Postprandial Apolipoprotein B48– and B100–Containing Lipoproteins in Type 2 Diabetes: Do Statins Have a Specific Effect on Triglyceride Metabolism?

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There is little information about the effect of an alteration of low-density lipoprotein (LDL) turnover on chylomicron and very–low-density lipoprotein (VLDL) metabolism, yet chylomicron remnant particles are thought to be particularly atherogenic. This study examined the effect of inhibition of cholesterol synthesis on postprandial lipoproteins. Eight type 2 diabetic patients were examined before treatment with the 3-hydroxy-3-methyl glutaryl coenzyme A (HMGCoA) reductase inhibitor cerivastatin, after 4 weeks on active treatment, and 4 weeks after stopping treatment. On each occasion, blood was collected fasting and at 2-hour intervals for up to 8 hours after a high-fat meal. Chylomicrons and VLDLs were isolated by sequential ultracentrifugation. Compositional analysis was performed including the measurement of apolipoprotein B48 (apo B48) and apo B100 using polyacrylamide gradient gel electrophoresis. During statin treatment, there was a significant reduction in the postprandial chylomicron apo B48 area under the curve (AUC) from 23 ± 16 to 17 ± 10 ($P < .01$) and apo B100 in the chylomicron fraction from 166 ± 148 to 70 ± 70 ($P < .05$). Postprandial cholesterol (362 ± 193 to 74 ± 39, $P < .005$), triglyceride (2,222 ± 1,440 to 746 ± 329), and phospholipid (518 ± 267 to 205 ± 94) also decreased ($P < .005$). In the VLDL fraction, the postprandial cholesterol and triglyceride AUC were significantly reduced by statin (316 ± 228 to 171 ± 78, $P < .05$, and 1,733 ± 833 to 857 ± 468, $P < .02$, respectively). Four weeks after cessation of treatment, the chylomicron fraction triglyceride AUC had returned to the pretreatment level, but postprandial chylomicron cholesterol and VLDL cholesterol, triglyceride, and phospholipid were significantly lower than baseline ($P < .05$). Plasma total cholesterol and LDL cholesterol were significantly reduced with treatment (6.2 ± 0.5 to 4.3 ± 1.0 mmol/L, $P < .001$, and 4.5 ± 0.4 to 2.8 ± 1.0 mmol/L, $P < .01$, respectively) and returned to baseline following cessation of treatment. Fasting plasma triglycerides decreased significantly on treatment (2.4 ± 1.0 to 1.7 ± 0.2 mmol/L, $P < .05$) but remained significantly lower than baseline 4 weeks later (1.8 ± 0.3 mmol/L, $P < .05$). This study suggests major postprandial lipoprotein changes on statin therapy which may account, in part, for the beneficial effects of statins in the prevention of myocardial infarction.

ATHEROSCLEROSIS resulting in stroke, myocardial infarction, and gangrene is up to 4 times more common in diabetes than in the general population. A major abnormality in diabetes occurs in the postprandial phase,[1-5] and of course, we spend most of the time in this state. There is evidence to suggest that the chylomicron remnant particle is particularly atherogenic.[6-8] Very recently, plasma triglyceride-rich lipoprotein remnants have been associated with sudden cardiac death in nondiabetic patients,[9] and Kugiyama et al[10] have shown in patients with coronary artery disease that higher levels of remnant lipoproteins in fasting serum predict future coronary events. However, there is very little information on whether the intestinally derived apolipoprotein B48 (apo B48)–containing chylomicron particle is more or less atherogenic than the hepatically derived apo B100–containing particle. The recent discovery of a specific apo B48 receptor in the macrophage[11] explains, at least in part, the focal accumulation of chylomicron remnants within the subendothelial space.[12] The metabolic abnormalities in diabetes are particularly evident postprandially, and thus, it might be expected that in diabetes the chylomicron remnant particle would make a major contribution to atherogenesis. It should be remembered that although the chylomicron, by definition, is the lipoprotein particle derived from the intestine containing apo B48 rather than apo B100, ultracentrifugation separates lipoproteins in relation to density. It is not generally recognized that the postprandial chylomicron fraction actually contains more hepatically derived versus intestinally derived particles.

