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Lipoprotein(a) is a predictor for cardiovascular mortality of hemodialysis patients

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Lipoprotein(a) is a predictor for cardiovascular mortality of hemodialysis patients.

Background. Although hemodialysis (HD) patients have been associated with elevations in serum lipoprotein(a) [Lp(a)] levels, relatively little has been published on the link between Lp(a) and the risk for atherosclerotic cardiovascular death in HD patients.

Methods. Lipoprotein(a) was measured in 390 HD patients. The relationship between Lp(a) and mortality (overall and cardiovascular) was determined during 28 months of prospective follow-up.

Results. Hemodialysis patients demonstrated Lp(a) concentrations that were approximately two times as high as that of healthy controls (median, 16 vs. 8 mg/dl, $P < 0.001$; mean, 22.9 vs. 12.1 mg/dl, $P < 0.01$). Lp(a) showed a significant correlation between albumin, total cholesterol, low-density lipoprotein cholesterol, and C-reactive protein. The high-Lp(a) group [Lp(a) $\geq$ 30 mg/dl] showed significantly higher mortality than the low-Lp(a) group [Lp(a) $<$ 30 mg/dl] in a Kaplan–Meier survival analysis ($P < 0.05$). Multiple logistic regression analysis demonstrated albumin, age, and diabetic state as significant risk factors for overall death. However, if confined to atherosclerotic cardiovascular death, Lp(a) ($P < 0.01$), age, and diabetic state were the only independent contributors.

Conclusions. Lp(a) is an independent risk factor for atherosclerotic cardiovascular death in Japanese patients receiving chronic dialysis therapy.

Dyslipidemia is common in end-stage renal disease (ESRD) patients and is associated with increased mortality. Lipoprotein(a) [Lp(a)] is a genetically determined risk factor for vascular disease and has a potential link between coagulation and the development of atherosclerosis [1–4]. Its levels vary markedly among ethnic groups and several pathological conditions [5–8]. Elevated Lp(a) in hemodialysis (HD) patients has been reported [2–4, 6], but its role in the development of vascular complications or atherosclerotic death has yet to be fully proven. This study was designed to determine the relationship between increased Lp(a) and the cardiovascular mortality in Japanese HD patients.

Key words: albumin, atherosclerosis, cardiovascular disease, dyslipidemia, end-stage renal disease.

METHODS

Serum Lp(a) was measured simultaneously in all patients treated in our dialysis unit as of November, 1995. The subjects were 390 patients on HD [241 men and 149 women, 333 nondiabetes mellitus (non-DM) and 57 DM] and 105 normal controls. The patients' mean age was 56.6 $\pm$ 14.1 (SD) years old, and the mean HD duration was 10.1 $\pm$ 7.5 years (range 0.3 to 30.0). Serum Lp(a) was measured by latex-enhanced turbidimetric assay and albumin by bromocresol green. The subjects were divided into two groups according to the 75th percentile Lp(a) value (30 mg/dl), comprising the high-Lp(a) group (mean 50.2 mg/dl, $N = 98$) and the low-Lp(a) group (mean 13.1 mg/dl, $N = 292$). The age of the high- and low-Lp(a) groups was 58.5 $\pm$ 13.4 vs. 55.9 $\pm$ 14.3 years old (P = NS), and the albumin concentration was 3.8 $\pm$ 0.5 vs. 4.0 $\pm$ 0.4 ($P < 0.05$). The relationship between Lp(a) and death of presumed atherosclerotic origin was determined during 28 months of follow-up. The cause of death was ascertained by chart review. Statistical evaluation was performed with simple regression, chi-square test, unpaired Student's *t*-test, Mann–Whitney's *U*-test, and multiple logistic regression analysis, which allows for adjustment of confounders. Covariates included in multiple logistic regression analysis were age, gender, albumin, Lp(a), and diabetic state. C-reactive protein was excluded because it has a significant correlation with both albumin and Lp(a). Calculations were performed using the SPSS® for Windows (version 7.5) statistical software. P values of less than 0.05 were considered statistically significant.

