Persistent abnormalities in lipoprotein composition and cholesteryl ester transfer following lovastatin treatment

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Abstract Optimally effective lipid-lowering agents should not only restore plasma lipids to normal levels but also correct potentially atherogenic alterations in lipoprotein composition and function often present in hyperlipidemic patients. Lovastatin, a competitive inhibitor of cholesterol biosynthesis, clearly lowers plasma cholesterol levels. Its effects on lipoprotein composition and cholesteryl ester transfer (CET), a key step in reverse cholesterol transport, however, are not known. Since abnormalities in CET and lipoprotein composition are present in patients with hypercholesterolemia, we studied these parameters of plasma lipoprotein transport in twelve hypercholesterolemic (HC; Type IIa) subjects (six male, six female) before and 2 months after lovastatin treatment (20 mg qd). Before lovastatin, the free cholesterol (FC)/lecithin (L) ratio in plasma, a new index of cardiovascular risk that reflects lipoprotein surface composition, was abnormally increased (1.18 ± 0.26 vs controls 0.83 ± 0.14; $P<0.001$) in very low density lipoproteins (VLDL) and high density lipoprotein-3 (HDL_3), and remained so after treatment despite significant declines in whole plasma cholesterol (311.7 ± 68.2 vs 215.6 ± 27.2 mg/dl; $P<0.001$), low density lipoprotein (LDL)-cholesterol (206.3 ± 47.9 vs 146.8 ± 29.4; $P<0.001$), and apolipoprotein B (149 ± 30 vs 110 ± 17; $P<0.005$). The percentage of cholesteryl ester in plasma that was esterified in these patients was slightly higher than that of the reference group before lovastatin, and fell significantly ($P<0.025$) after treatment to levels that reflected a relative increase of almost 20% in lipoprotein FC. In contrast to the minimal amount of cholesteryl ester that was transferred initially from HDL to VLDL + LDL in normolipidemic control subjects, CET in all HC patients before lovastatin was significantly accelerated at 1, 2, and 4 h ($P<0.001$). Two months treatment with lovastatin had no discernible effect on CET which remained abnormally increased. These findings indicate that potentially atherogenic abnormalities in lipoprotein composition and function present in patients with hypercholesterolemia persist despite near normalization of plasma lipids after treatment with lovastatin. —**Bagdade, J. D., J. T. Lane, N. Stone, M. C. Ritter, and P. V. Subbaiah.** Persistent abnormalities in lipoprotein composition and cholesteryl ester transfer following lovastatin treatment. *J. Lipid Res.* 1990. **31:** 1263–1269.

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Increased awareness that active intervention reduces cardiovascular risk in patients with hypercholesterolemia (1, 2) and dyslipidemia (3) has resulted in the widespread use of a number of lipid-lowering drugs when dietary treatment is inadequate. As a group, the fibric acid derivatives are well tolerated, but their capacity to reduce cardiovascular risk appears to accrue primarily to those patients with disturbances in triglyceride transport alone or in association with an elevation of LDL (4). While niacin (2) and the bile acid sequestrant cholestyramine (1) effectively lower plasma cholesterol and have been shown in large clinical trials to reduce risk, they are not well tolerated by many patients (5) at the doses recommended to maximally lower cholesterol levels. Probucol has the advantages of being effective, well tolerated, and having anti-oxidant properties (6, 7), but its use in the United States has been limited because of concern about the fact that it also reduces HDL levels (5, 6, 8). Consequently, there has been a growing need for a pharmacologic agent that lowers cholesterol, is free from untoward effects, and at the same time also lowers cardiovascular risk. Lovastatin, the first member of a recently introduced unique new class of drugs that competitively inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in cholesterol biosynthesis, appears to satisfy the first two of these criteria. Its efficacy and low profile of short-term adverse effects has resulted in its

Abbreviations: CETP, cholesteryl ester transfer protein; HC, hypercholesterolemia; TC, total cholesterol; CET, cholesteryl ester transfer; FC, free cholesterol; VLDL, very low density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein; LCAT, lecithin: cholesterol acyltransferase; L, lecithin; TG, triglyceride.