Many studies have shown a relation between triglyceride-rich lipoproteins and low-density lipoprotein (LDL) composition.[13-15] There is little in the literature about the effect of an alteration of LDL turnover on postprandial lipoproteins. We have shown that the fractional catabolic rate of LDL in diabetes is dependent on LDL composition, including glycation.[16] In that study, simvastatin significantly decreased LDL residence time and was associated with a reduction in LDL glycation with no change in diabetic control. A recent review on the metabolic modes of action of the statins demonstrates our lack of understanding of the subject, particularly the relationship between cholesterol and triglyceride in the assembly of very–low-density lipoprotein (VLDL).[17]

The present study investigates the effect of the 3-hydroxy-3-methyl glutaryl coenzyme A (HMGCoA) reductase inhibitor, cerivastatin, on postprandial intestinally and hepatically derived lipoproteins in type 2 diabetes. Our hypothesis is that a major effect of the statins is their beneficial effect on chylomicron metabolism by reducing the number and altering the composition of postprandial lipoprotein particles.

SUBJECTS AND METHODS

Eight type 2 (non–insulin-dependent) diabetic patients (6 females and 2 males; body mass index, 25 to 35 kg/m^2; mean, 29.0 ± 3.3; age, 40 to 70 years; mean, 66.7 ± 11.0) with plasma cholesterol greater than 5.2 mmol/L and plasma triglycerides greater than 1.5 mmol/L were investigated. These subjects were randomly recruited for the study from

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Submitted September 20, 1999; accepted February 22, 2000.

Supported by Bayer UK.

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0026-0495/00/4908-0023$10.00/0

doi:10.1053/meta.2000.7744

the patients attending our diabetic clinic. Patients with evidence of hepatic or renal disease, unstable hypertension, proliferative retinopathy, unstable angina, or recent myocardial infarction (within 3 months) or patients with familial hypercholesterolemia or those using any lipid-lowering agent in the previous 3 months were excluded from the study. Diabetes was treated in 2 of the patients with diet alone, 4 with metformin, 1 with sulfonylurea, and 1 with insulin. Approval was obtained for the study from the Hospital Ethics Committee, and all patients provided informed consent.

Study Design

At the end of a 4-week run-in period to ensure the stability of weight and diabetic control, fasting baseline blood samples were taken. Patients were treated with cerivastatin 0.3 mg/d (Bayer, Leverkusin, Germany) for 4 weeks and the tests were repeated. Cerivastatin treatment was then stopped and the patients were evaluated for a further 4 weeks, with blood samples obtained at the end of this period. Fasting plasma lipids, blood glucose, insulin, and hemoglobin A_{1c} (HbA_{1c}) were determined on each occasion, and fasting chylomicrons and VLDL were isolated for compositional analysis.

Test Meal

On each occasion, subjects were given an 1,100-kcal breakfast. The breakfast contained 55% of calories as fat, 25% carbohydrate, and 20% protein, and included 0.6 g cholesterol. The breakdown of the fat content was saturated fat 22.5 g, polyunsaturated fat 34.1 g, and monounsaturated fat 26.4 g. Blood samples were taken at 2, 4, 6, and 8 hours postprandially for chylomicron and VLDL isolation.

Lipoprotein Preparation and Analysis

Blood was centrifuged to separate the plasma and cells, and the following preservatives were added to prevent degradation of apo B: PPACK (1 mmol/L), phenylmethylsulfonyl fluoride, sodium azide (0.02%), and EDTA (0.1 mg/mL). Chylomicrons (density $<$ 1.006 g/mL) were isolated during a 30-minute centrifugation at 20,000 rpm, and VLDL (density $<$ 1.006 g/mL) was isolated from the infranate by ultracentrifugation for 24 hours at 40,000 rpm.[5,18] Lipoprotein triglyceride, phospholipid, and cholesterol levels were measured using enzymatic colorimetric methods (Boehringer, Mannheim, Germany) and protein was determined by a modification of the Lowry method.[19] Interassay and intraassay variations were 4.2% and 5.0% for cholesterol, 3.8% and 4.8% for triglyceride, and 4.9% and 4.7% for phospholipid.

