Effect of Atorvastatin on Low-Density Lipoprotein Subtypes in Patients With Different Forms of Hyperlipoproteinemia and Control Subjects

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Atorvastatin is a potent hydroxy-methyl-glutaryl–coenzyme A (HMG-CoA) reductase inhibitor that decreases low-density lipoprotein (LDL) cholesterol and triglyceride concentrations, but little is known about its effects on LDL subtype distribution in different types of hyperlipoproteinemia. Thus, we evaluated the influence of atorvastatin (10 mg/d, 4 weeks) on lipid concentrations and LDL subtype distribution in patients with hypercholesterolemia (n = 9; LDL cholesterol, 227 ± 30 mg/dL; triglycerides, 137 ± 56 mg/dL), patients with type 2 diabetes and dyslipoproteinemia (n = 11; LDL cholesterol, 163 ± 34 mg/dL; triglycerides, 260 ± 147 mg/dL), and controls (n = 10; LDL cholesterol, 116 ± 20 mg/dL; triglycerides, 130 ± 47 mg/dL). Cholesterol concentration was determined in 7 LDL subfractions isolated by density gradient ultracentrifugation before and during atorvastatin treatment. Atorvastatin decreased LDL cholesterol (−36%, −28%, and −41%, all *P* < .01) and triglyceride (−4%, NS; −2%, NS; −24%, *P* < .05) concentrations but had little effect on high-density lipoprotein (HDL) cholesterol (−1%, NS; +10%, *P* < .05; +6%, NS) in hypercholesterolemic, diabetic, and control subjects, respectively. In all 3 groups, a significant reduction in cholesterol in each LDL subfraction was observed. Large-buoyant (LDL-1, LDL-2) and intermediate-dense (LDL-3, LDL-4) LDL were reduced more than small-dense (LDL-5 through LDL-7) LDL in hypercholesterolemic (−45%, −35%, and −32%, *P* < .05) and control subjects (−48%, −44%, and −25%, *P* < .05), but in diabetic patients cholesterol reduction was uniform in all LDL subtypes (−32%, −27%, and −29%, *P* = .45). Thus, atorvastatin decreases cholesterol concentration in all LDL subfractions in hypercholesterolemic, diabetic, and control subjects. However, the relative reduction of individual LDL subtypes differed between these groups. This finding suggests that the effect of atorvastatin on LDL subtype distribution depends on the type of underlying hyperlipoproteinemia.

AN INCREASED low-density lipoprotein (LDL) cholesterol concentration is a well-known risk factor for the development and progression of coronary heart disease.[1] LDL can be separated into subtypes of different size and density by density gradient ultracentrifugation[2] and gradient gel electrophoresis.[3] In vitro experiments[4-6] and epidemiologic studies[7-10] have shown that small-dense LDL is more atherogenic than large-buoyant LDL. These findings can be partly explained by the association of small-dense LDL with elevated levels of plasma triglycerides and decreased levels of high-density lipoprotein (HDL) cholesterol,[11] but there is evidence that additional mechanisms contribute to the atherogenity of small-dense LDL.[12,13] Small-dense LDLs show decreased binding activity to the LDL receptor compared with intermediate-dense LDL[6] and thus have a longer residence time in plasma, which predisposes them to oxidative modification.[4,14,15] Furthermore, they are retained in the arterial intima by their enhanced capacity to bind to intimal proteoglycan.[5] The net effect is an increased uptake by macrophages, which are transformed to foam cells.[15]

Atorvastatin is a potent HMG-CoA reductase inhibitor that decreases LDL cholesterol[16,17] and triglyceride[18] concentrations, but there is little and inconsistent information on its effect on LDL subtype distribution.[19-23] This may partly be because the effect of atorvastatin on LDL subtypes may depend on the underlying hyperlipoproteinemia. Therefore, we evaluated whether patients with severe hypercholesterolemia and patients with diabetic dyslipoproteinemia differ from normolipidemic controls with respect to the change in LDL subtype distribution induced by atorvastatin treatment.

