Effect of atorvastatin on postprandial lipoprotein metabolism in hypertriglyceridemic patients

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Abstract Postprandial lipoprotein metabolism is impaired in hypertriglyceridemia. It is unknown how and to what extent atorvastatin affects postprandial lipoprotein metabolism in hypertriglyceridemic patients. We evaluated the effect of 4 weeks of atorvastatin therapy (10 mg/day) on postprandial lipoprotein metabolism in 10 hypertriglyceridemic patients (age, 40 ± 3 years; body mass index, 27 ± 1 kg/m^2; cholesterol, 5.74 ± 0.34 mmol/l; triglycerides, 3.90 ± 0.66 mmol/l; HDL-cholesterol, 0.85 ± 0.05 mmol/l; and LDL-cholesterol, 3.18 ± 0.23 mmol/l). Patients were randomized to be studied with or without atorvastatin therapy. Postprandial lipoprotein metabolism was evaluated with a standardized oral fat load. Plasma was obtained every 2 h for 14 h. Large triglyceride-rich lipoproteins (TRLs) (containing chylomicrons) and small TRLs (containing chylomicron remnants) were isolated by ultracentrifugation, and cholesterol, triglyceride, apolipoprotein B-100 (apoB-100), apoB-48, apoC-III, and retinyl-palmitate concentrations were determined. Atorvastatin significantly ($P < 0.01$) decreased fasting cholesterol (−27%), triglycerides (−43%), LDL-cholesterol (−28%), and apoB-100 (−31%), and increased HDL-cholesterol (+19%). Incremental area under the curve (AUC) significantly ($P < 0.05$) decreased for large TRL-cholesterol, -triglycerides, and -retinyl-palmitate, while none of the small TRL parameters changed. These findings contrast with the results in normolipidemic subjects, in which atorvastatin decreased the AUC for chylomicron remnants (small TRLs) but not for chylomicrons (large TRLs). We conclude that atorvastatin improves postprandial lipoprotein metabolism in addition to decreasing fasting lipid levels in hypertriglyceridemia. Such changes would be expected to improve the atherogenic profile.—Parhofer, K. G., E. Laubach, and P. H. R. Barrett. **Effect of atorvastatin on postprandial lipoprotein metabolism in hypertriglyceridemic patients. *J. Lipid Res.* 2003. 44: 1192–1198.**

Supplementary key words triglyceride-rich lipoprotein • chylomicrons • chylomicron remnants • retinyl palmitate

Hypertriglyceridemia is a very common abnormality that confers a high atherogenic potential, particularly in the context of diabetes (1). To counter this, many hypertriglyceridemic diabetic patients are treated with HMG-CoA-reductase inhibitors, and recent studies support that diabetic patients benefit from such treatment (2, 3).

Despite increasing evidence of the importance of lipid-independent effects (pleiotropic effects) of statins, much of the beneficial effect may be related to changes in lipid metabolism. The inhibition of HMG-CoA-reductase leads to an up-regulation of the LDL receptor, resulting in an increased catabolism of LDL particles and thus lower LDL-cholesterol concentration (4). However, lipoproteins other than LDL, including postprandial triglyceride-rich lipoproteins (TRLs), can also be internalized into hepatocytes via the LDL receptor pathway (5–7). It is likely, therefore, that statins have profound effects on postprandial lipoprotein metabolism, particularly in hypertriglyceridemic patients. Because the concentration of postprandial lipoproteins is an independent risk factor for cardiovascular disease (8–12), such changes in postprandial metabolism may be one of the mechanisms by which risk reduction is achieved with statin therapy.

We and others have previously shown that atorvastatin improves postprandial lipoprotein metabolism in normolipidemia, obesity, combined hyperlipidemia, and in patients with coronary heart disease (13–18). However, only a few studies provided data on the mechanism by which such therapy improves postprandial lipoprotein metabolism. Furthermore, no data are available on hypertriglyceridemic patients, who have the most pronounced postprandial hyperlipidemia. In this study, we test the hypothesis that atorvastatin improves postprandial lipoprotein metabolism in patients with isolated hypertriglyceridemia. The primary end point in this study was the apolipoprotein B-48 (apoB-48) response following a standardized fat

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Abbreviations: apo, apolipoprotein; AUC, area under the curve; BMI, body mass index; LPL, lipoprotein lipase; TRL, triglyceride-rich lipoprotein.

