Effects of Atorvastatin on Triglyceride-Rich Lipoproteins, Low-Density Lipoprotein Subclass, and C-Reactive Protein in Hemodialysis Patients

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Dyslipidemia is an important risk factor for cardiovascular disease in patients with chronic renal failure (CRF). We evaluated the safety and efficacy of atorvastatin in patients with dyslipidemia associated with CRF who were undergoing hemodialysis (HD). Thirty-five patients who were receiving HD were given atorvastatin (10 mg/d) for 3 months. Chylomicron (CM), light and dense very–low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and light and dense low-density lipoprotein (LDL) were separated by ultracentrifugation. Apolipoprotein (apo) B was measured by electroimmunoassay. Mean LDL particle diameter was measured by gradient gel electrophoresis. Atorvastatin therapy reduced LDL-cholesterol (C) by 36% and remnant-like particle (RLP)-C by 58%. Atorvastatin significantly reduced apo B, apo CIII, and apo E in VLDL by 40% to 46% and IDL-apo B by 66%. Atorvastatin also significantly reduced cholesterol in CM, light VLDL, and dense VLDL without consistently affecting triglyceride (TG) in these lipoproteins. Atorvastatin similarly reduced both light and dense LDL-apo B by 38%. LDL particle size in the HD patients significantly increased during atorvastatin treatment from 25.7 ± 0.4 to 26.2 ± 0.6 nm. High sensitive C-reactive protein (HS-CRP) was halved by atorvastatin decreasing from 0.08 ± 0.05 to 0.04 ± 0.03 mg/dL. Atorvastatin treatment did not affect the creatinine kinase level, and no classical adverse effects were observed during the study. These results suggest that atorvastatin is safe and effective for the management of dyslipidemia in patients with CFR who are receiving HD, which may help to suppress the development of atherosclerosis.

PATIENTS WITH chronic renal failure (CRF) have a markedly higher prevalence of cardiovascular disease (CVD) than the general population.[1-3] Dyslipidemia is considered as a major cause of CVD in patients with CRF.[3-6] Because prognosis is largely governed by CVD-related events in patients receiving hemodialysis (HD), management of dyslipidemia plays an important role in therapy. The plasma lipid profile in patients with CRF is characterized by increased levels of triglyceride (TG), decreased levels of high-density lipoprotein (HDL)-cholesterol (C), and no marked change in low-density lipoprotein-cholesterol (LDL-C) compared with general populations.[5,7] Remnants, such as remnant-like particle (RLP)[6,7] and intermediate-density lipoprotein (IDL),[8] are considered potent atherogenic lipoproteins and have been reported to be markedly increased in patients with CRF.[9-12] Recently, a smaller and denser subclass of LDL (small dense LDL) also has received considerable attention as a potent atherogenic lipoprotein.[13-15] It has been reported to have a high prevalence of small dense LDL in patients with CRF.[16]

Although substantial evidence suggests that treatment of dyslipidemia with an inhibitor of hepatic hydroxymethyl glutaryl-coenzyme A (HMG-CoA) reductase (statin) reduces mortality and morbidity associated with CVD, only a few studies have examined the efficacy of statins on dyslipidemia in patients with CRF,[17,18] probably because persons with abnormal renal function have an increased risk of rhabdomyolysis.[19] The early detection of statin-induced rhabdomyolysis in patients receiving HD is straightforward because HD is performed 3 or 4 times per week. We used atorvastatin to treat dyslipidemia in patients because of several reasons. First, atorvastatin is metabolized in the liver and excreted via bile with less than 5% excreted via the kidney.[20] Second, hypertriglyceridemia is more common than hypercholesterolemia among patients with CRF. A number of clinical studies have shown that atorvastatin more effectively lowers TG levels than other statins.[21] Third, remnant lipoproteins can be taken up by LDL receptors.[22,23] Atorvastatin strongly induces LDL receptors and thus reduces remnant lipoproteins.[24] High sensitive C-reactive protein (HS-CRP) is considered a sensitive marker for the development of atherosclerosis.[25] We therefore examined HS-CRP levels before and after treatment with atorvastatin in patients receiving HD to examine whether this statin can suppress chronic inflammation in large vessels.