MATERIALS AND METHODS

Patients

The effect of atorvastatin (10 mg/d; 4 weeks) on LDL subtypes was examined in 3 study groups (Table 1): (1) patients with severe hypercholesterolemia (LDL cholesterol ≥200 mg/dL, n = 9), (2) patients with type 2 diabetes mellitus and dyslipoproteinemia (triglycerides > 150 mg/dL, LDL cholesterol ≥ 125 mg/dL, preponderance of small-dense LDL, n = 11), and (3) normolipidemic controls (LDL cholesterol < 150 mg/dL, triglycerides < 200 mg/dL, n = 10). Nine of the diabetic patients concomitantly participated in a study comparing the effects of atorvastatin and fenofibrate on lipids and hemorheology.[22] Before inclusion in the study, all subjects were without lipid-lowering medication for a minimum of 6 weeks. The LDL subtype distribution was determined before and during atorvastatin treatment.

We also present data of 9 patients suffering from severe hypercholesterolemia (47.4 ± 3.2 years, male-female ratio 2 to 7, body mass index 25.5 ± 3.9 kg/m^2, cholesterol 395 ± 98 mg/dL, LDL cholesterol 305 ± 85 mg/dL, HDL cholesterol 57 ± 12 mg/dL, triglycerides 162 ± 80 mg/dL) who were treated with higher doses of atorvastatin (20 to 60 mg/d).

Preparative and Analytic Methods

Fasting (12 hours) ethylenediaminetetraacetic acid (EDTA)–plasma was obtained in the morning, and lipid analyses were done immediately; determination of LDL-subtypes was done within 6 weeks from aliquots frozen at −80°C.

Plasma lipids. Total plasma cholesterol and triglyceride concentrations were determined by enzymatic methods using an autoanalyzer

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Submitted November 2, 2000; accepted January 29, 2001.

Supported in part by a grant from the Friedrich-Baur-Stiftung, Munich, Germany, and by a grant from Gödecke Parke-Davis, Freiburg, Germany.

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0026-0495/01/5008-0007$35.00/0

doi:10.1053/meta.2001.24879

Table 1. Demographic and Anthropometric Data of Patients With Severe Hypercholesterolemia, Patients With Diabetic Dyslipoproteinemia, and Normolipidemic Controls Before Atorvastatin Treatment

	n	Age (yr)*	Male: Female	BMI (kg/m^2)*
Hypercholesterolemia	9	45.0 ± 14.9	6:3	22.6 ± 2.0
Diabetes mellitus	11	60.4 ± 6.8	3:8	30.0 ± 3.0
Controls	10	30.3 ± 1.7	10:0	22.1 ± 3.0

* Mean ± SD.

(EPOS; Eppendorf, Hamburg, Germany). Preparative ultracentrifugation was performed (18 hours, $d = 1.006$ g/mL, 270,000*g*, 4°C; Beckman Ti 50.4 rotor, Palo Alto, CA) to isolate very-low-density lipoprotein (VLDL). Cholesterol and triglyceride concentrations were determined in the supernatant and total cholesterol in the infranatant (containing HDL and LDL). After precipitation of apolipoprotein B containing lipoproteins by dextran sulphate and magnesium acetate HDL cholesterol was determined in the infranatant. LDL cholesterol was calculated by subtraction of HDL cholesterol from total cholesterol in the infranatant.