B48 and Apo B100 Analysis

Chylomicron and VLDL apo B48 and apo B100 were separated by sodium dodecyl sulfate (SDS)–polyacrylamide gel electrophoresis using 4% to 15% gradient gels (BioRad, Hercules, CA).[4,5] Nondelipidated lipoprotein samples (10 μg protein) were reduced in SDS sample buffer (2% mercaptoethanol, 4% SDS, 0.01% bromophenol blue, 0.1 mmol/L Tris, and 20% glycerol, pH 6.8) using a 1:1 ratio of sample to buffer for 4 minutes at 96°C. Samples (20 μL) were applied to the gel and run at 60 mA in 0.019 mol/L Tris and 0.192 mol/L glycine. Gels were stained for 1 hour with Coomassie Brilliant Blue (0.1% in methanol:acetic acid:water 4:1:5) and destained with several changes of the same solvent. Since the chromogenicity of apo B48 has been shown to be similar to that of apo B100,[20] a protein standard was prepared from LDL (density 1.025 to 1.063 g/mL) of a single individual prepared by sequential ultracentrifugation,[21] stored at −20°C, and used throughout the study to quantify apo B100 and apo B48. Staining was linear within the range of 0.1 to 2 μg protein. Three concentrations of LDL apo B100 within this range, depending on the expected apoprotein concentration, were applied to all gels. The bands were quantified by densitometry using Vilber Lourmat equipment (Vilber Lourmat Biotechnology, Marne le Vallee, France). Video images of the gels were generated and imported into Bio1D v6.32 software (Vilber) for analysis. Density values were assigned to the apo B100 bands of the human LDL and a standard curve was constructed. The values were recalculated by linear regression, and curves with a correlation coefficient greater than .95 were accepted. The concentrations of apo B48 and apo B100 were determined from this standard. Results are expressed as micrograms per milliliter of plasma. The interassay and intraassay variations (n = 6) for apo B48 were 3.9% and 6.0%, and for apo B100, 3.1% and 4.5%, respectively.

Statistics

The primary endpoints for the study were chylomicron and VLDL postprandial composition. Statistical analysis was performed using the paired Student's *t* test for comparison of lipoprotein levels before and after treatment. The area under the curve (AUC) measurements were obtained using Graphpad Prism 2 for Macintosh (Graphpad Software, San Diego, CA). The postprandial AUC and ANOVA were made both incrementally from fasting and from zero to determine postprandial changes independently of fasting values. Results are expressed as the mean ± SD in the text and tables and as the mean ± SEM in the figures. Interassay and intraassay variation is expressed as the standard deviation/mean ×100. A *P* value less than .05 was regarded as statistically significant.

RESULTS

Patient characteristics are presented in Table 1. There was no significant change in diabetic control throughout the study as shown by both fasting blood glucose and HbA_{1c}. There was a significant reduction in fasting plasma cholesterol ($P < .001$) that returned in all patients to the initial level following 4 weeks' cessation of cerivastatin. Plasma LDL also decreased significantly on cerivastatin ($P < .01$) and returned to pretreatment levels at the end of the study. There was no change in HDL cholesterol. Fasting plasma triglycerides decreased from a mean of 2.4 ± 1.0 mmol/L to 1.7 ± 0.2 mmol/L ($P < .05$) and remained at this level following 4 weeks' cessation of therapy (1.8 ± 0.3 mmol/L).

