Lysophosphatidylcholine predicts cardiovascular disease in Korean hemodialysis patients: Analysis at 5 years of follow-up

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Introduction

Unlike general population, there is less of an association between dyslipidemia and the presence of cardiovascular disease (CVD) in hemodialysis patients. Lysophosphatidylcholine (LPC) consists of a glycerin frame, one fatty acid and a phosphochloine. LPC is a major component of oxidized LDL and is generated by phospholipase A_2-dependent hydrolysis of phosphatidylcholine (Fig. 1). LPC has been shown to modulates many biologic effects of oxidized LDL including induction of monocyte chemotaxis, expression of adhesion molecules and growth factors in endothelial cells, stimulation of smooth muscle cell proliferation, gene transcription and secretion of pro-inflammatory cytokines.

Among dialysis patients, a number of lipid abnormalities have been identified, including low levels of HDL, elevated triglycerides levels, and normal or near-normal levels of total cholesterol and LDL. The long-term contribution of oxidized LDL and LPC to CVD has not been evaluated in hemodialysis patients. The objective of present study was to address this issue. long term risk of CVD in this population.

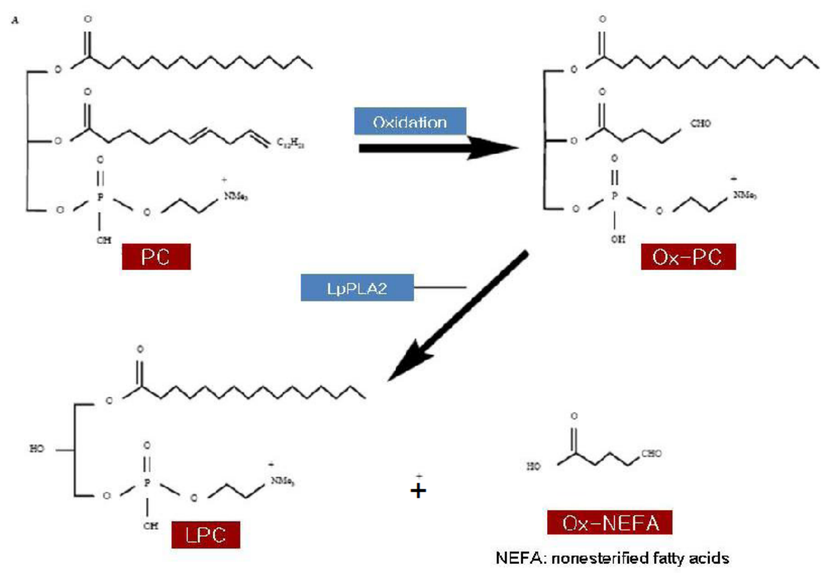

Fig. 1. Hydrolysis of oxidized phospholipids by Lp-PLA2 (PC: phosphatidylcholine).

Methods

Study patients

A prospective follow-up study of 69 chronic hemodialysis patients was conducted for 60 months (August 2004-July 2009) and cardiovascular morbidity and mortality were determined. Exclusion criteria were: less than 18 year old, dialysis duration of less than 3 months, history of acute infection or systemic inflammatory disease within 3 months, malignancy or chronic liver disease. The mean hemodialysis duration was 40.6 months (range 3 to 172 months). Fifty-four patients (78.3%) undergoing dialysis had arteriovenous fistula. The underlying renal diseases consisted of diabetes mellitus (53.6%).

Study design

The endpoints of the study were new fatal and non-fatal cardiovascular events requiring admission. Coronary artery disease, cerebrovascular disease and peripheral artery disease were defined as CVD. Oxidation of LDL was assessed by using an enzyme linked immunosorbent assay kit (Mercodia, Uppsala, Sweden). LPC concentrations were determined as described previously, based on the standard curve for 18:0 LPC. Patient serum samples were mixed with LPC assay reagents, and their changes in absorbance were assayed.

Results

A total of 69 patients was evaluated for CVD. Patients were observed over an average follow-up of 43 months (2-60 months). During the study period, 20 patients (29%) died, 12 patients were transferred to other centers, and 5 patients were transplanted. There were 18 cardiovascular events (26%) including 6 deaths among the hemodialysis patients.

The subjects were divided two groups according to serum LPC levels at baseline (median value of LPC: 254 μM/L) (Table 1). The low LPC level group showed higher pulse pressure and decreased phosphorus level compared to the high LPC level group. Age, gender, blood pressure, total cholesterol, triglyceride, HDL, LDL, oxidized LDL, albumin and CRP levels were not significant different between two groups. The low LPC level group had much more increased risk of CVD compared to the high LPC level group (P = 0.01, Table 2). There was also significant difference in the probability of the cardiovascular events-free rate between two groups (log-rank test, P = 0.017, Fig. 2). The subjects were also divided two groups according to serum oxidized LDL levels at baseline (median value: 31.1 U/L). But, oxidized LDL levels were not significant different between groups with CVD and without CVD.