LDL subfractionation. LDL subfractions were separated by isopycnic density gradient ultracentrifugation as described elsewhere[2,24]: in brief, dry solid KBr was added to the plasma to increase the density to 1.21 g/mL. A discontinuous density gradient was constructed by 2 mL of a NaCl/KBr solution ($d = 1.26$ g/mL), 3 mL plasma ($d = 1.21$ g/mL), 2 mL of a NaCl/KBr solution ($d = 1.063$ g/mL), 2.5 mL of another NaCl/KBr solution ($d = 1.019$ g/mL), and 2 mL of a NaCl solution ($d = 1.006$ g/mL). All solutions contained NaN_3 (0.1%) and EDTA (0.04%). Densities were measured by a precision density meter (Anton Paar DMA 38, Graz, Austria). Ultracentrifugation was performed in a Beckmann SW 40 Ti rotor at 40,000 rpm for 48 hours at 15°C. Fifteen fractions were collected successively by aspiration of 0.5 mL with an Eppendorf pipette beginning at the top of each gradient. Seven LDL subfractions were isolated corresponding to fractions 5 through 11. They refer to the following density intervals : LDL-1, 1.020 to 1.024 g/mL; LDL-2, 1.025 to 1.029 g/mL; LDL-3, 1.030 to 1.034 g/mL; LDL-4, 1.035 to1.040 g/mL; LDL-5, 1.041 to 1.047 g/mL; LDL-6, 1.048 to 1.057 g/mL; LDL-7, 1.058 to 1.066 g/mL. LDL-1 and -2 were defined as large-buoyant LDL (1.020 to 1.029 g/mL), LDL-3 and -4 as intermediate-dense LDL (1.030 to 1.040 g/mL), and LDL-5 through LDL-7 as small-dense LDL (1.041 to 1.066 g/mL). Density limits were determined by a standard curve derived from control gradients established with a NaCl/KBr solution ($d = 1.21$ g/mL). Intra-assay and interassay variability was <5%. For quality control, each run contained 2 control gradients. Furthermore, to avoid assay drift, all samples from 1 subject were analyzed simultaneously. LDL subtypes are expressed as the amount of cholesterol in each LDL subfraction.

Statistical analysis. In each patient, lipid concentrations and LDL subtypes (before and during atorvastatin treatment) were compared with a nonparametric test (Wilcoxon-test). Furthermore, the relative reduction of cholesterol in each LDL subfraction during atorvastatin treatment was calculated in each treatment group. The extent of the relative cholesterol reduction in large-buoyant or intermediate-dense compared with small-dense LDL subfractions was evaluated by the Wilcoxon test for pairs. The Mann-Whitney *U* test was used to investigate differences among hypercholesterolemic, diabetic, and control subjects with respect to the extent of relative cholesterol reduction in large-buoyant, intermediate-dense, and small-dense LDL subfractions. Similarly, the effect of statin dose on the relative cholesterol reduction in individual LDL subfractions was evaluated comparing patients treated with 10 and 20 to 60 mg/d atorvastatin. Spearman-rho correlation coefficients (double-sided test for significance) were calculated to examine the correlation between baseline triglyceride concentrations and the relative amount of small-dense LDL-subtypes.

RESULTS

At baseline, patients with hypercholesterolemia and diabetic dyslipoproteinemia were characterized by more small-dense LDL in absolute and relative terms than controls (controls, 32 ± 7 mg/dL, 28%; hypercholesterolemia, 82 ± 17 mg/dL, 37%; diabetic dyslipoproteinemia, 84 ± 13 mg/dL, 53%). In all subjects and in patients with diabetic dyslipoproteinemia, the pretreatment triglyceride concentration correlated positively with the relative amount of small-dense LDL (all: $r = .63$, $P < .01$; diabetic dyslipoproteinemia, $r = .62$, $P = .05$; hypercholesterolemia, $r = .38$, NS; controls, $r = .0$, NS).

In patients with hypercholesterolemia, patients with diabetic dyslipoproteinemia, and controls, atorvastatin resulted in significant reductions in cholesterol (−23%, −25%, and −28%, $P < .05$) and LDL cholesterol (−36%, −28%, and −41%, $P < .01$), whereas triglycerides were significantly reduced only in controls (−24%, $P < .05$). In the diabetic patients, the change in triglyceride concentrations was not uniform, with an increase in some (n = 3) and no change or a decrease in the others. However, HDL cholesterol increased in all patients with diabetic dyslipoproteinemia (+10%, $P < .05$), whereas there was no significant change in the other groups (Table 2).