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challenge. We also wanted to evaluate whether the response to atorvastatin is similar to that observed in normolipidemic controls studied previously (13).

METHODS

Ten otherwise healthy hypertriglyceridemic patients were recruited for this study. None were taking any medication. Participating patients [eight men, two women, age 40 ± 3 years, body mass index (BMI) 27 ± 1 kg/m^2] were advised not to change their diet throughout the study. Postprandial lipoprotein metabolism was evaluated on two occasions, once prior to and once following 4 weeks of atorvastatin therapy (10 mg/day). Patients were randomized to be studied with or without atorvastatin therapy. Compliance was checked by pill count. Liver function tests (aminotransferase aspartal, aminotransferase alamine, γ-glutanyl transpeptidase) were administered, and alkaline phosphatase and creatine-kinase were determined in patients prior to and during atorvastatin therapy. The ethics committee of the Ludwig-Maximilians University, Munich approved the study protocol, and all patients gave informed written consent.

The postprandial studies were performed as previously described (13, 19). Each postprandial study was performed following a 12 h fast. After fasting blood was obtained, patients received a fatty meal (1,305 kcal; 87% from fat, 7% from carbohydrates, and 6% from protein) enriched with 80,000 units of vitamin A. Following the fat load, blood samples were taken every 2 h for 14 h. During that time, patients ate no calories but were allowed to drink water without restriction.

Blood samples were drawn in light-protected tubes containing EDTA-sodium. Ultracentrifugation was performed to obtain two fractions of TRLs (13). The fraction containing chylomicrons was called large TRL; the fraction containing chylomicron remnants and VLDL was called small TRL. This corresponds to Svedberg flotation (Sf) rate of >400 for large TRL and Sf20-400 for small TRL. Cholesterol, triglycerides, apoB-100, apoB-48, and retinyl-palmitate concentrations were determined in plasma (not apoB-48) and in the TRL fractions.

Triglyceride and cholesterol concentrations were measured using a commercial kit (Boehringer Mannheim, Mannheim,

TABLE 1. Fasting lipid parameters before and after 4 weeks of atorvastatin therapy (10 mg/day)

		Without Atorvastatin	With Atorvastatin	Change[a] (%)
Cholesterol	mmol/l	5.74 ± 0.34	4.14 ± 0.26	−27[b]
Triglyceride	mmol/l	3.90 ± 0.66	1.91 ± 0.26	−43[b]
LDL-cholesterol	mmol/l	3.18 ± 0.23	2.28 ± 0.15	−28[b]
HDL-cholesterol	mmol/l	0.85 ± 0.05	0.98 ± 0.05	+19[c]
Apo-B	mg/l	1,200 ± 210	830 ± 170	−31[b]
ApoC-III	mg/l	211 ± 23	168 ± 26	−23
Large TRL-cholesterol	mmol/l	0.30 ± 0.10	0.07 ± 0.03	−65[b]
Large TRL-triglyceride	mmol/l	1.04 ± 0.39	0.40 ± 0.14	−43
Large TRL-apoB-100	mg/l	34 ± 17	12 ± 5	−58
Large TRL-apoB-48	mg/l	4.7 ± 2.4	2.5 ± 1.2	−42
Small TRL-cholesterol	mmol/l	0.99 ± 0.15	0.39 ± 0.05	−40[b]
Small TRL-triglyceride	mmol/l	1.78 ± 0.22	0.91 ± 0.12	−46[b]
Small TRL-apoB-100	mg/l	122 ± 7	66 ± 3	−46[b]
Small TRL-apoB-48	mg/l	13 ± 2.5	6.1 ± 1.2	−52[b]

Apo, apolipoprotein; TRL, triglyceride-rich lipoprotein. Mean ± SEM.

[a] Change refers to mean percentage change.

[b] Indicates $P < 0.01$.

[c] Indicates $P < 0.05$.