MATERIALS AND METHODS

Thirty-five outpatients with CRF who were undergoing HD were enrolled. The HD patients included 12 with diabetic nephropathy and 23 nondiabetic patients with chronic nephritis. None of the patients or controls had clinical or laboratory evidence of abnormal hepatic or thyroid function or infectious diseases. None had been given agents for treatment of hyperlipidemia. Five HD patients with diabetic nephropathy were receiving sulfonylureas or alpha-glucosidase inhibitors, and 4 were receiving insulin. The dosages of these drugs were not changed during atorvastatin therapy. Each patient gave written informed consent, and the ethics committee of Yokohama Daiichi Hospital and Showa University approved the study protocol.

The HD patients were treated with atorvastatin (10 mg/d) for 3 months. No other lipid-lowering drugs were used during the study. Blood samples were collected after an overnight fast. Apolipoprotein (apo) B–containing lipoproteins were separated from plasma by ultracentrifugation (Hitachi CP-65G; Hitachi, Tokyo, Japan) using an RP 55T-708 rotor (Hitachi) to yield very–low-density lipoprotein (VLDL) (density <1.006 g/mL), IDL ($d = 1.006$ to 1.019 g/mL), light LDL ($d = 1.019$ to 1.044 g/mL), and dense LDL ($d = 1.044$ to 1.063 g/mL)

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Table 1. Plasma Levels of Lipids, Apolipoproteins, RLP-C, and Mean LDL Particle Diameter and HS-CRP at Baseline and 1 and 3 Months After Treatment With Atorvastatin in HD Patients

	Baseline	1 Month	3 Months
TC (mg/dL)	211 ± 47	153 ± 33‡	157 ± 35‡
TG (mg/dL)	208 ± 119	178 ± 118*	178 ± 99*
HDL-C (mg/dL)	39 ± 15	38 ± 9	40 ± 10
LDL-C (mg/dL)	133 ± 46	79 ± 32	85 ± 36‡
Apo A1 (mg/dL)	106 ± 22	110 ± 19	115 ± 18†
Apo B (mg/dL)	109 ± 27	82 ± 19‡	84 ± 21‡
Apo C2 (mg/dL)	5.4 ± 2.5	5.0 ± 1.9	5.0 ± 1.8
Apo C3 (mg/dL)	16.0 ± 4.8	13.6 ± 4.0‡	14.1 ± 3.5‡
Apo E (mg/dL)	4.7 ± 1.3	3.8 ± 0.8‡	3.7 ± 0.7‡
RLP-C (mg/dL)	18.7 ± 14.9	8.4 ± 7.0†	8.0 ± 5.6†
LDL size (nm)	25.7 ± 0.5	25.9 ± 0.6	26.2 ± 0.6†
HS-CRP (mg/dL)	0.0820 ± 0.0558	0.0500 ± 0.0359*	0.0424 ± 0.0337*

NOTE. Data represent mean ± SD.
*$P < .05$; †$P < .01$; ‡$P < .001$ *v* baseline.

fractions as described by Havel et al.[26] The lipoprotein fraction with a density of less than 1.006 was further separated into chylomicron (CM) (Svetberg flotation rate [Sf] > 400), light LDL (Sf 60 to 400), and dense LDL (Sf 20 to 60) by ultracentrifugation with a swing bucket rotor (Hitachi RPS 40T-2) according to the method of Karpe et al.[27] The apo B concentration in each lipoprotein fraction was measured by rocket electroimmunoassay using antihuman apo B antibody (Serotec, Oxford, UK). Apo CII, CIII, and E in plasma and VLDL were measured by by an immunoturbidometric assay (Daiichi Chemicals, Tokyo, Japan). Mean LDL particle diameter was determined by 2% to 16% polyacrylamine gel electrophoresis as described by Nicolus et al.[28] RLP-C was measured by the method of Nakajima et al.[9] Glucose, TG, cholesterol, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine kinase (CK), and creatinine were measured by standard laboratory procedures. HDL-C was measured after polyanion precipitation of apo B–containing lipoproteins from the plasma. The LDL-C level was estimated by the Friedewald formula.[29] HS-CRP was measured with a test kit (latex immunoassay; Behring Nephrometer BN, Dade Behring, Tokyo, Japan) To avoid the effects of acute infection, we excluded samples of HS-CRP levels of more than 0.2 mg/dL, which is the lowest cut-off value for conventional measurement techniques for CRP.

Statistical Analysis

Student's paired *t* test was used to assess differences in plasma variables between baseline and after 1 month and 3 months of atorvastatin treatment in the HD patients.