Table 2. Lipid Concentrations in Patients With Severe Hypercholesterolemia, Patients With Diabetic Dyslipoproteinemia, and Controls Before and During Treatment With 10 mg/d Atorvastatin

	Cholesterol (mg/dL)*		Change	LDL Cholesterol (mg/dL)*		Change	HDL Cholesterol (mg/dL)*		Change	Triglycerides (mg/dL)*		Change
	Before	During	(%)†	Before	During	(%)†	Before	During	(%)†	Before	During	(%)†
HC	295.1 ± 37	221.4 ± 46	−23.4‡	227.3 ± 30	143.9 ± 31	−35.7§	52.9 ± 20	52.0 ± 19	−0.6‖	136.6 ± 56	131.2 ± 64	−3.9‖
D mell	263.5 ± 44	197.4 ± 41	−24.5§	162.6 ± 34	114.8 ± 31	−27.9§	44.8 ± 10	48.7 ± 11	+9.6†	259.6 ± 147	209.6 ± 66	−1.8‖
Controls	186.6 ± 22	134.2 ± 27	−28.4§	115.8 ± 20	69.0 ± 17	−40.7§	44.6 ± 8	46.8 ± 8	+5.8‖	130.1 ± 47	91.0 ± 38	−23.6‡

Abbreviations: HC, hypercholesterolemia; D mell, diabetic dyslipoproteinemia.

* Mean ± SD.

† Mean.

‡ $P < .05$.

§ $P < .01$.

‖ Not significant for differences in lipid concentrations before and during atorvastatin therapy, Wilcoxon test.

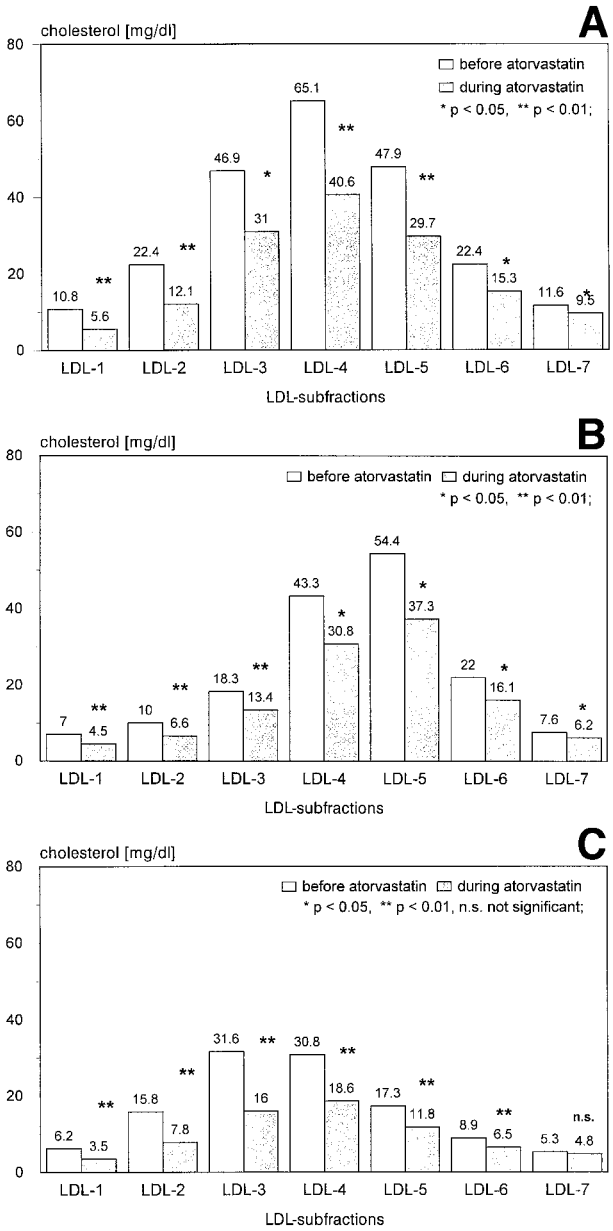

Fig 1. Cholesterol concentration [mg/dl] in different LDL-subfractions before and during atorvastatin treatment (10 mg/d, 4 weeks) in (A) patients with severe hypercholesterolemia (n = 9), (B) patients with diabetic dyslipoproteinemia (n = 11), and (C) normolipidemic controls (n = 10).