RESULTS

A cross-sectional analysis of serum Lp(a) demonstrated a skewed distribution with a median value of 16 mg/dl (range 1.0 to 147) in HD patients and with 8 mg/dl

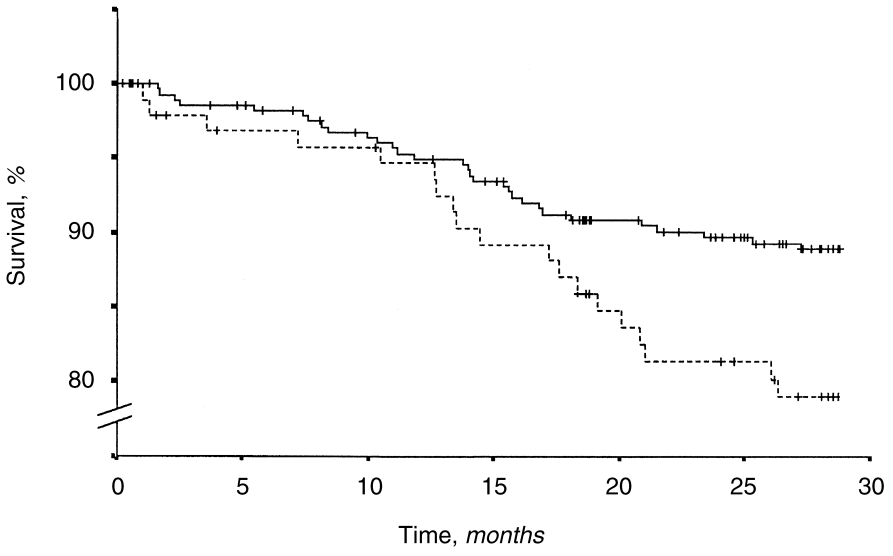

Fig. 1. Kaplan-Meier statistical analysis. Percent survival over 28 months in 390 patients stratified by Lp(a) ≥ 30 mg/dl (dashed line) vs. < 30 mg/dl (solid line). $P < 0.05$.

(range 0.1 to 56.0) in normal controls. No significant differences in Lp(a) levels were found in diabetic state and gender groups. Serum Lp(a) was positively correlated with total cholesterol, low-density lipoprotein cholesterol, and C-reactive protein and was inversely correlated with serum albumin ($r = -0.149$, $P < 0.01$). No correlation was evident between Lp(a) levels and the patient's age or duration on HD. Forty-nine patients died during the observation period, and 18 of them (36.7%) were due to atherosclerotic cardiovascular causes—8 in the high-Lp(a) group and 10 in the low-Lp(a) group. Cardiovascular death included three acute myocardial infarctions, seven strokes, three sudden deaths, and five other atherosclerotic causes. The high-Lp(a) group showed a significantly higher mortality than the low-Lp(a) group in the Kaplan–Meier survival analysis ($P < 0.05$; Fig. 1). However, albumin concentration in high-Lp(a) group was significantly lower than the low-Lp(a) group. Using a multiple logistic regression model, independent predictors for overall mortality were albumin ($P < 0.05$), age ($P < 0.001$), and diabetic state ($P < 0.001$). In contrast to this, independent predictors for atherosclerotic cardiovascular death were only Lp(a) ($P < 0.01$), age ($P < 0.001$), and diabetic state ($P < 0.05$). Cardiovascular death risk in patients with Lp(a) 30 mg/dl and over was 3.9 times higher than patients with Lp(a) less than 30 mg/dl when adjusted for albumin, age, and diabetic state (Fig. 2). Each year of age increased the cardiovascular death risk by 1.07 times, whereas DM increased it 3.4 times compared with non-DM patients.

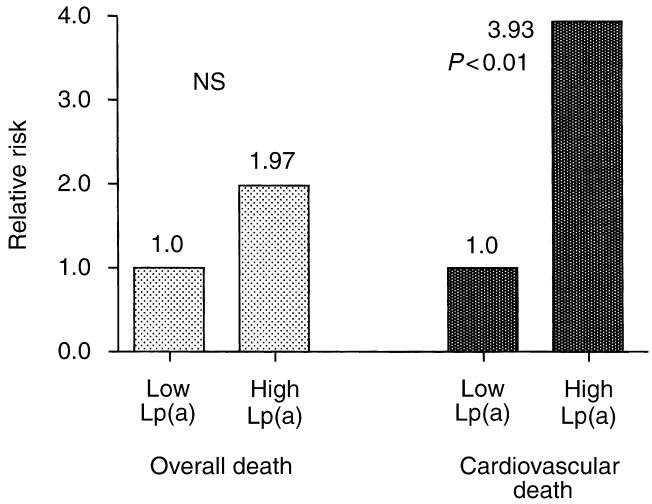

Fig. 2. Relative risk for death in relation to overall and atherosclerotic causes. Adjustments were made for age, diabetic state, and albumin concentration ($N = 390$). High Lp(a): ≥ 30 mg/dl; low Lp(a): < 30 mg/dl.