RESULTS

All subjects completed 3 months atorvastatin treatment. Table 1 shows the plasma levels of lipids, apolipoproteins, RLP-C, mean LDL particle diameter, and HS-CRP at baseline and after at 1 and 3 months of treatment with atorvastatin in the HD patients. After 1 month of treatment, the total C and LDL-C levels decreased by 27% and 34%, respectively. Similar levels were maintained after 3 months of treatment. Atorvastatin decreased plasma TG levels by 12% to 14% during treatment. The HDL-C level was not changed, but apo AI significantly increased during atorvastatin treatment. The plasma apo B level significantly decreased by 23%, and the apo CIII and apo E levels were slightly decreased by atorvastatin, but the apo CII level was unchanged. Atorvastatin reduced the elevated level of RPL-C by 58% in the HD patients. The average LDL particle diameter significantly increased after 3 months of treatment with atorvastatin. HS-CRP was halved by treatment with atorvastatin for 3 months.

Table 2 shows the concentrations of cholesterol, TG, and apo B in VLDL, IDL, light LDL, and dense LDL fractions in the HD patients at baseline and after 1 and 3 months of atorvastatin treatment. VLDL-C, TG, and apo B levels decreased by 17% to 20%, 17% to 23%, and 41%, respectively, during atorvastatin treatment. VLDL apo CIII and apo E levels also significantly decreased. IDL-C, TG, and apo B levels significantly decreased by 21% to 25%, 22% to 31%, and 40% to 53%, respectively, during treatment. Cholesterol, TG, and apo B levels in the light LDL fraction decreased by 29% to 33%, 20% to 22%, and 38% to 60%, respectively, during atorvastatin treatment. Cholesterol, TG, and apo B levels in the dense LDL fraction decreased by 20% to 27%, 53% to 60%, and 26% to 32%, respectively. The light LDL/dense LDL apo B ratio (wt/wt) was not altered by treatment with atorvastatin (2.81 ± 1.90 at baseline *v* 2.83 ± 1.84 after 3 months of treatment).

Table 3 shows the cholesterol, TG, and apo B levels in TG-rich lipoproteins with a density of less than 1.006 g/mL at baseline and after 1 and 3 months of treatment with atorvastatin. Atorvastatin did not decrease CM-TG or CM-apo B, but significantly decreased the CM-C level. Similarly, atorvastatin did not consistently decrease light VLDL-TG or light VLDL-apo B, but significantly decreased light VLDL-C. In contrast to these more buoyant lipoproteins, atorvastatin significantly decreased TG, cholesterol, and apo B levels in the dense VLDL fraction.

Table 4 shows the plasma ALT, AST, and CK levels during atorvastatin treatment in the HD patients. The ALT level slightly increased, but this small increment was considered clinically insignificant. AST and CK levels were altered by treatment. Compliance with atorvastatin therapy was very good for all HD patients, and no adverse reactions to atorvastatin treatment were observed.

DISCUSSION

Statin primarily reduce LDL-C with only a modest decrease in TG. HD patients more frequently have hypertriglyceridemia

Table 2. Concentrations of C, TG, and Apo B in VLDL, IDL, Light LDL, and Dense LDL Fractions in HD Patients at Baseline and 1 and 3 Months After Atorvastatin Treatment

	Baseline	1 Month	3 Months
VLDL-C (mg/dL)	29 ± 18	23 ± 19	24 ± 15
VLDL-TG (mg/dL)	105 ± 82	69 ± 60†	84 ± 78*
VLDL-Apo B (mg/dL)	13 ± 6	8 ± 4‡	7 ± 4‡
VLDL-Apo c3 (mg/dL)	4.3 ± 3.1	2.2 ± 1.7‡	2.8 ± 2.4*
VLDL-Apo E (mg/dL)	0.9 ± 0.8	0.5 ± 0.5*	0.5 ± 0.5*
IDL-C (mg/dL)	14 ± 6	11 ± 5‡	10 ± 5‡
IDL-TG (mg/dL)	17 ± 12	12 ± 10‡	12 ± 15*
IDL-Apo E (mg/dL)	9 ± 4	5 ± 2‡	3 ± 2‡
L-LDL-C (mg/dL)	69 ± 30	46 ± 17‡	43 ± 15‡
L-LDL-TG (mg/dL)	20 ± 6	15 ± 5‡	13 ± 5‡
L-LDL-Apo B (mg/dL)	39 ± 16	26 ± 9‡	24 ± 9‡
L-LDL-C (mg/dL)	29 ± 11	21 ± 8‡	21 ± 8‡
D-LDL-TG (mg/dL)	6 ± 3	3 ± 3‡	2 ± 2‡
D-LDL-Apo B (mg/dL)	18 ± 9	12 ± 7‡	11 ± 6‡