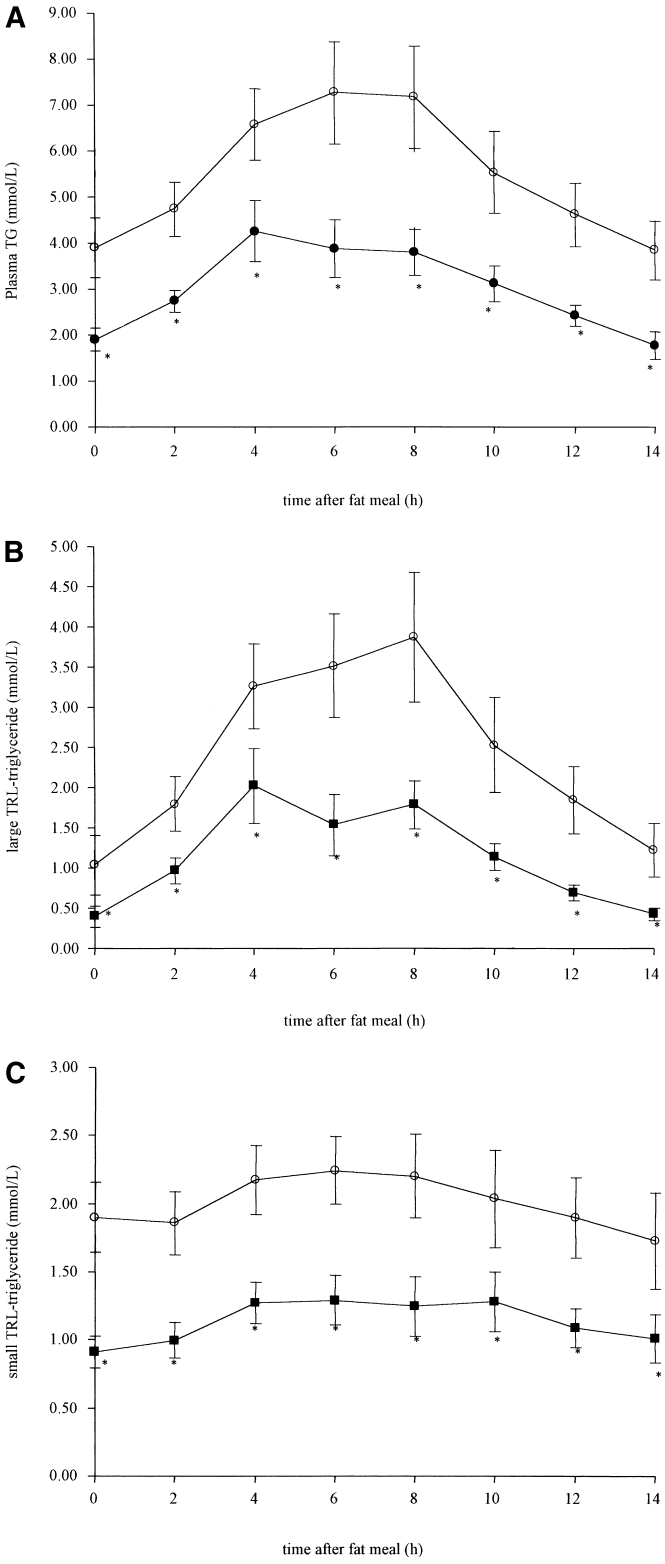

Fig. 1. Lipid concentrations following the oral fat load before and during atorvastatin therapy. Plasma triglycerides (A), large triglyceride-rich lipoprotein (TRL)-triglycerides (B), and small TRL-trigycerides (C) are shown as means ± SEM. Open and closed symbols represent data obtained before and during atorvastatin therapy, respectively; * indicates significant ($P < 0.05$) differences compared with before atorvastatin.

Germany). Concentrations of apoB and apoC-III were determined by immunonephelometry. Proteins of the TRL fractions were separated by polyacrylamide gel electrophoresis (5%) and stained with Coomassie Blue (20). The protein bands corresponding to apoB-100 and apoB-48 were scanned by laser densitometry. Concentrations of apoB-48 were estimated based on the assumption that apoB-100 and apoB-48 have the same chromogenicity. Retinyl-palmitate concentrations in plasma and the TRL fractions were determined by reverse-phase HPLC as described previously (13, 21).

Postprandial metabolism was quantified by calculating the area under the curve (AUC) using the 14 h concentration data. The incremental AUC, the area between the plasma concentration and a baseline drawn between the concentrations observed at 0 h and 14 h, was also calculated using the SAAM-II program (SAAM Institute Inc., Seattle, WA).