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becoming the most widely used cholesterol-lowering agent in the United States despite the paucity of information regarding its long-term toxicity and capacity to reduce risk in humans.

We have recently described a number of disturbances in lipoprotein surface and core lipid composition in patients with hypercholesterolemia which we believe might alter their normal metabolism and contribute to their accelerated atherogenesis (9). Optimal drug therapy for these patients should not only normalize their plasma lipid levels, but also correct these potentially atherogenic alterations in lipoprotein composition. While lovastatin clearly reduces plasma cholesterol levels, it effects on lipoprotein composition and cholesteryl ester transfer (CET), a key step in reverse cholesterol transport, are unknown. Since we have recently observed that patients with hypercholesterolemia have disturbances in CET (10) which we believe are causally related to their alterations in lipoprotein composition, we sought in this study to determine the impact of lovastatin treatment on these specific abnormalities.

MATERIALS AND METHODS

Subjects

Twelve hypercholesterolemic patients were recruited for study (six males, six females; ages 26–71 yrs; mean 53.4 ± 14.9, mean ± SD). They had fasting cholesterol levels in the pretreated state measured on two or more occasions that were greater than two standard deviations from the mean defined by Lipid Research Clinic standards (11) for their age and sex and normal fasting triglyceride levels. No effort was made to characterize the molecular basis for the cholesterol elevation in any patient. All patients had followed American Heart Association phase I diets for at least 4 months prior to study. No subject had renal disease, was a vegetarian, a cigarette smoker, an athlete, had diabetes, or was receiving drugs known to affect lipid metabolism except for three mean who took 10, 15, 25 g of colestid daily, respectively, and two women who received conjugated estrogens 0.625 mg/day. These subjects had been receiving these medications for more than 3 years and they were continued during the period of treatment with lovastatin. Their plasma lipid levels were stable for a period of 6 months prior to starting lovastatin. Informed consent was obtained. Reference values for plasma lipids and lipoprotein composition were obtained from prior study in our laboratory of 39 healthy, nonobese normolipidemic subjects (ages 25–60).

Methods

Venous blood samples from the above patients were obtained after a 12–14 h overnight fast prior to and 2 months after treatment with lovastatin (20 mg daily). On each occasion VLDL was isolated from plasma by preparative ultracentrifugation at 10°C in a 40.3 rotor at 40,000 rpm for 18 h ($d < 1.006$ g/ml). From the infranatant, LDL, HDL_2, and HDL_3 were separated by differential precipitation with dextran sulfate-Mg^{2+} (12). Other aliquots of plasma obtained prior to and after lovastatin were kept frozen at −20°C and were used later to measure, by enzymatic methods, cholesterol (Boehringer Mannheim) and triglyceride (Sigma) in the same assay.

Free cholesterol was estimated with the same constituents of the cholesterol kit except cholesteryl ester hydrolase was omitted. Cholesteryl ester was calculated from the difference of total and free cholesterol. ApoA-I, A-II, and B were determined in plasma by radioimmunoassay (13, 14). For phospholipid estimations, 0.3-ml aliquots of whole plasma and each lipoprotein fraction were removed, mixed with 0.1 ml of 0.15 M NaCl–1 mM EDTA solution, and extracted by the Bligh and Dyer procedure (15). All lipid extracts were spotted on activated silica gel (E. Merck) thin-layer plates (0.5 mm thickness), and the four major phospholipids (lysolecithin, sphingomyelin, lecithin, and phosphatidylethanolamine) were separated using a solvent system of chloroform–methanol–acetic acid–water 25:15:4:2 (by volume). The phospholipids were scraped into glass tubes and the lipid phosphorus was determined by the modified Bartlett's procedure (16).