Figure 1 shows the distribution of cholesterol in each of the 7 LDL subfractions before and during atorvastatin treatment in patients with hypercholesterolemia (Fig 1A), patients with diabetic dyslipoproteinemia (Fig 1B), and controls (Fig 1C). Treatment with atorvastatin significantly decreased cholesterol in each LDL subfraction with the exception of LDL-7 in controls (5.3 mg/dL *v* 4.8 mg/dL, NS).

Patients with hypercholesterolemia, patients with diabetic dyslipoproteinemia, and controls had an absolute reduction of LDL cholesterol by 83 mg/dL, 48 mg/dL, and 47 mg/dL, respectively. Large-buoyant LDLs were reduced by 15 mg/dL, 6 mg/dL, and 11 mg/dL; intermediate-dense LDLs by 40 mg/dL, 17 mg/dL, and 28 mg/dL; and small-dense-LDLs by 28 mg/dL, 25 mg/dL, and 8 mg/dL, respectively.

The reduction of cholesterol in the individual LDL subfractions is shown in Fig 2 and Table 3. Patients with hypercholesterolemia (Fig 2A) and controls (Fig 2C) showed a greater cholesterol reduction in large-buoyant (LDL-1 and LDL-2) than in small-dense LDL (LDL-5 through LDL-7) (large-buoy-

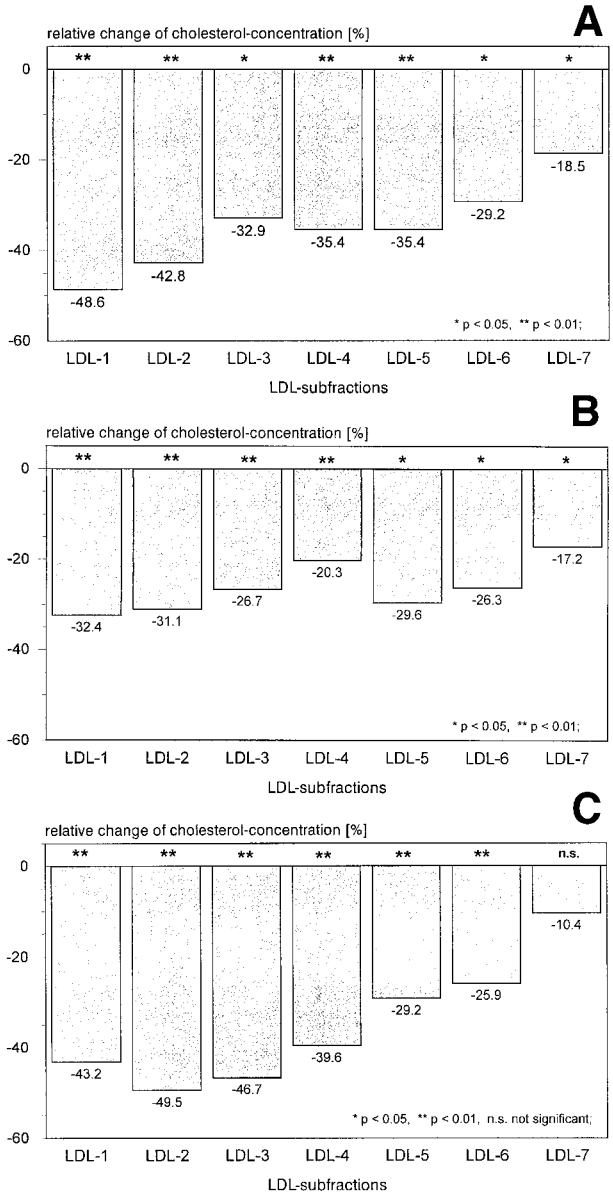

Fig 2. Relative reduction of cholesterol concentration (%) in individual LDL subfractions during atorvastatin treatment (10 mg/d, 4 weeks) in (A) patients with severe hypercholesterolemia (n = 9), (B) patients with diabetic dyslipoproteinemia (n = 11), and (C) normolipidemic controls (n = 10).