Results are presented as mean ± SEM. Differences between parameters obtained before and during atorvastatin therapy were evaluated by paired Student's *t*-test analysis. Associations between variables were identified with the Pearson's product moment correlation coefficient. The results obtained from 10 normolipidemic subjects studied previously (13) are included for comparison purposes. All statistical tests were performed using SPSS software (SPSS, Inc., Chicago, IL). The critical *P* value for significance was 0.05.

RESULTS

All patients tolerated atorvastatin well, and no side effects were reported. Furthermore, there was no change in liver function tests or creatine kinase. Fasting cholesterol (−27%), triglycerides (−43%), apoB-100 (−31%), LDL-cholesterol (−28%), large TRL-cholesterol (−65%), small TRL-cholesterol (−40%), small TRL-triglycerides (−46%), small TRL-apoB-48 (−52%), and small apoB-100 (−46%) concentrations decreased significantly, and HDL-cholesterol (+19%) increased significantly during atorvastatin therapy (**Table 1**). In addition, there was a nonsignificant decrease in plasma apoC-III (−23%), large TRL-triglyceride (−43%), large TRL-apoB-48 (−42%), and large TRL-apoB-100 (−59%).

Figure 1 shows the mean triglyceride concentrations before and during atorvastatin therapy in plasma (Fig. 1A), large TRL (Fig. 1B), and small TRL (Fig. 1C). The total AUC for plasma, large TRL, and small TRL measurement variables, with the exception of large TRL-apoB-48 and small TRL-retinyl-palmitate ($P = 0.061$), decreased significantly during atorvastatin therapy. The incremental AUC decreased significantly for large TRL-triglyceride, cholesterol, apoB-100, and retinyl-palmitate. In contrast, small TRL-triglyceride, cholesterol, retinyl-palmitate, and apoB-48 incremental AUCs did not change with atorvastatin therapy. Incremental AUCs for plasma retinyl-palmitate and large TRL-apoB-48 were lower during atorvastatin treatment, although this failed to reach statistical significance (**Table 2**).

Atorvastatin treatment of the hypertriglyceridemic patients affected the maximum peak height in both TRL fractions and reduced the time to peak in large TRL (triglycerides: 5.8 ± 1.0 h vs. 6.8 ± 1.9 h, $P = 0.1$) with the exception of retinyl-palmitate. We also noted (before and during atorvastatin therapy) that the retinyl-palmitate curve peaks later than any other measurement variable in both TRL fractions (unpublished observations).

The fasting triglyceride concentration was correlated with the incremental AUC of large TRL-triglycerides ($r = 0.63$, $P < 0.05$) and small TRL-triglycerides ($r = 0.64$, $P < 0.05$). As expected, these associations were also significant when the total AUC was used in the analysis. There was, however, no significant correlation between atorvastatin-induced LDL-cholesterol or triglyceride reduction and any of the AUCs at baseline or changes in the AUC with atorvastatin.

TABLE 2. Incremental AUC following an oral fat load before and after 4 weeks of atorvastatin therapy (10 mg/day)

	Incremental AUC			
	Without Atorvastatin	With Atorvastatin	Change[a]	*P*
			%	
Plasma				
Triglyceride (mmol/l/h)	29.4 ± 4.6	19.8 ± 2.6	−17	0.131
Cholesterol (mmol/l/h)	3.01 ± 0.68	2.25 ± 0.14	−21	0.380
Retinyl-palmitate (μg/dl/h)	1,198 ± 210	600 ± 112	−27	0.061
Large TRL				
Triglyceride (mmol/l/h)	24.0 ± 4.0	13.0 ± 2.3	−40	0.018
ApoB-48 (mg/l/h)	103 ± 22	60 ± 13	−19	0.116
ApoB-100 (mg/l/h)	122 ± 27	55 ± 10	−34	0.028
Cholesterol (mmol/l/h)	2.66 ± 0.50	1.31 ± 0.22	−41	0.021
Retinyl-palmitate (μg/dl/h)	972 ± 156	443 ± 88	−38	0.023
Small TRL				
Triglyceride (mmol/l/h)	5.6 ± 0.88	4.4 ± 0.65	8	0.458
ApoB-48 (mg/l/h)	3.34 ± 0.70	3.61 ± 0.58	0	0.736
ApoB-100 (mg/l/h)	3.8 ± 2.0	9.5 ± 5.4	−1.5	0.340
Cholesterol (mmol/l/h)	0.97 ± 0.34	1.25 ± 0.26	10	0.790
Retinyl-palmitate (μg/dl/h)	196 ± 35	112 ± 21	−17	0.107

AUC, area under the curve; TRL, triglyceride-rich lipoprotein. Mean ± SEM.
[a] Change refers to mean percentage change.