Cholesteryl ester transfer in plasma

In nine patients treated with lovastatin alone, the mass transfer of cholesteryl esters from HDL to the apoB-containing lipoproteins was measured before and after lovastatin treatment using a method in which freshly drawn plasma was incubated at 37°C in a metabolic shaker in the presence of 1.5 mM 5,5'-thiobis (2-nitrobenzoic acid; DTNB) to inhibit LCAT (17). Aliquots (quintuplicate) of plasma were removed prior to and after 1, 2, 4, and 6 h of incubation, chilled on ice, and VLDL + LDL were isolated by precipitation with 0.1 vol of heparin–$MnCl_2$ to give final concentrations of $MnCl_2$ (0.092 M) and heparin (1.3 mg/ml) (18). $MnCl_2$ at this concentration has been found not to precipitate any significant quantity of apoE-containing HDL (19). At each sampling interval, the transfer of cholesteryl esters from HDL to VLDL + LDL was determined from the measurement of the decrease in the mass of cholesteryl ester present in the supernatant containing HDL.

Statistical methods

Student's *t*-test for pairs was used to determine the significance of the changes that were observed in CET and lipoprotein composition after lovastatin treatment. No statistical comparisons were made between values obtained in the reference and treatment groups.

TABLE 1. Changes in plasma lipids and apolipoproteins before and after lovastatin treatment

	Before	After	Ref. Group
		mg/dl ± SD	
Total cholesterol	311.7 ± 68.2	215.6 ± 27.2****	185.3 ± 36.7
Total triglyceride	156.5 ± 41.7	136.1 ± 32.9	94.8 ± 39.4
LDL-C	206.3 ± 47.9	146.8 ± 29.4****	112.9 ± 29.0
HDL-C	48.7 ± 10.6	50.8 ± 10.2	53.8 ± 11.1
HDL_2-C	9.3 ± 5.2	10.1 ± 6.6	11.1 ± 3.6
HDL_3-C	40.6 ± 9.9	38.1 ± 8.0	37.7 ± 6.7
ApoB	149 ± 30	110 ± 17***	108.2 ± 24.4
Free cholesterol (FC)	96.6 ± 18.8	80.3 ± 17.8****	59.7 ± 11.6
Cholesteryl ester/TC	0.68 ± 0.08	0.62 ± 0.06**	0.66 ± 0.16
FC/lecithin (mol/mol)	1.18 ± 0.26	1.15 ± 0.26	0.83 ± 0.13

*, $P < 0.05$; **, $P < 0.025$; ***, $P < 0.01$; ****, $P < 0.001$.

RESULTS

Prior to lovastatin treatment, the hypercholesterolemic patients demonstrated characteristic increases in total plasma cholesterol (CL, LDL-C, free cholesterol (FC), and apoB (**Table 1**). HDL_2-C was slightly lower and HDL_3 higher than the levels in the corresponding HDL subfractions of the normolipidemic reference group; total HDL-C concentrations, however, were similar. Since plasma and lipoprotein lipids were quantitatively and qualitatively similar in the three colestipol-treated HC patients at baseline and the changes observed after lovastatin were similar to the responses observed in the other nine patients, compositional data of all twelve subjects were pooled. Lovastatin therapy resulted in significant declines in plasma total and free cholesterol LDL-C ($P<0.001$). No change occurred in total HDL-C or in its subfractions.

