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Role of hepatic lipase in intermediate-density lipoprotein and small, dense low-density lipoprotein formation in hemodialysis patients

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Background. It has been reported that remnant lipoproteins and small, dense low-density lipoproteins (LDLs) are risk factors for cardiovascular disease. To determine whether these risk factors are present in hemodialysis (HD) patients who are suffering from a high incidence of atherosclerotic vascular disease, we measured concentrations of remnant lipoproteins and LDL particle diameter in HD patients and compared these with controls. We also measured lipoprotein lipase (LPL) and hepatic triglyceride lipase (HTGL) that play important roles in the generation of remnant lipoproteins and small, dense LDL, and we correlated these changes with plasma lipoprotein abnormalities in HD patients.

Methods. Lipoproteins were separated by ultracentrifugation. Apoprotein B in very low-density lipoprotein (VLDL), and intermediate-density lipoprotein (IDL) fractions were measured by a sensitive enzyme-linked immunosorbent assay method. The average LDL particle diameter was measured by gradient gel electrophoresis.

Results. Plasma triglyceride, total cholesterol, and high-density lipoprotein (HDL) cholesterol concentrations were comparable between HD patients and controls, whereas LDL cholesterol was significantly lower in HD patients. The average LDL particle diameter was not significantly different between HD patients and controls. LDL particle diameter was inversely related to plasma triglyceride concentrations in all of the subjects. VLDL triglyceride, VLDL cholesterol, and VLDL apoprotein B were comparable between HD patients and controls. IDL triglyceride, IDL cholesterol, and IDL apoprotein B concentrations were all significantly increased in HD patients compared with those in controls. LPL mass was not altered, but HTGL activity was significantly decreased in HD patients. The HTGL activity was inversely related to IDL concentrations.

Conclusions. These results suggest that a prominent characteristic of lipoprotein abnormalities in HD patients is a marked increase in IDL particle number. In addition, small, dense LDL is not associated with uremic dyslipidemia. Because HTGLs promote the conversion from IDL to LDL and the generation of lipid-poor LDL, a decrease in HTGL activity may contribute to the accumulation of IDL particle and may prevent small, dense LDL formation in HD patients.

Key words: cardiovascular disease; hepatic triglyceride lipase; intermediate-density lipoprotein; small, dense low-density lipoprotein.

It has been well known that atherosclerotic vascular disease frequently occurs in uremic patients receiving long-term hemodialysis (HD) and that cardiovascular disease is the leading cause of death in these patients [1, 2]. The mechanisms for developing atherosclerosis in HD patients are multifactorial. However, plasma lipid abnormalities have been identified as significant risk factors for cardiovascular disease in such patients. Previous studies have revealed that an increase in plasma triglyceride and a decrease in high-density lipoprotein (HDL) cholesterol concentrations were prominent characteristics of lipid abnormalities associated with uremic patients [3]. However, recent studies reported that very low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL) were increased in uremic patients without apparent hyperlipidemia [4, 5].

Recent epidemiological studies suggest, however, that a predominance of smaller and less dense LDL (small, dense LDL) is highly atherogenic, and it may be a new risk factor of coronary heart disease [6]. Do these nontraditional risk factors, for example, small, dense LDL and IDL, increase in HD patients? In this study, we measured remnant lipoproteins and small, dense LDL in HD patients and compared those with controls. Because lipoprotein lipase (LPL) and hepatic triglyceride lipase (HTGL) play important roles in regulating triglyceride-rich lipoprotein metabolism and in generating remnant lipoproteins and small, dense LDL, we measured these lipases and investigated their relationships with plasma lipoprotein abnormalities in HD patients.

METHODS

The subjects in this study were 19 nondiabetic HD patients and 17 age- and gender-matched controls with

normal renal function. The HD patients were composed of 17 chronic glomerulonephritis patients and 2 polycystic kidney disease patients. Blood samples were drawn from all patients after they fasted over night. VLDL (density < 1.006), IDL ($d = 1.006$ to 1.019), and LDL ($d = 1.019$ to 1.063) were separated by ultracentrifugation. Apoprotein B concentrations in VLDL and IDL were measured by a sensitive enzyme-linked immunosorbent assay (ELISA) method [7]. LDL particle diameter was measured by 2 to 16% gradient polyacrylamide gel electrophoresis [8]. HTGL activity in postheparin plasma collected 10 minutes after intravenous injection of heparin (30 unit/kg body wt) was measured as the rate of radiolabeled fatty acids liberated from a [^{14}C] trioleine emulsion in gum arabic. Immunoreactive LPL mass in postheparin plasma was measured by sandwich-enzyme immunoassay [9]. Data were expressed as mean ± SD. Student's unpaired *t*-test and Pearson's simple regression analysis were employed for the statistical analysis. *P* values of less than 0.05 were considered significant.

RESULTS

Plasma triglyceride, total cholesterol, and HDL cholesterol concentrations were similar to those of our controls, whereas LDL cholesterol concentrations were significantly lower in HD patients. The average of LDL particle diameter was not significantly different between HD patients and controls (259 ± 4 vs. 262 ± 4 Å). There was a significant correlation between plasma triglyceride concentrations and the LDL particle diameter in all of the subjects ($r = -0.55$, $P = 0.0005$). VLDL cholesterol, VLDL triglyceride, and VLDL apoprotein B concentrations in HD patients were comparable to those of the controls. However, IDL cholesterol (0.235 ± 0.137 vs. 0.124 ± 0.048 mmol/liter, $P < 0.05$), IDL triglyceride (0.076 ± 0.035 vs. 0.047 ± 0.016 mmol/liter, $P < 0.05$), and IDL apoprotein B (14.2 ± 8.7 vs. 8.9 ± 3.9 mg/dl, $P < 0.05$) concentrations were all significantly increased in HD patients as compared with those of the controls. Immunoreactive LPL mass was not altered; however, HTGL activity was significantly decreased in HD patients compared with those of the controls (8.6 ± 3.3 vs. 16.3 ± 5.7 μmol ffa/ml/hr, $P < 0.05$). IDL triglyceride ($r = -0.413$, $P = 0.0123$), IDL cholesterol ($r = -0.439$, $P = 0.0074$), IDL apoprotein B concentrations ($r = -0.514$, $P = 0.0013$) were inversely related to HTGL activity.

DISCUSSION

We postulated that IDL and small, dense LDL, which were considered as nontraditional risk factors for cardiovascular disease would be increased in HD patients. We found an increased IDL particle number as previously reported [4, 5]. However, we did not find an increased incidence of small, dense LDL in HD patients. In contrast, Bofinger et al demonstrated that HD and peritoneal dialysis patients had atherogenic lipid profiles that were associated with a predominance of small, dense LDL [10]. Their study also indicated that triglyceride and VLDL cholesterol concentrations were elevated in dialysis patients. In their study, mean plasma triglyceride concentrations were significantly high compared with the subjects of our study. This might be a reason that their results were different from ours, as LDL particle diameter was strongly associated with plasma triglyceride concentrations. In addition, we found that HTGL activity was decreased in HD patients and that there were significant inverse correlations between HTGL activity and IDL levels. These findings, together with the fact that HTGL plays critical roles in the conversion of IDL and in the generation of lipid-poor LDL, indicate that a reduction in HTGL activity may contribute to the accumulation of IDL particle number and may prevent the generation of small, dense LDL in HD patients.

In conclusion, our results indicate that a prominent characteristic of lipid abnormalities in HD patients is a marked increase in IDL particle number. In our study, small, dense LDL particles were not increased.

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