There was no significant change in fasting apo B48 or apo B100 in the chylomicron fraction following statin treatment or in fasting chylomicron cholesterol or triglyceride (Fig 1). Fasting apo B48 and apo B100 were similar in the VLDL fraction at the 3 visits (Fig 2), but there was a significant

Table 1. Patient Characteristics, Diabetic Control, and Lipoproteins Before, During, and After Cerivastatin Treatment

Parameter	Baseline	1 Month on Statin	1 Month Post-Statin
Weight (kg)	76.0 ± 7.5	76.4 ± 7.1	75.8 ± 8.0
HbA_{1c} (%)	6.7 ± 0.4	6.7 ± 0.6	6.6 ± 0.7
Blood glucose (mmol/L)	6.8 ± 0.6	7.0 ± 1.6	7.2 ± 1.2
Plasma cholesterol (mmol/L)	6.2 ± 0.5	4.3 ± 1.0‡	6.4 ± 0.6
LDL cholesterol (mmol/L)	4.5 ± 0.4	2.8 ± 1.0†	4.8 ± 0.6
HDL cholesterol (mmol/L)	1.1 ± 0.2	1.1 ± 0.9	1.2 ± 0.2
Plasma triglyceride (mmol/L)			
Mean	2.4 ± 1.0	1.7 ± 0.2*	1.8 ± 0.3*
Range	1.7-4.5	1.4-2.1	1.3-2.1
Median	2.4	1.6	1.8

NOTE. Results are the mean ± SD.

*$P < .05$ *v* baseline.

†$P < .01$, ‡$P < .001$ *v* baseline and 1 month post-statin.

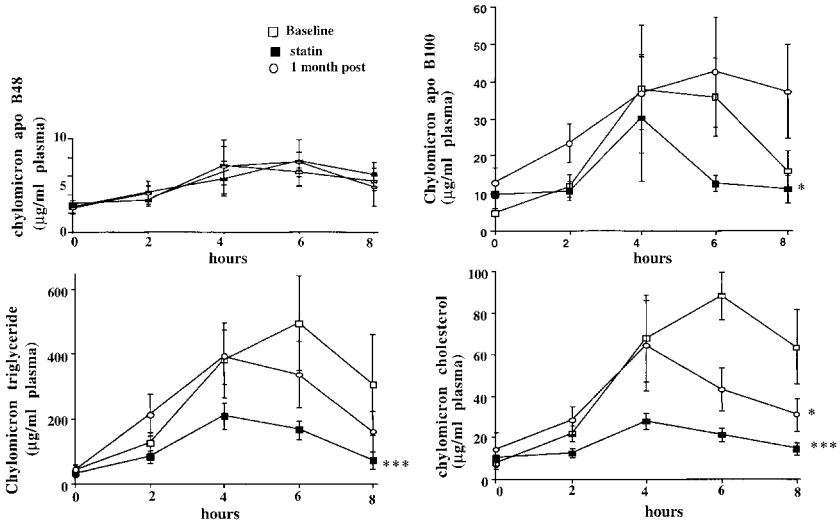

Fig 1. Effect of statin on chylomicron fraction apo B48, apo B100, triglyceride, and cholesterol at fasting and 2, 4, 6, and 8 hours after a high-fat meal measured at baseline (□), after 1 month of statin treatment (■), and at 1 month post-statin (○) in type 2 diabetic patients. *$P < .05$, **$P < .02$, ***$P < .005$ *v* baseline (error bars represent the SEM).

reduction in fasting VLDL cholesterol (125 ± 88 to 65 ± 35 μg/mL plasma, $P < .05$) and triglyceride (363 ± 138 to 235 ± 121 μg/mL plasma, $P < .005$) on statin therapy. Fasting triglyceride was still significantly reduced after 1 month of follow-up study (199 ± 110 μg/mL plasma, $P < .003$).

The postprandial chylomicron and VLDL composition (AUC) are shown in Table 2. Postprandial chylomicron fraction apo B48 was significantly lower on statin treatment ($P < .01$) and there was a significant decrease in apo B100 ($P < .05$) that returned to pretreatment levels 1 month after cessation of statin. There was a significant reduction in postprandial cholesterol in the chylomicron fraction on statin ($P < .005$), and at 4 weeks off treatment, the AUC was still significantly lower than baseline ($P < .02$). The chylomicron fraction triglyceride AUC significantly decreased on cerivastatin ($P < .005$), but although it was still lower, it was not significantly different from baseline when repeated at 1 month off statin. Chylomicron phospholipid showed a similar decrease on statin ($P < .005$) and returned to baseline 1 month off statin.