The changes observed in whole plasma and lipoprotein surface lipid composition after lovastatin are shown in **Table 2** and **Table 3**. The FC level in plasma was abnormally increased before treatment primarily as a consequence of the increase in LDL and fell significantly ($P<0.001$) after lovastatin. Similarly, the increase in plasma phospholipid concentrations before lovastatin reflected the overall increase in LDL mass, and all declined after therapy in a manner which was generally proportional to the decline in LDL-C. No significant quantitative changes were observed in VLDL or HDL phospholipids after lovastatin. The plasma FC/lecithin

TABLE 2. Effect of lovastatin treatment on phospholipid composition of whole plasma and lipoprotein fractions

	Lysolecithin μmol/ml	Sphingomyelin μmol/ml	Lecithin μmol/ml	PI μmol/ml	PE μmol/ml	S/L mol/mol	FC/L mol/mol
				mean ± SD			
Whole plasma							
Before	0.184 ± 0.05	0.574 ± 0.15	2.20 ± 0.58	0.126 ± 0.04	0.153 ± 0.03	0.265 ± 0.06	1.18 ± 0.26
After	0.177 ± 0.04	0.476 ± 0.16**	1.84 ± 0.39**	0.09 ± 0.03	0.130 ± 0.06	0.262 ± 0.05	1.15 ± 0.26
Ref group	0.198 ± 0.06	0.473 ± 0.10	1.81 ± 0.40		0.140 ± 0.06	0.254 ± 0.06	0.83 ± 0.13
VLDL							
Before	0.012 ± 0.01	0.039 ± 0.02	0.189 ± 0.12	0.022 ± 0.01	0.032 ± 0.01	0.235 ± 0.09	1.43 ± 0.50
After	0.012 ± 0.01	0.029 ± 0.02	0.154 ± 0.07	0.020 ± 0.01	0.024 ± 0.01	0.183 ± 0.09	1.28 ± 0.56
Ref group		0.047 ± 0.02	0.159 ± 0.09			0.347 ± 0.15	0.76 ± 0.23
LDL[a]							
Before	0.046 ± 0.02	0.375 ± 0.13	1.02 ± 0.29	0.048 ± 0.02	0.063 ± 0.03	0.364 ± 0.07	1.55 ± 0.38
After	0.034 ± 0.02**	0.297 ± 0.09**	0.82 ± 0.19**	0.042 ± 0.02	0.049 ± 0.04*	0.358 ± 0.06	1.63 ± 0.32
Ref group		0.279 ± 0.08	0.686 ± 0.15			0.405 ± 0.07	1.79 ± 0.58
HDL_2							
Before	0.044 ± 0.04	0.053 ± 0.04	0.179 ± 0.09	0.043 ± 0.05	0.047 ± 0.05	0.277 ± 0.20	0.61 ± 0.30
After	0.039 ± 0.05	0.049 ± 0.04	0.177 ± 0.10	0.037 ± 0.04	0.045 ± 0.05	0.268 ± 0.21	0.87 ± 0.26*
Ref group	0.041 ± 0.03	0.035 ± 0.03	0.092 ± 0.1		0.062 ± 0.04	0.285 ± 0.20	0.66 ± 0.15
HDL_3							
Before	0.087 ± 0.05	0.072 ± 0.03	0.550 ± 0.12	0.031 ± 0.03	0.040 ± 0.04	0.134 ± 0.06	0.60 ± 0.25
After	0.101 ± 0.04	0.086 ± 0.03	0.582 ± 0.10	0.47 ± 0.03	0.053 ± 0.03	0.149 ± 0.05	0.62 ± 0.12
Ref group	0.169 ± 0.04	0.077 ± 0.03	0.509 ± 0.11		0.058 ± 0.02	0.149 ± 0.05	0.43 ± 0.07

Before versus after treatment: *, $P < 0.05$; **, $P < 0.025$; ***, $P < 0.001$.
[a]Fraction d = 1.019–1.063 g/ml.