Table 3. Cholesterol Concentration in Large-Buoyant, Intermediate-Dense, and Small-Dense LDL in Patients With Severe Hypercholesterolemia, Patients With Diabetic Dyslipoproteinemia, and Control Subjects Before and During Treatment With 10 mg/d Atorvastatin

	Large-Buoyant LDL (mg/dL)*		Change (%)†	Intermediate-Dense LDL (mg/dL)*		Change (%)†	Small-Dense LDL (mg/dL)*		Change (%)†
	Before	During		Before	During		Before	During	
HC	33.1 ± 11	17.7 ± 8	−45.2§	112.0 ± 27	72.0 ± 24	−34.6§	82.0 ± 17	54.5 ± 12	−31.6§
D mell	17.1 ± 8	11.1 ± 5	−31.8§	61.6 ± 25	44.2 ± 21	−26.7‡	84.0 ± 13	59.5 ± 21	−28.9‡
Controls	22.0 ± 8	11.3 ± 5	−48.1§	62.4 ± 14	34.6 ± 8	−43.9§	31.6 ± 7	23.2 ± 5	−25.0§

Abbreviations: HC, hypercholesterolemia; D mell, diabetic dyslipoproteinemia.
* Mean ± SD.
† Mean.
‡ $P < .05$.
§ $P < .01$.

ant *v* small-dense LDL, −45% *v* −32% in hypercholesterolemic patients, $P = .028$; −48% *v* -25% in controls, $P = .013$). Furthermore, controls showed a greater reduction of cholesterol in intermediate-dense than in small-dense LDL (−44% *v* −25%, $P = .037$). Table 4 indicates the fraction of cholesterol in large-buoyant, intermediate-dense, and small-dense LDL. Atorvastatin induced a shift in the LDL subtype profile in hypercholesterolemic and control subjects; in relative terms, large-buoyant LDL was reduced by 13.9% in hypercholesterolemic patients ($P < .05$) and by 12.9% in controls ($P < .05$), and small-dense LDL increased by 6.8% ($P = .10$) and 26.5% ($P < .05$), respectively.

In patients with diabetic dyslipoproteinemia, atorvastatin induced a uniform reduction of cholesterol in all LDL subfractions (Fig 2B; large-buoyant, −32%; intermediate-dense, −27%; small-dense, −29%; $P = .45$). Thus, in relative terms, atorvastatin treatment did not influence the LDL subtype profile in diabetic patients (Table 4).

When the study groups were compared with respect to the relative reduction of cholesterol in individual LDL subfractions, significant differences were observed only between diabetic patients and controls; diabetic patients had a smaller decrease in large-buoyant and intermediate-dense LDL during atorvastatin treatment (diabetics *v* controls, -32% vs. −48% for large-buoyant LDL, $P = .029$; −27% *v* −44% for intermediate-dense LDL; $P = .024$).

In a separate group of patients with severe hypercholesterolemia who were treated with higher doses (20 to 60 mg/d) of atorvastatin (cholesterol, −37%, $P < .001$; LDL cholesterol, −44%, $P < .001$; HDL cholesterol, −6.4%, NS; triglycerides, −15%, NS), we observed a more pronounced relative cholesterol reduction in each LDL subfraction compared with hypercholesterolemic patients treated with 10 mg/d. However, the effect on the LDL subtype profile was similar in both groups (Fig 3).

DISCUSSION

Atorvastatin decreased cholesterol concentration in all LDL subfractions in patients with severe hypercholesterolemia, patients with diabetic dyslipoproteinemia, and control subjects. However, in relative terms cholesterol reduction in the individual subfractions differed between these groups. Thus, patients with hypercholesterolemia and controls showed a more pronounced reduction in large-buoyant and intermediate-dense LDL than in small-dense LDL, whereas in diabetic patients there was a more uniform reduction in all LDL subtypes. These changes are also reflected by a different influence of atorvastatin on the LDL subtype profile; patients with hypercholesterolemia and controls showed a shift in LDL subtype profile with a relative reduction in large-buoyant and a relative increase in small-dense LDL subtypes, whereas LDL subtype distribution remained unchanged in patients with diabetes mellitus.