The results of Cox proportional hazard analysis for CVD are summarized in Table 3. In univariate analysis, previous history of cardiovascular events, low LPC level (≤254 μM/L), diabetes mellitus and duration of dialysis were found to be significantly risk factors for CVD. In adjusted Cox model, previous CVD (HR, 5.68; 95% CI, 1.94-16.63, P = 0.002) and low LPC level (HR, 3.45; 95% CI, 1.04-11.42, P = 0.042) had significant independent risks for development of CVD. However, neither diabetes mellitus nor duration of dialysis was significantly associated with the risk of CVD in the study population

Table 1. Clinical parameters of the hemodialysis patients according to LPC at baseline

Parameters	Low LPC level group (n = 35)	High LPC level group (n = 34)	*P* value
Age (yr)	58.1 ± 11.8	54.3 ± 12.2	0.187
Gender (% female)	49	59	0.472
Diabetes mellitus (%)	60	44	0.232
Previous CVD (%)	29	24	0.785
Duration of dialysis (yr)	2.7 ± 3.3	4.1 ± 3.1	0.067
Smoking (%)	17	21	0.766
Statin (%)	29	44	0.216
Anti-platelet drug (%)	80	74	0.578
Predialytic SBP (mmHg)	154.0 ± 21.0	147.6 ± 14.8	0.153
Predialytic DBP (mmHg)	83.0 ± 11.6	85.4 ± 9.5	0.344
Pulse pressure (mmHg)	71.0 ± 16.1	62.2 ± 12.9	0.015
Oxidized LDL (U/L)	31.0 ± 8.1	34.2 ± 9.7	0.137
LPC (μM/L)	214.7 ± 30.5	322.8 ± 43.5	< 0.001
LPC/(LDL + HDL)	1.88 ± 0.41	2.85 ± 0.68	< 0.001
Total cholesterol (mg/dL)	131.7 ± 24.0	138.2 ± 30.1	0.322
HDL-cholesterol (mg/dL)	40.0 ± 12.8	37.6 ± 11.0	0.392
LDL-cholesterol (mg/dL)	75.6 ± 18.9	80.5 ± 21.6	0.320
Phosphorus (mg/dL)	4.2 ± 1.5	5.0 ± 1.5	0.036
Creatinine (mg/dL)	7.7 ± 2.6	8.5 ± 3.0	0.238
Albumin (g/dL)	3.6 ± 0.5	3.7 ± 0.4	0.249
CRP (mg/L)	2.8 ± 2.7	3.0 ± 2.7	0.825
Intact-PTH (pg/mL)	139.7 ± 136.1	163.6 ± 241.7	0.623

Table 2. LPC levels of the hemodialysis patients according to development of CVD at the end of follow-up

Outcomes	Low LPC level group (n = 35)	High LPC level group (n = 34)	*P* value
CVD	14 (40%)	4 (12%)	0.01
Mortality	13 (37%)	7 (21%)	0.19

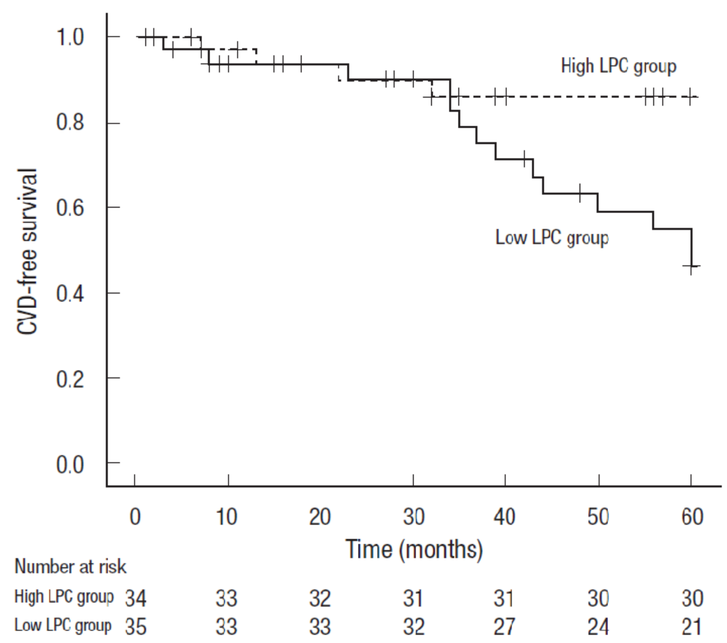

Fig. 2. Kaplan-Meier estimate of CVD-free survival in hemodialysis patients according to LPC levels. The test demonstrated a statistically significant value (log-rank test, $P = 0.017$).

Table 3. Cox proportional hazard model of CVD

Variables	HR (95% CI)	*P* value
Unadjusted		
Low LPC level (≤ 254 μM/L)	3.53 (1.16-10.73)	0.026
Age (per 1 yr)	1.03 (0.98-1.07)	0.243
Female gender	1.36 (0.53-3.44)	0.522
CRP	1.14 (0.98-1.32)	0.097
Albumin	0.73 (0.23-2.31)	0.591
Phosphorus	1.07 (0.77-1.48)	0.698
Pulse pressure	1.02 (0.98-1.05)	0.320
Previous CVD	5.67 (2.20-14.59)	< 0.001
Diabetes mellitus	8.42 (1.93-36.65)	0.005
Duration of dialysis (per 1 yr)	0.75 (0.59-0.97)	0.028
Adjusted		
Low LPC level (≤ 254 μM/L)	3.45 (1.04-11.42)	0.042
Previous CVD	5.68 (1.94-16.63)	0.002
Diabetes mellitus	4.48 (0.98-20.39)	0.052
Duration of dialysis (per 1 yr)	0.86 (0.68-1.09)	0.219

Conclusions

The present study examined whether a serum level of LPC or oxidized LDL predicts CVD in a cohort of 69 hemodialysis patients who were followed up for 5 year. We demonstrated that lower LPC and previous history of CVD are the major risk factors for CVD. To our knowledge, this is the first study to demonstrate that a decreased LPC concentration is an independent predictor of a higher risk of CVD in hemodialysis patients. Larger-scale longitudinal studies are needed to confirm our results and to explore this phenomenon in dialysis population.

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