DISCUSSION

The cholesterol-lowering effect of atorvastatin is widely acknowledged. This study was performed to assess the effect of atorvastatin on postprandial lipoprotein metabolism in hypertriglyceridemia. In addition to significantly decreasing fasting cholesterol, triglycerides, and LDL-cholesterol and increasing HDL-cholesterol, atorvastatin also decreased the incremental AUC of large TRL (containing chylomicrons) triglyceride, cholesterol, and retinyl-palmitate following an oral fat load and reduced the time to peak of large TRL-triglyceride and apoB-48 concentration. Atorvastatin treatment did not change any incremental AUCs in the small TRL fraction (containing chylomicron remnants). This contrasts with results in normolipidemic subjects, in which, using the same experimental protocol, atorvastatin only decreased the AUC in the chylomicron-remnant fraction (13).

In our study, the decrease in fasting plasma triglyceride concentration was profound but within the limits previously described in hypertriglyceridemic patients (17, 22, 23). Atorvastatin's triglyceride-lowering effect is believed to be related to the strong inhibition of cholesterol biosynthesis, which also reduces the secretion of lipoproteins (24, 25). Triglyceride reduction may also be related to the fact that VLDL and LDL compete for the same removal mechanisms (6, 7); thus, a profound reduction in the number of LDLs may also increase the removal of VLDLs. Statins also reduce apoC-III (26), a protein that inhibits lipoprotein lipase (LPL)-mediated hydrolysis (27). This reduction is thought to occur via the peroxisome proliferator-activated receptor α effect of statin on the AI/CIII/AIV gene cluster, leading to decreased apo-CIII mRNA and presumably protein concentrations (26). This is in good agreement with recently published studies indicating that atorvastatin does not affect LPL mass (28) but increases LPL activity (29). This increased LPL activity results in a more effective hydrolysis of fasting and postprandial TRLs. Evidence for this improvement comes not only from the reduced incremental AUC of large TRL but also from the shorter time to peak concentration, a feature consistent with increased turnover of chylomicrons.

Although initial studies (30–35) evaluating the effect of statins on postprandial lipoprotein metabolism have shown conflicting results, recent studies using atorvastatin have uniformly shown positive effects on postprandial lipoprotein metabolism (13–18). In patients with mild hypertriglyceridemia (plasma triglyceride concentration 2.4 ± 0.9 mmol/l), pravastatin did not affect postprandial lipoprotein metabolism determined from a single triglyceride concentration measured 8 h after a standardized meal (32). In contrast, lovastatin decreased the AUC of retinyl-palmitate in the chylomicron and chylomicron-remnant fractions in five patients with elevated triglycerides (2.3 ± 0.3 mmol/l), but did not affect the postprandial response in normolipidemic subjects (30). In patients with coronary heart disease, Schaefer and colleagues showed that atorvastatin (40 mg/day), which almost normalized fasting triglycerides, also normalized remnant-like particle concentration following a standardized meal (17). In patients with combined hyperlipidemia, it was shown that atorvastatin causes reductions of postprandial plasma concentrations of all TRLs (15, 16, 18). In one study, atorvastatin therapy reduced cholesterol ester transfer from HDL to TRL, a pathway that is enhanced in untreated combined hyperlipidemia (15). The same investigators demonstrated that the initial rise of the chylomicron concentration curve following a standardized mixed meal was not affected by atorvastatin, indicating a lack of effect on chylomicron secretion. This is in good agreement with our previous study in normolipidemic subjects (13) and the current study in hypertriglyceridemic subjects.