TABLE 3. Effects of lovastatin on lipoprotein core lipid composition in twelve hypercholesterolemic patients

	Before	After	Ref Group
		mean ± SD	
VLDL (mg/dl)			
Free cholesterol	9.9 ± 6.5	7.0 ± 2.6	5.2 ± 3.2
Esterified cholesterol	7.1 ± 5.0	3.5 ± 2.5	3.7 ± 3.1
Triglyceride	78.9 ± 31.5	63.2 ± 18.6*	44.0 ± 26.3
TG/CE	15.2 ± 10.2	21.3 ± 10.6	17.1 ± 10.8
CE/TC	0.41 ± 0.16	0.31 ± 0.17**	0.40 ± 0.16
LDL (mg/dl)[a]			
Free cholesterol	58.0 ± 10.5	51.2 ± 12.4	38.0 ± 9.5
Esterified cholesterol	148.2 ± 46.0	95.6 ± 27.2***	74.9 ± 24.4
Triglyceride	49.6 ± 11.0	43.1 ± 11.9****	31.2 ± 7.7
TG/CE	0.37 ± 0.18	0.50 ± 0.20**	0.56 ± 0.27
CE/TC	0.71 ± 0.07	0.64 ± 0.10**	0.66 ± 0.09
HDL_2 (mg/dl)			
Free cholesterol	4.0 ± 2.4	5.5 ± 2.6**	2.6 ± 2.1
Esterified cholesterol	5.3 ± 3.8	4.6 ± 3.9	9.6 ± 3.9
Triglyceride	3.7 ± 2.2	4.5 ± 3.0	4.6 ± 1.9
TG/CE	0.52 ± 0.30	1.30 ± 1.5	0.48 ± 0.27
CE/TC	0.49 ± 0.28	0.39 ± 0.28	0.78 ± 0.13
HDL_3 (mg/dl)			
Free cholesterol	11.9 ± 3.0	13.8 ± 2.8	8.3 ± 1.6
Esterified cholesterol	28.7 ± 11.6	24.3 ± 8.9	28.4 ± 6.4
Triglyceride	14.5 ± 4.8	15.1 ± 4.9	17.2 ± 3.2
TG/CE	0.59 ± 0.35	0.67 ± 0.27	0.68 ± 0.15
CE/TC	0.68 ± 0.14	0.62 ± 0.10	0.77 ± 0.03

Before versus after treatment: *, $P < 0.05$; **, $P < 0.025$; ***, $P < 0.01$; ****, $P < 0.001$.
[a]Fraction d = 1.019–1.063 g/ml.

(L) ratios in plasma, VLDL, and HDL_3 all were abnormally elevated before treatment and remained so after lovastatin. In contrast, the only apparent abnormality in the sphingomyelin/L ratio before therapy was present in VLDL where it was reduced and it fell further after treatment.

The percentage of cholesterol in plasma that was esterified (expressed as the CE/TC ratio) was slightly higher than that of the reference group before lovastatin (Table 1), and fell significantly thereafter in plasma ($P<0.025$, Table 1), and VLDL ($P<0.025$) and LDL ($P<0.025$) (Table 3). The core lipid contents of VLDL and LDL in the HC patients also fell after treatment toward the levels of the reference group. Before therapy, the TG/CE ratio tended to be lower in VLDL and LDL; after lovastatin, this ratio moved toward normal in LDL and exceeded normal in VLDL.

Cholesteryl ester transfer

The CET responses of the hypercholesterolemic patients before lovastatin treatment differed markedly from those of controls (**Fig. 1**). Whereas the net mass of CE transferred from HDL to VLDL + LDL was small initially and increased slowly with time in controls, the hypercholesterolemic group demonstrated a prompt initial increment in the movement of CE from HDL that was significantly greater than that of controls at 1, 2, and 4 h ($P<0.001$). In all nine patients, no change in CET was observed despite the changes that occurred in plasma lipids.