NOTE. Data represent mean ± SD.
*$P < .05$; †$P < .01$; ‡$P < .001$ *v* baseline.

than hypercholesterolemia. Thus, fibrates rather than statins seem to be suitable to treat dyslipidemia in HD patients. Unfortunately, most of the administrated dose of fibrate is excreted into the urine, and rhabdomyolysis has been reported in subjects with renal dysfunction who received fibrates.[30] In contrast, statins are excreted primarily via the bile tract, with low excretion into the urine. Theoretically, statins can thus be used for the management of dyslipidemia in HD patients. However, there have been sporadic reports of rhabdomyolysis developing in patients with renal dysfunction during statin treatment.[31] Only a few studies have examined the effect of statins on dyslipidemia in HD patients, probably because the safety of statin treatment has not been established in patients with CRF. However, given the very high incidence of CVD-related events in HD patients, it is important to evaluate the safety and efficacy of statin treatment in HD patients with dyslipidemia. Recently, Harris et al[32] have reported that atorvastatin had markedly lowered LDL-C and modestly decreased TG in patients receiving continuous ambulatory peritoneal dialysis. Although they used a higher dose of atorvastatin (20 to 40 mg) than that given to HD patients in our study, the overall adverse event profile with atorvastatin was similar to that with placebo during 4 months.

Plasma lipoprotein abnormalities in CRF are characterized by an increase in remnant lipoproteins and a decrease in HDL-C.[5,7,8] Attman et al[7] and Shoji et al[5] have reported that IDL is remarkably increased in CRF, irrespective of whether dialysis has or has not been started. In addition, an increase in IDL is reported to be associated with the severity of atherosclerosis in HD patients.[8] It is still laborious to measure chylomicron remnant. However, kits for measuring RLP-C are now commercially available and widely used, which reflects apo B-48 containing and apo E–enriched lipoproteins, such as chylomicron remnant.[9] RLP-C was markedly decreased by atorvastatin treatment. The RLP-C level strongly correlates with the plasma TG level.[9] Although the percent reduction in plasma TG was only 13% during atorvastatin treatment in the HD patients, the reduction in RLP-C was 59%, suggesting that remnant lipoproteins, but not all TG-rich lipoproteins, are selectively decreased by this statin. Similar to RLP-C, the high level of IDL in the HD patients was significantly reduced by treatment with atorvastatin. Atorvastatin also significantly decreased VLDL-apo B, but the effect on VLDL-TG was less obvious, suggesting that atorvastatin primarily stimulates particle clearance without significantly affecting lipolysis. We further examined the effect of atorvastatin on TG-rich lipoproteins fractions, including

Table 3. C, TG, and Apo B Levels in the TG-Rich Lipoproteins of Density Less Than 1.006 g/mL at Baseline and 1 and 3 Months After Treatment With Atorvastatin

	Baseline	1 Month	3 Months
CM-C (mg/dL)	11 ± 12	6 ± 10*	8 ± 10*
CM-TG (mg/dL)	44 ± 71	36 ± 73	39 ± 70
CM-Apo B (mg/dL)	0.27 ± 0.44	0.25 ± 0.58	0.26 ± 0.45
L-VLDL-C (mg/dL)	18 ± 11	12 ± 8*	12 ± 7*
L-VLDL-TG (mg/dL)	48 ± 38	39 ± 28*	40 ± 28
L-VLDL-Apo B (mg/dL)	4.4 ± 4.0	3.9 ± 2.7	3.4 ± 2.2
D-VLDL-C (mg/dL)	13 ± 6	10 ± 5†	8 ± 5†
D-VLDL-TG (mg/dL)	21 ± 11	18 ± 11	15 ± 14*
D-VLDL-Apo B (mg/dL)	4.0 ± 2.3	3.2 ± 1.9*	2.8 ± 1.5*

NOTE. Data represent mean ± SD.
*$P < .05$; †$P < .001$ *v* baseline.