Intuitively, we expected that atorvastatin in hypertriglyceridemic patients would also decrease the AUC of small and possibly large TRL. Our finding that atorvastatin primarily decreases the AUC of large TRL (containing chylo-

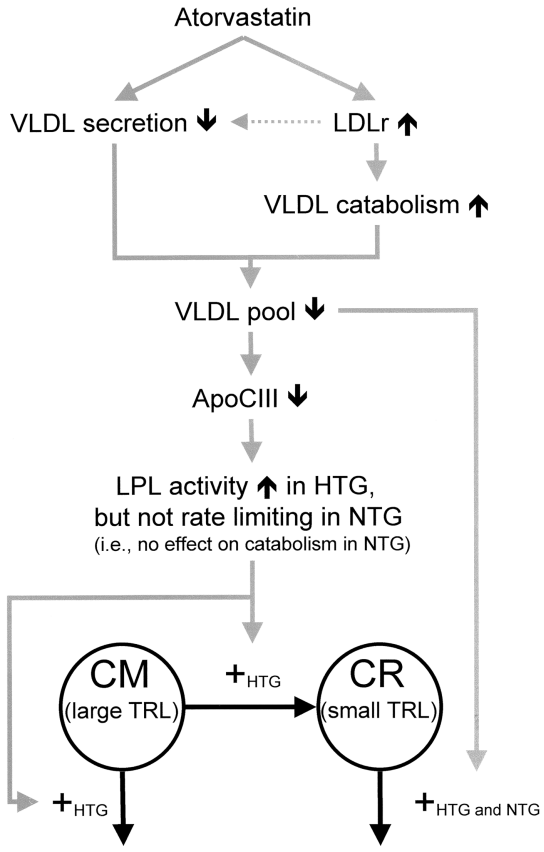

Fig. 2. Potential mechanisms of action of atorvastatin on postprandial lipoprotein metabolism in normolipidemic subjects and hypertriglyceridemic patients. Atorvastatin modulates LDL receptor activity and VLDL apolipoprotein B (apoB) secretion. As a result, the VLDL pool is reduced, thus decreasing competition for clearance mechanisms and hence improving chylomicron remnant (CR) clearance. Furthermore, a reduced VLDL pool decreases apoC-III concentration. In normolipidemic (NTG) subjects, lipoprotein lipase (LPL) activity can either not be further stimulated by lower apoC-III or is not rate-limiting for CM metabolism, whereas in hypertriglyceridemia (HTG), an increased LPL activity results in an enhanced hydrolysis of chylomicron (CM) particles. This increased conversion of CM to CR balances the increased catabolism of CR.

microns), while not affecting small TRL (containing chylomicron remnants), was somewhat surprising. Potential mechanisms of action of atorvastatin on postprandial lipoprotein metabolism in normolipidemic and hypertriglyceridemic patients are shown in **Fig. 2**. In normolipidemia, lipolysis of chylomicrons proceeds normally, and chylomicron metabolism is not stimulated with atorvastatin, although atorvastatin modulates an improvement in chylomicron remnant metabolism resulting from decreased competition from VLDL particles for removal via a receptor-mediated process (6, 7). In hypertriglyceridemia, increased turnover of the chylomicron remnants is coupled to an increased conversion of chylomicrons to chylomicron remnants. The combined effect of these processes would negate any observable changes in small TRL incremental AUC. Thus, although the mechanism by which atorvastatin affects postprandial lipoprotein metabolism is similar in normolipidemia and hypertriglyceridemia, the observed changes differ because of differences at baseline.

Our finding of differential effects on small and large TRLs contrasts with a recently published study showing an equivalent effect of 40 mg atorvastatin/day on all postprandial TRLs in patients with combined hyperlipidemia (18). However, in contrast to that study, our patients are characterized by isolated hypertriglyceridemia, and received only 10 mg atorvastatin/day. Although it has been shown that increasing atorvastatin from 10 to 80 mg/day has no significant effect on fasting triglycerides (23), higher doses of atorvastatin may have a more pronounced effect on postprandial lipoprotein metabolism. Finally, the differences between studies may be related to differences in methodologies (e.g., isolation of different TRL fractions, collecting data over 6 h vs. 14 h).