At baseline, patients with severe hypercholesterolemia

Table 4. Fraction of Cholesterol in Large-Buoyant, Intermediate-Dense, and Small-Dense LDL Subfractions in Patients With Severe Hypercholesterolemia, Patients With Diabetic Dyslipoproteinemia, and Control Subjects Before and During Treatment With 10 mg/d Atorvastatin

	Large-Buoyant LDL (%)*		Change (%)†	Intermediate-Dense LDL (%)*		Change (%)†	Small-Dense LDL (%)*		Change (%)†
	Before	During		Before	During		Before	During	
HC	14.6 ± 4.3	12.1 ± 3.5	−13.9‡	48.8 ± 7.0	49.2 ± 8.0	0.9§	36.5 ± 8.7	38.7 ± 8.3	6.8§
D mell	10.2 ± 2.9	9.5 ± 2.6	−4.5‖,§	36.6 ± 10.5	38.2 ± 12.2	6.9§	53.3 ± 11.0	52.3 ± 14.0	−2.1§
Controls	18.6 ± 4.3	15.8 ± 4.0	−12.9‡	53.6 ± 4.9	50.3 ± 2.3	5.4§	28.0 ± 7.8	34.0 ± 4.1	26.5†

Abbreviations: HC, hypercholesterolemia; D mell, diabetic dyslipoproteinemia.
* Mean ± SD.
† Mean.
‡ $P < .05$.
§ Not significant for differences in % of cholesterol before and during atorvastatin therapy, Wilcoxon test.

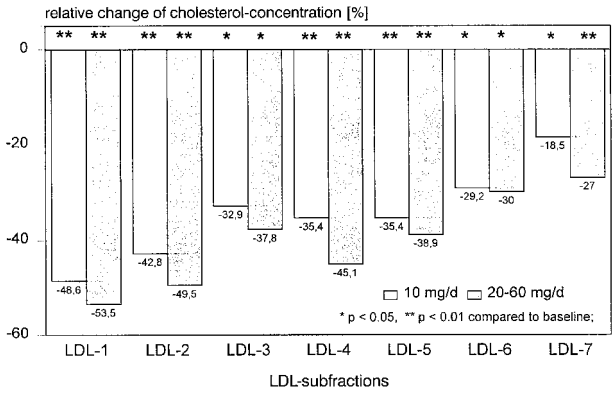

Fig 3. Relative reduction of cholesterol concentration (%) in individual LDL subfractions during atorvastatin treatment in patients with severe hypercholesterolemia treated with 10 mg/d (n = 9) or higher doses (20 to 60 mg/d; n = 9). Differences between groups were not significant.

showed a near normal LDL subtype distribution, with a predominance of intermediate-dense LDL. In absolute terms, the reduction was strongest for intermediate-dense LDL. The diabetic group was characterized by a predominance of small-dense LDL, and atorvastatin mainly reduced small-dense LDL in absolute terms.

No study has directly compared the effect of atorvastatin on LDL subtype distribution in different types of hyperlipoproteinemia and in normolipidemic subjects. In 9 patients with LDL hypercholesterolemia, Landray et al[23] observed an improvement in the LDL subfraction profile under atorvastatin treatment. Furthermore, in patients with familial hypercholesterolemia Hoogerbrugge et al[19] showed an increase in LDL size during atorvastatin treatment, suggesting a shift in the LDL density distribution to less dense LDL subtypes. However, the increase in LDL size in the study of Hoogerbrugge et al[19] was significant only in men. The low number of subjects in each of our study groups and the lack of female controls did not allow sex-specific analysis. However, the combined analysis of all subjects in all study groups did not reveal a significant difference between men and women. Several factors may explain the observed difference between the 3 studies. Different methods were used to define LDL subtypes (gradient gel electrophoresis[19] *v* disc polyacrylamide electrophoresis[23] *v* density gradient ultracentrifugation in our study). Furthermore, Hoogerbrugge et al[19] used between 40 and 80 mg/d of atorvastatin, and Landray et al[23] used a mean dose of 56 mg/d, (significantly higher doses than in our study), which were associated with a significant reduction in triglyceride concentrations. However, triglyceride reduction and change in LDL subtype distribution were not correlated in our study (data not shown).