Table 4. Plasma ALT, AST, and CK Levels During Atorvastatin Treatment in the HD Patients

	Baseline	1 Month	3 Months
ALT (IU/L)	13 ± 6	14 ± 6	14 ± 5*
AST (IU/L)	10 ± 5	11 ± 7	13 ± 7
CK (IU/L)	110 ± 61	112 ± 75	125 ± 117

NOTE. Data represent mean ± SD.
*$P < .05$ *v* baseline.

chylomicron, light VLDL, and dense VLDL. Cholesterol in all these lipoprotein fractions was decreased by atorvastatin, whereas TG in these fractions was not consistently reduced. These results suggest that cholesterol-rich particles rather than TG-rich particles are preferentially decreased by atorvastatin treatment, supporting our hypothesis that remnant lipoprotein, which is cholesterol-rich, is more selectively cleared than other TG-rich lipoproteins by statin treatment. Apo B in CM or light VLDL was not significantly decreased by atorvastatin, whereas apo B in dense VLDL was significantly decreased. Because LDL receptor affinity is inversely related to lipoprotein buoyancy,[33] the effect of atorvastatin on lipoprotein particle uptake should be more obvious in lipoprotein fractions with low TG content, such as dense VLDL. Taken together, our results strongly suggest that atorvastatin potently reduces remnant lipoprotein characterized by cholesterol-rich, TG-depleted, and dense particles.

As expected, atorvastatin markedly decreased LDL-C. In this study we also examined the effect of atorvastatin on LDL subclass, namely lighter fraction and denser fraction. Denser fraction is defined as LDL-III, which is associated with a high incidence of CHD-related events.[34] Atorvastatin similarly decreased apo B in light and dense LDL. There was no change in the ratio of light/dense LDL apo B during treatment, indicating that dense LDL particles are not preferentially cleared by atorvastatin. Van den Akker et al[35] also failed to find changes of LDL subclasses separated by ultracentrifugation after the treatment with atorvastatin in HD patients. Although preferential reduction in dense LDL over light LDL was not observed, we found mean LDL size measured by gradient gel electrophoresis was significantly increased by atorvastatin treatment. Because atrovastatin lowers TG in HD patients, it is not surprising that LDL size is enlarged by treatment with this statin. Conversely, the statins without hypotriglyceridemic action are not expected to enlarge LDL size. Atorvastatin enlarged LDL size and decreased dense LDL mass in HD patients, which qualitatively and quantitatively reduces small dense LDL. We previously examined the effect of atorvastatin on lipoprotein fractions in hyperlipidemic subjects.[36] In that study, we found a 27% decrease of RLP and no change of LDL size after atorvastatin treatment for 3 months, suggesting that atorvastatin may particularly ameliorate dyslipidemia associated with CRF/HD. We did not examine diabetic and nondiabetic HD patients separately in this study, because the number of patients was too small for statistical analysis. Because diabetes has a major influence on lipoprotein metabolism, we should examine differences between diabetic and nondiabetic HD patients before treatment and compare their response to atorvastatin in a large number of patients.

HS-CRP is considered a marker of the severity of atherosclerosis because this disease process involves chronic inflammation in large vessels.[25] Several studies have reported that HS-CRP levels in HD patients are higher than in normal subjects.[37] To avoid effects of acute infection on the HS-CRP value, we excluded patients with a CRP level of more than 0.2 mg/dL (the lowest cut-off point by conventional procedures for CRP measurement), which may have underestimated the actual CRP value in HD patients. Nevertheless, our study design may be useful for evaluating the effects of statins on the subclinical range of CRP. Atorvastatin markedly decreased HS-CRP in the HD patients. Because statins have pleiotrophic effects that directly suppress atherosclerosis, it remains unknown whether the lowering of HS-CRP by atorvastatin is attributable to the improvement in the plasma lipoprotein profile or not. Nevertheless, our results suggest that atorvastatin can slow the development of atherosclerosis, a leading cause of death in HD patients. Long-term prospective studies are required to confirm the antiatherosclerotic effect of atorvastatin in HD patients.

In conclusion, HD patients had elevated levels of remnant lipoprotein and smaller sized LDL. Atorvastatin safely improved the dyslipidemia in HD patients, which may help to suppress the development of atherosclerosis.

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