Compared with 10 normolipidemic men (13) studied using the same protocol, the incremental AUCs for plasma and for large and small TRL-triglycerides were significantly higher ($P < 0.05$) in the hypertriglyceridemic patients. During treatment, plasma and large TRL-triglycerides were lower but still remained elevated compared with the normolipidemic subjects. In contrast, small TRL-triglycerides were not different between the treated hypertriglyceridemic and normolipidemic subjects. Thus, atorvastatin therapy improves but does not normalize postprandial lipoprotein metabolism (**Fig. 3**). This contrasts with the previous findings of Schaefer et al. (17), who described normalization of fasting and postprandial lipoprotein metabolism with atorvastatin (40 mg/day). However, it should be noted that the normolipidemic subjects used for comparison here and shown in Fig. 3 represent a somewhat different population, insofar as they were younger (30 ± 2 years), leaner (BMI 22 ± 3 kg/m^2) and included only males, factors that may affect postprandial lipoprotein concentrations independently of the underlying hypertriglyceridemia. The optimal group for comparison would have been an age- and BMI-matched control group. As discussed above, it is also unclear whether higher doses of atorvastatin can further normalize postprandial lipoprotein metabolism and whether the effect on postprandial lipoprotein metabolism is a class effect of statins, is specific to atorvastatin, or is linked to the effect on fasting triglycerides.

Although we intended to isolate chylomicrons and chylomicron remnants/VLDL, the presence of apoB-100 in the chylomicron fraction suggested that this fraction also contained large VLDL particles (Table 2). Thus, the ultracentrifugation method used does not separate lipoprotein fractions containing chylomicrons and chylomicron remnants, but rather heterogeneous particle populations containing apoB-100 and apoB-48 that we have called large and small TRL, respectively. This contamination with apoB-100-containing particles, however, has little impact upon our key finding that atorvastatin affects the incremental AUC of large TRL more than that of small TRL. It is also of interest that apoB-100 concentration is not constant, but increases following the oral fat load. This has been observed previously (18) and is consistent with the concept that apoB-100- and apoB-48-containing particles compete for the same removal mechanisms. In addition, the increased flux of substrate in the postprandial state may also affect the secretion of apoB-100-containing lipoproteins from the liver.

The effects of atorvastatin on the total AUC were much more pronounced than on the incremental AUC, reflecting the strong effect of atorvastatin on fasting lipids. These changes in fasting values are probably more important from a clinical point of view, particularly since fasting values and postprandial values correlate. However, in or-

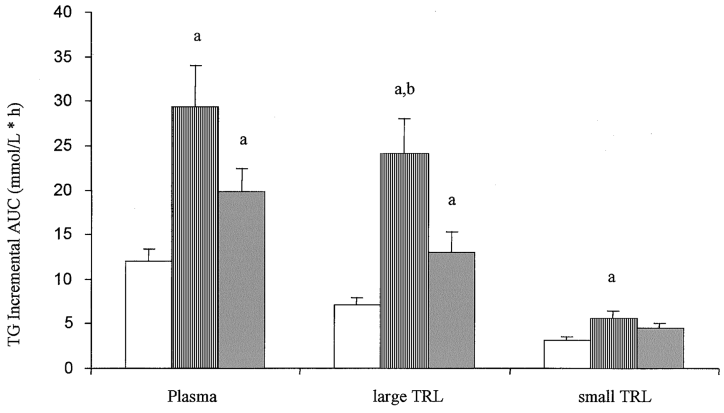

Fig. 3. Incremental area under the curve (mean ± SEM) of plasma, large TRL-, and small TRL-triglycerides in normolipidemic subjects [open bar, 10 subjects (13)], and in hypertriglyceridemic patients without (striped) and with (gray) atorvastatin. [a] Indicates significantly ($P < 0.05$) different compared with normolipidemic subjects; [b] indicates significantly ($P < 0.05$) different compared with treated hypertriglyceridemic patients.

der to further understand postprandial lipoprotein metabolism and, in particular, whether and to what extent statins affect these pathways, it is important to focus on the incremental AUC.

Although the AUC of TRL is a function of lipoprotein production and clearance, there is no evidence that atorvastatin affects the secretion of postprandial lipoproteins from the intestine (36, 37). Because the secretion and composition of postprandial lipoproteins are driven primarily by dietary lipid components, it is unlikely that the decrease in HMG-CoA-reductase activity alters the secretion of postprandial lipoproteins.

In summary, 10 mg atorvastatin per day for 4 weeks improves, but does not normalize, postprandial lipoprotein metabolism in hypertriglyceridemic patients. In agreement with previous studies, this study found that it is clear that atorvastatin improves fasting and postprandial lipoprotein metabolism in normolipidemia, hypertriglyceridemia, and combined hyperlipidemia.

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