DISCUSSION

Untreated patients with hypercholesterolemia have a broad range of qualitative alterations in the surface and core lipid constituents of their plasma lipoproteins that are not confined to LDL (9). These include a number of

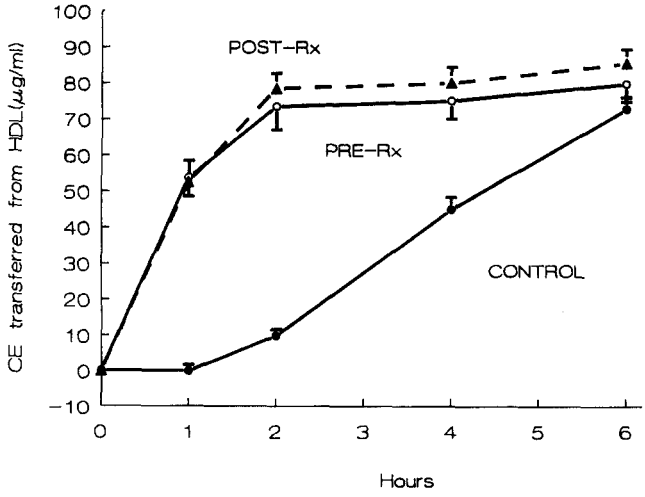

Fig. 1. Mass of cholesteryl ester transferred from HDL to the apoB-containing lipoproteins in hypercholesterolemic (n = 9) and control subjects (n = 12) before (pre-Rx) and after (post-Rx) treatment with lovastatin (mean ± SEM). Control values differ significantly from pre- and post-treatment values at 1, 2, and 4 h ($P<0.001$).

changes, that are not apparent in routine laboratory studies, and principally involve the relative amounts of FC, phospholipids, and core lipids in VLDL and HDL. Our finding an increase in the plasma FC/lecithin (L) ratio in these subjects is consistent with the earlier report of Kuksis et al. (20) in which this expression of lipoprotein surface lipids was found to be a new and powerful correlate of cardiovascular risk in hypercholesterolemic Lipid Research Clinic Study participants. Surprisingly, the FC/L ratio of our patients' LDL tended to be lower than the level observed in the reference group. This finding indicates that this parameter of the surface FC and phospholipid content of their (numerically increased) LDL particles was affected differently by the alterations in lipoprotein transport that caused their hypercholesterolemia, and contributed to the increase observed in the FC/L ratio of plasma, VLDL, and HDL_3.

An increase in the amount of sphingomyelin (S) relative to lecithin has been described in LDL from patients with familial hypercholesterolemia (21). This change is believed to be a consequence of the prolonged residence time of LDL in plasma in patients with LDL-receptor deficiency. We do not find such a disturbance in the S/L ratio in LDL in this cohort of patients. This finding likely reflects the genetic heterogenicity of our study group and the inclusion of patients whose LDL elevation resulted from other molecular mechanisms.

The nature of the alterations present in surface and core lipid composition and the accelerated rate of cholesterol ester transfer (CET) that we observed in these and similar patients (22) suggest that they might be related. It is now recognized that the FC content of lipoproteins influences the heteroexchange of CE from HDL to VLDL and of TG from VLDL to HDL. In particular, the FC/phospholipid ratios in donor and acceptor lipoproteins establish gradients that determine the directional flux of cholesterol among lipoproteins and between lipoproteins and cells (23). Since Morton (24) has demonstrated that lipoprotein FC is a positive regulator of CET, we believe that the increase in CET we find in these HC patients may result from the enrichment of their VLDL with FC. It is still possible, however, that the acceleration we observe in CET results from an increase in cholesteryl ester transfer protein or changes in the donor lipoproteins.

The initial lack of net transfer of CE in the control subjects is more difficult to explain. One possibility is that differences in the core lipid composition of LDL and HDL in the controls favor the heteroexchange of TG from HDL from CE from LDL. If the rate of this interaction between HDL and LDL in controls is similar to that between HDL and VLDL, there may be little net change in the CE content of HDL as we observed. Another explanation for the lack of net CE transfer in control HDL is that LCAT in controls is more resistant to the inhibitory effects of DTNB than LCAT in the hypercholesterolemic patients. If this were the case, esterification of cholesterol would continue in control HDL while CET was taking place. Under these conditions, little net change in HDL-CE also would occur as we observed. These possibilities require further examination.

