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LDL-apheresis contributes to survival extension and renal function maintenance of severe diabetic nephropathy patients: A retrospective analysis

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ABSTRACT

Aims: Low-density lipoprotein (LDL)-apheresis removes various molecules including LDL/oxidized LDL and inflammatory cytokines and recovers clinical laboratory parameters. It is not yet known whether these advantages of LDL-apheresis improve the prognosis of patients with diabetic nephropathy accompanied by nephrotic syndrome.

Methods: In this study, three groups of patients were retrospectively surveyed in a single center, and followed for approximately 3 years: an LDL-apheresis cohort (LDL-a; $N = 20$); a control cohort meeting the selection criterion of severe proteinuria $\geq$3 g/24 h (control-All; $N = 55$); and a subgroup of control-All with more severe proteinuria $\geq$5 g/24 h (control-mSP; $N = 10$), and evaluated the outcomes as survival and renal dysfunction and death/renal dysfunction free rate.

Results: Death/renal dysfunction free rate was significantly higher in LDL-a than control-All ($\chi^2 = 4.50$; $P = 0.03$) and control-mSP ($\chi^2 = 27.68$; $P < 0.001$).

Conclusion: These results suggest the possibilities which LDL-apheresis is considered to contribute to survival extension and renal function maintenance of severe diabetic nephropathy patients.

1. Introduction

Diabetic nephropathy is the most common cause of end-stage renal disease (ESRD) [1,2]. The incidence of end-stage kidney disease requiring chronic hemodialysis caused by diabetic nephropathy has increased rapidly during the last two decades worldwide, and morbidity associated with renal dysfunction involving chronic hemodialysis initiation remains greater than for those without diabetic nephropathy [3,4]. In the pathogenesis of diabetic nephropathy, proteinuria, hyperlipidemia, hyperglycemia, and hypertension are established risk markers observed for progressive renal function loss [5–7]. Several clinical trials have been carried out using drugs such as angiotensin II receptor blockers (ARB) that improve these markers, and the results reported that such drugs conferred improvement in proteinuria and reduction of death and renal dysfunction rates for diabetic nephropathy with proteinuria [8]. However, there is still insufficient data concerning prognosis improvement for severe diabetic nephropathy accompanied by nephrotic syndrome.

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Some investigators have reported that low-density lipoprotein (LDL)-apheresis is effective in reducing proteinuria excretion in patients with steroid-resistant nephrotic syndrome, focal glomerulosclerosis, and diabetic nephropathy [9,10]. In addition, LDL-apheresis removes various molecules such as oxidized LDL and inflammatory cytokines or chemokine and improves clinical laboratory parameters [11–16], and may reduce renal lesions. We found that LDL-apheresis reduced excretion of podocytes [17], which have a key role in maintaining the integrity of the glomerular filtration barrier [18–20]. These results suggest that the effects of LDL-apheresis are exerted by removal of oxidative/inflammatory molecules and modulation of the inflammatory cascade in the glomerulus, and that it is a potentially effective treatment for diabetic nephropathy with severe proteinuria [17]. It is unknown whether these advantages of LDL-apheresis improve prognosis in terms of mortality or renal dysfunction. The purpose of the present study is to estimate, by means of a retrospective review, the prognosis of diabetic nephropathy with severe proteinuria treated with LDL-apheresis therapy.

1.1. Subjects

The present study is a single-center, retrospective review of diabetic nephropathy patients, consisting of an LDL-apheresis cohort and a control cohort with one subgroup. The LDL-apheresis cohort (LDL-a) is composed of all patients who underwent LDL-apheresis therapy at Shin-Matsudo Central General Hospital, Chiba, Japan prior to 2010 ($N = 20$). The control cohort is composed of all patients at the same hospital who met the inclusion criteria of severe proteinuria $\geq$3 g/24 h from 2008 to 2010 and who were traceable (control-All; $N = 55$); a subgroup of the control cohort comprises the patients in control-All with severe proteinuria $\geq$5 g/24 h (control-mSP; $N = 10$) near to that of LDL-a.