DISCUSSION

The importance of Lp(a) as a risk factor for an atherosclerotic death in patients with chronic renal failure remains to be established. Only a small number of articles have been published showing that Lp(a) has a relationship to a cardiovascular event [2, 3] or blood access occlusion [4]. The result of this prospective study demonstrated the clear association between high Lp(a) and cardiovascular mortality in a large number of cases ($N = 390$). The pathogenesis of atherosclerosis due to high Lp(a) includes interference with fibrinolytic cascade and promotion of smooth muscle cell proliferation by reducing the activation of transforming growth factor-β via plasminogen inhibition [9]. Lp(a) levels are genetically determined and differ considerably among ethnic groups [1]. This study suggests that that Lp(a) could be an atherosclerotic risk factor in Japanese patients on HD.

Although Lp(a) levels are predominantly genetic con-

trolled, there are several studies showing that Lp(a) levels are elevated in patients with nephrotic syndrome [8], continuous ambulatory peritoneal dialysis [5], ESRD with malnutrition, or inflammation [6]. It has been suggested to behave like an acute-phase reactant [7]. A low serum albumin has been established as a potent risk factor for death in HD patients. The high-Lp(a) group with higher mortality had clearly lower albumin levels and was slightly older than the low-Lp(a) group. Therefore, we performed a multiple logistic regression analysis that can adjust these covariates. As a result, albumin, age, and diabetic state were significant predictors for overall death, as we expected; however, if confined to atherosclerotic cardiovascular death, Lp(a) became a very potent risk factor independent from age and diabetic state. It should be noted that Lp(a) of 30 mg/dl and over has nearly the same risk as DM.

This study indicates that a high Lp(a) level in HD patients can be a potent predictor for atherosclerotic cardiovascular death. Elevated Lp(a) concentration in ESRD is also suggested to be partially secondary to malnutrition or inflammation [6, 7] because Lp(a) levels significantly inversely correlated with serum albumin. Therefore, a high level of Lp(a) may be important in the underlying pathophysiology of cardiovascular mortality in HD patients.

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REFERENCES

1. Kronenberg F, Utermann G, Dieplinger H: Lipoprotein(a) in renal disease. *Am J Kidney Dis* 27:1–25, 1996
2. Webb AT, Reaveley DA, O'Donnel M, O'Conner B, Seed M, Brown EA: Lipids and lipoprotein(a) as risk factors for vascular disease in patients on renal replacement therapy. *Nephrol Dial Transplant* 10:354–357, 1995
3. Cressman MD, Heyka RJ, Paganini EP, O'Neil J, Skibinski CI, Hoff HF: Lipoprotein(a) is an independent risk factor for cardiovascular disease in hemodialysis patients. *Circulation* 86:475–482, 1992
4. Goldwasser P, Michel MA, Collier J, Mittman N, Fein PA, Gusik SA, Avram MM: Prealbumin and lipoprotein(a) in hemodialysis: Relationships with patient and vascular access survival. *Am J Kidney Dis* 22:215–225, 1993
5. Yang WS, Min WK, Park JS, Kim SB: Effect of increasing serum albumin on serum lipoprotein(a) concentration in patients receiving CAPD. *Am J Kidney Dis* 30:507–513, 1997
6. Stenvinkel P, Heimburger O, Tuck CH, Berglund L: Apo(a)-isoform size, nutritional status and inflammatory markers in chronic renal failure. *Kidney Int* 53:1336–1342, 1998
7. Kario K, Matsuo T, Kobayashi H, Matsuo M, Asada R, Koide M: High lipoprotein (a) levels in chronic hemodialysis patients are closely related to the acute phase reaction. *Thromb Haemost* 74:1020–1024, 1995
8. Wanner C, Rader D, Bartens W, Kramer J, Brewer HB, Schollmeyer P, Wieland H: Elevated plasma lipoprotein(a) in patients with the nephrotic syndrome. *Ann Intern Med* 119:263–269, 1993
9. Grainger DJ, Kirschenlohr HL, Metcalfe JC, Weissberg PL, Wade DP, Lawn RM: Proliferation of human muscle cells promoted by lipoprotein(a). *Science* 260:1655–1658, 1993