15). The current study provides additional evidence concerning this issue in the Japanese population.

Regarding the etiological association of whether reduced GFR causes an increase in Lp(a) or vice versa, both appear to be true. Concerning the reduced GFR-induced increase in Lp(a), as clarified by Kronenberg et al., Lp(a) levels begin to increase with decreasing GFR, increasing to fourfold higher in patients with nephrotic-range proteinuria than in healthy controls (27). Concentrations are increased and influenced by the GFR and the amount of proteinuria. This may be due to increased synthesis, similar to that in patients with nephrotic syndrome or those treated by peritoneal dialysis. In patients undergoing hemodialysis, a catabolic block is the reason for this increase (28). Concerning the Lp(a) increase-induced reduction in the GFR, Lp(a) has marked homology with plasminogen, and it has been shown in vitro to competitively inhibit the fibrin-dependent activation of plasminogen to plasmin, which plays a crucial role in the catabolism of extracellular matrix proteins, resulting in a reduced GFR (29). Furthermore, a recent Mendelian randomization study showed that reduced Lp(a) levels since birth appear to have a protective effect against the development of CKD (19), suggesting that Lp(a) itself has some etiological role in the development of CKD.

**Lp(a) in patients with CKD**

In addition to the development of CKD itself, Lp(a) levels have been shown to be associated with adverse events in patients with CKD (30, 31). Accordingly, the assessment of

| Characteristics | Model 1 | Model 2 |
|-----------------|---------|---------|
| OR (95% CI)     | p value | OR (95% CI) | p value |
| Age             | 1.03 (1.02-1.04) | 3.3×10^-4 | 1.03 (1.02-1.04) | 5.9×10^-4 |
| Male            | 1.54 (1.22-1.96) | 8.4×10^-10 | 1.74 (1.22-1.96) | 7.9×10^-9 |
| BMI             | 0.99 (0.96-1.01) | 0.21 | 0.99 (0.97-1.01) | 0.32 |
| Hypertension    | 5.58 (4.18-7.57) | <2×10^-16 | 6.05 (4.04-7.96) | <2×10^-16 |
| Diabetes        | 1.32 (1.09-1.61) | 0.0053 | 1.45 (1.11-1.84) | 0.0021 |
| Smoking         | 0.99 (0.79-1.25) | 0.95 | 0.99 (0.81-1.21) | 0.89 |
| LDL cholesterol | 0.99 (0.99-1.00) | 0.15 | 0.99 (0.99-1.00) | 0.21 |
| Lp(a) (per 10 mg/dL) | 1.12 (1.08-1.17) | 1.3×10^-7 | 1.10 (1.03-1.24) | 2.9×10^-6 |

**Table 5.** Factors Associated with CAD.

| Characteristics | Model 1 | Model 2 |
|-----------------|---------|---------|
| OR (95% CI)     | p value | OR (95% CI) | p value |
| Age             | 1.04 (1.03-1.05) | <2×10^-16 | 1.04 (1.03-1.05) | <2×10^-16 |
| Male            | 1.52 (1.21-1.92) | 3.8×10^-4 | 1.55 (1.18-1.99) | 1.2×10^-4 |
| BMI             | 0.99 (0.97-1.01) | 0.48 | 0.99 (0.98-1.01) | 0.64 |
| Hypertension    | 3.71 (2.89-4.80) | <2×10^-16 | 4.32 (2.64-4.97) | <2×10^-16 |
| Diabetes        | 1.12 (0.93-1.36) | 0.22 | 1.25 (0.75-1.65) | 0.55 |
| Smoking         | 3.32 (2.65-4.18) | <2×10^-16 | 3.70 (2.67-4.10) | <2×10^-16 |
| LDL cholesterol | 1.00 (0.99-1.01) | 0.78 | 1.00 (0.99-1.01) | 0.82 |
| Triglycerides   | 1.00 (1.00-1.00) | 0.55 | 1.00 (1.00-1.00) | 0.49 |
| Lp(a) (per 10 mg/dL) | 1.11 (1.06-1.16) | 1.7×10^-6 | 1.09 (1.04-1.14) | 6.8×10^-5 |
| CAD             | 1.17 (1.02-1.34) | 0.0024 |
the Lp(a) levels in the routine management of patients with any-stage CKD is recommended.

**Study limitations**

Several limitations associated with the present study warrant mention. First, this was a retrospective, cross-sectional, observational analysis. Thus, this study cannot show the causal relationship between Lp(a) and CKD directly. Prospective randomized control studies are needed to confirm this issue. However, it investigated one of the largest sample sizes regarding Lp(a) and CKD in a Japanese population, potentially contributing to a better understanding of this issue in populations of different ethnicities. In addition, study findings regarding factors associated with CKD were quite consistent with those in previous studies. Second, the study investigated subjects who had their serum Lp(a) levels measured for any reason, which may have resulted in some bias. In hospitals, most patients who undergo any type of surgery requiring prolonged bed rest and those with any risk factors for systemic atherosclerosis undergo a routine serum Lp(a) level assessment. These factors, along with the large sample size, may have diluted the referred bias. Third, the assay used in this study may have been affected to some extent by the number of Kringle IV domains (32). Therefore, further studies using an assay insensitive to apo(a) isoform size heterogeneity should be performed in a Japanese population. Fourth, we failed to observe a significant association between the LDL-C level and CAD in this study. However, 949 (22.4%) of the study subjects were taking some sort of lipid-lowering agent, which likely affected the association between the LDL-C level and CAD in this cross-sectional study.

In conclusion, serum Lp(a) was associated with the development of CKD, independent of other classical risk factors in the Japanese population, which is an association similar to that observed in populations of other ethnicities. Therefore, the assessment of Lp(a) levels is recommended in Japanese patients with a high risk of developing CKD.

Our study was approved by the Institutional Research Review Boards of Kanazawa University. All patients provided their written informed consent before taking part in the study.

The authors state that they have no Conflict of Interest (COI).

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