The acceleration we find here in CET is consistent with recent reports obtained from hypercholesterolemic patients (25–27) and animal models (28). These results do not, however, agree with those previously published by Fielding et al. (29). We have no ready explanation for this discrepancy. While it is not yet clear whether facilitated lipid transfer is atherogenic, it is of interest that those species that lack CETP activity such as rats and dogs are resistant to atherosclerosis, while those that have it such as the man and rabbit are notoriously susceptible (30). When CETP activity normally increases in the postprandial state, it leads to an enrichment of the less dense lipoproteins, VLDL and LDL, with CE (31). Since the core lipid composition of these particles resembles chylomicron remnants that accumulate abnormally in patients with dyslipidemia who are atherosclerosis-prone (32) and in animals with diet-induced atherosclerosis, Zilversmit (33) has suggested that postprandial lipoproteins may be atherogenic. The trend we observe here, of reduced TG/CE ratios in VLDL and LDL before treatment with lovastatin, is consistent with CET being accelerated in vivo.

Despite growing awareness of the important influence that the composition of lipoproteins has on their physiology (22, 34), there have until recently been relatively few attempts to correlate in the same patients the impact of lipid-lowering drugs on lipoprotein composition and some parameter of function. The effects of drug-induced changes in lipoprotein composition on their metabolism is illustrated in the recent report of Young et al. (35) in which LDL particles from colestipol-treated hypercholesterolemic patients became cholesterol-depleted, had an increased density, and were not normally cleared by apoB, E receptor pathways. Indeed, there is preliminary evidence that lovastatin reduces the in vivo affinity of LDL from treated patients for the LDL receptor (36). In related studies, Berglund et al. (37) have found that the kinetic behavior and composition of LDL from lovastatin-treated guinea pigs are similarly altered.

The profile of quantitative changes in plasma lipids we observed after treatment with lovastatin closely resembles those described previously in similar patients (8). Lovastatin, however, had virtually no effect on the underlying disturbances in lipoprotein composition that were present before treatment. In light of lovastatin's known inhibitory effects on cholesterol synthesis, it is surprising that the FC/L ratio of plasma, and of VLDL, LDL, and HDL_3 were unchanged. Although lovastatin reduces the cytoplasmic pool of cholesterol in cells and decreases the cholesterol content of LDL (8), our data indicate that it does not decrease the content of FC relative to lecithin in

any of the lipoprotein fractions and in fact increased it in HDL_2. These data in humans are consistent with those of Berglund et al. (37) showing that the LDL FC/PL ratio was subnormal in lovastatin-treated guinea pigs.

It is also of interest that the FC/CE ratios of plasma, VLDL, and LDL all decreased significantly after lovastatin treatment. This finding indicates that relatively less of the total circulating cholesterol was present as CE after lovastatin. This change could result from lowered LCAT activity, though there is no evidence so far that reductase inhibitors have this effect (38, 39). Before treatment, 68% of the total cholesterol present was esterified; after treatment, this fell to 62%. This increase in FC from 32 to 38% of total cholesterol represents a relative increase of almost 20%. We have not observed changes of this type in related studies in HC patients after treatment with either marine lipids (9) or probucol (10). The physiological consequences of these changes are unclear.

Thus, while the total number of LDL, and to some extent VLDL, particles in lovastatin-treated patients is reduced (8), the abnormalities present in their composition before treatment are not only largely unaffected, but new disturbances also appear to result from therapy. In light of the evidence that compositional abnormalities of the type we find in these HC patients, which have been shown previously to modify lipoprotein function (10, 24, 25), were unchanged by lovastatin, it is not surprising that the disturbance we find in CET also persisted.

While there are now encouraging preliminary data indicating that lovastatin treatment combined with colestipol may slow progression and induce regression in men with coronary disease and elevated apoB levels (40), our data show that major abnormalities in lipoprotein composition and function persist in treated patients which could continue to make independent contributions to atherogenesis.

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