In another study in patients with hypertriglyceridemia receiving 20 or 80 mg/d atorvastatin, no significant change in LDL subtype distribution was observed.[20] In addition, nondiabetic[21] as well as diabetic[22] patients with mixed hyperlipoproteinemia showed a uniform reduction in all LDL subtypes with atorvastatin treatment.

Taken together, these results indicate that the influence of atorvastatin on LDL subtype distribution is not uniform and may depend on the underlying hyperlipoproteinemia as well as on the atorvastatin dose.

In our study, patients with hypercholesterolemia were not different from controls with respect to the relative reduction in cholesterol in individual LDL subfractions: both study groups showed a more pronounced reduction in large-buoyant and intermediate-dense than in small-dense LDL subtypes. This was also true when we examined the effect of higher doses of atorvastatin (20 to 60 mg/d; Fig 3). Because atorvastatin increases LDL receptor activity[17] and because intermediate-dense LDLs are better ligands for the LDL-receptor than small-dense LDLs,[6] up-regulation of LDL receptor activity should decrease intermediate-dense LDL more than small-dense LDL. However, the greater reduction in large-buoyant than in small-dense LDL is not fully explained by this phenomenon.

Patients with diabetic dyslipoproteinemia showed a uniform reduction of cholesterol in all LDL subfractions. This finding may be related to the presence of qualitatively altered lipoproteins such as glycated and oxidized LDL in all LDL subfractions.[25] Our results in diabetic patients are similar to those observed in patients suffering from combined hyperlipidemia.[21] a metabolic disorder sharing some characteristics with diabetic dyslipoproteinemia. Guerin et al[21] explained this finding by 2 independent mechanisms of atorvastatin: (1) up-regulation of LDL receptor activity decreases all (preferentially intermediate-dense) LDL subtypes and (2) the reduced production of VLDL-1 particles decreases precursors of small-dense LDL.[26,27] Because patients with type 2 diabetes mellitus are characterized by overproduction of VLDL-1,[26,28] this latter effect of atorvastatin may have a greater influence on the LDL subtype distribution in diabetic than in nondiabetic patients.

However, there are several other mechanisms by which atorvastatin may be involved in the metabolism of LDL subtypes besides increasing LDL receptor activity[17] and decreasing apolipoprotein B secretion.[29] Atorvastatin reduces cholesterol ester transfer from HDL to VLDL particles[21] and decreases hepatic lipase and lipoprotein lipase activity,[19] all of which is involved in the generation and processing of LDL particles.[15,26,27] Hepatic lipase activity was positively correlated with the amount of small-dense LDL,[27,30] whereas increased lipoprotein lipase activity was associated with a concomitant increase in large-buoyant LDL.[31,32] Because diabetic patients have increased activity of hepatic lipase but normal lipoprotein lipase activity,[33] reduction or normalization of hepatic lipase activity during atorvastatin treatment could also contribute to the reduction of small-dense LDL in diabetic patients. Because all of these effects are involved in the generation and degradation of small-dense LDL,[15] the change in LDL subtype distribution during atorvastatin treatment may be caused by a combined effect of several mechanisms.

From a clinical point of view, the lipid profile improves in all groups with atorvastatin therapy because the LDL concentration (including small-dense LDL) decreases. However, because this reduction is most pronounced in large-buoyant and intermediate-dense LDL in controls and hypercholesterolemic patients, the subtype shifts toward small-dense LDL in these groups. In patients with type 2 diabetes, no shift was observed because all LDL subtypes were reduced uniformly.

In summary, normolipidemic controls, patients with hypercholesterolemia, and patients with diabetic dyslipoproteinemia showed a reduction in cholesterol in each LDL subfraction during atorvastatin treatment (10 mg, 4 weeks). Similar to controls, patients with hypercholesterolemia had a greater reduction in large-buoyant and intermediate-dense LDL compared with small-dense LDL, whereas patients with diabetic dyslipoproteinemia showed a relatively uniform reduction in all LDL subtypes.

ACKNOWLEDGMENT

The authors thank I. Biller-Friedmann, E. Fleischer-Brielmeier, K. Henze, and Sabine Szász for excellent technical assistance.

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