2. Methods

2.1. Diagnosis criteria of diabetic nephropathy

Diabetic nephropathy was diagnosed based on the presence of following diabetic lesions: glomerulosclerosis such as nodular or diffuse (mesangial expansion), hyalinization of the renal arterioles, linear deposits of IgG in the glomerular basement membrane, and diffuse thickening of the glomerular basement on electron microscopy. If there is no renal biopsy data of diabetic lesions, as a substitute by evaluation of clinical laboratory tests: clinical syndrome characterized by persistent albuminuria (>300 mg/24 h) (also referred to as macroalbuminuria or proteinuria), a steady decline in glomerular filtration rate (GFR), and elevated blood pressure [21].

2.2. Clinical parameters and laboratory measurements

Body mass index was calculated as body weight (in kilograms) divided by height (in meters) squared. Hypertension was defined according to WHO criteria (systolic blood pressure [BP] > 160 mmHg and/or diastolic BP > 95 mmHg, or on antihypertensive treatment at baseline). Hypercholesterolemia was defined according to the criteria total cholesterol >220 mg/dL and LDL-cholesterol >140 mg/dL. Stroke was defined as a reported medical history of cerebral infarction or cerebral hemorrhage. Coronary artery disease (CAD) was defined as a reported history of myocardial infarction, angina, percutaneous coronary intervention, or coronary artery bypass graft. Retinopathy and neuropathy were determined from the reported medical history.

Samples of blood and urine taken at routine clinical checkups were analyzed at baseline for creatinine, total protein, LDL-cholesterol, and HbA1c and for protein and liver-type fatty acid binding protein (L-FABP), respectively.

2.3. Outcomes assessment

Baseline for LDL-a and the control cohorts is defined as the day of starting LDL-apheresis therapy or meeting the inclusion criteria, respectively. Surveillance for major events included screening hospitalization history until 3 years from baseline.

A major event was defined as any incident of stroke, CAD, renal dysfunction, or death. Renal dysfunction was defined as doubling of serum creatinine concentration, chronic hemodialysis initiation, or renal transplantation [8]. Doubling of serum creatinine concentration was defined as the first serum creatinine concentration that was twice the baseline, as confirmed by a second serum creatinine concentration obtained at about 3 months after the initial doubling.

2.4. LDL-apheresis

LDL-apheresis was performed using hollow polysulfone fibers (Sulflux; Kaneka Co. Ltd., Osaka, Japan) as the plasma separator and a dextran sulfate cellulose column (Liposorber; Kaneka Co. Ltd., Osaka, Japan) as the LDL absorber. About 3000 to 4000 mL of plasma (60 mL/kg body weight) was treated for 3 h in each apheresis session [9]. LDL-apheresis was performed in series twice a week for 3–6 weeks (6–12 times per patient).

2.5. Statistical analysis

Data are expressed as the mean $\pm$ SD. Differences in baseline characteristics between two cohorts were evaluated by the chi-square test, or Fisher's exact test for categorical variables or Student's t test for continuous variables. Survival, major event free, renal dysfunction free, and death/renal dysfunction free rates for the cohorts were estimated by the Kaplan–Meier method and analyzed by log-rank tests [22]. Prognostic factors of severe diabetic nephropathy were estimated by logistic regression analysis. Statistical analyses were performed using SPSS version 16.0.

3. Results

3.1. Characteristics of each cohort

Baseline characteristics of LDL-a and the control cohorts are listed in Table 1. Disease severity parameters such as eGFR (35.1 ± 17.7 mL/min/1.73 m^2 vs. 48.6 ± 26.6 mL/min/1.73 m^2; $P = 0.04$), total protein (3.9 ± 0.3 g/dL vs. 6.7 ± 0.7 g/dL; $P < 0.001$), LDL cholesterol (227.1 ± 33.0 mg/dL vs.

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