There was no significant change in the postprandial apo B48 or apo B100 AUC in the VLDL fraction during the study (Table 2). Postprandial cholesterol in the VLDL fraction significantly decreased on cerivastatin ($P < .05$) and remained significantly lower than the pre-statin baseline levels 4 weeks after cessation of the drug ($P < .02$). These reductions were amplified if fasting levels were taken into consideration ($P < .005$). The VLDL triglyceride AUC from fasting was significantly decreased by statin treatment ($P < .02$) and remained low 4 weeks after finishing statin treatment ($P < .02$). There was an even greater reduction with statin when fasting triglyceride was taken into account ($P < .0005$). There was a nonsignificant decrease in VLDL phospholipid on treatment that was significant when the fasting value was included ($P < .02$), with a significant decrease 4 weeks following cessation of treatment ($P < .02$) (Fig 2).

DISCUSSION

In this study, we have shown that statin treatment reduced triglyceride and cholesterol in both the chylomicron and VLDL fractions. The reduction was associated with a reduction in apo B48 and apo B100. There was a shift from larger to smaller postprandial lipoprotein particles with treatment.

We have previously shown considerable disturbances in postprandial lipoprotein metabolism both in people with diabe-

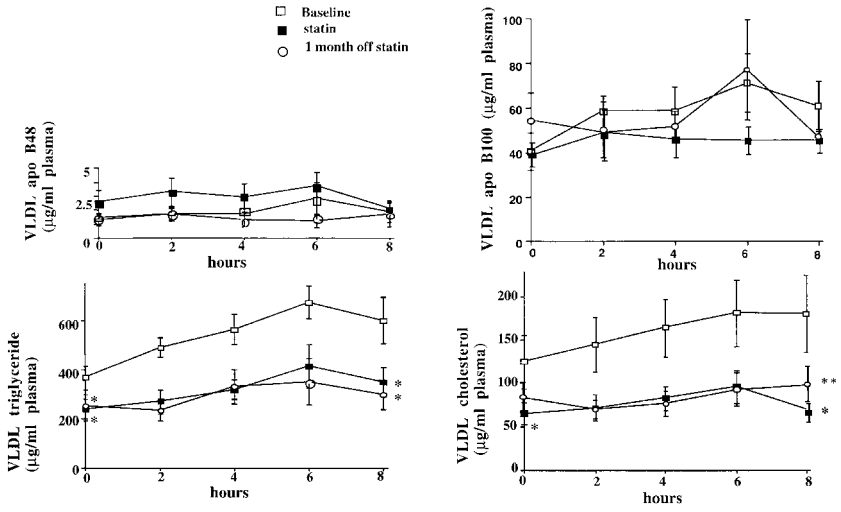

Fig 2. Effect of statin on VLDL fraction apo B48, apo B100, triglyceride, and cholesterol at fasting and 2, 4, 6, and 8 hours after a high-fat meal measured at baseline (□), after 1 month of statin treatment (■), and at 1 month post-statin (○) in type 2 diabetic patients. *$P < .05$, **$P < .005$, ***$P < .0005$ *v* baseline AUC (error bars represent the SEM).

Table 2. Postprandial Lipoproteins (AUC from fasting) Before, During, and After Cerivastatin Treatment

Parameter	Baseline	1 Month on Statin	1 Month Post-Statin	ANOVA (*P*)
Chylomicron				
Apo B48	23 ± 16	17 ± 10	28 ± 36	<.01
Apo B100	166 ± 148	70 ± 70*	153 ± 151	<.05
Triglyceride	2,222 ± 1,440	746 ± 329‡	1,714 ± 1,074	<.03
Cholesterol	362 ± 193	74 ± 39‡	233 ± 208†	<.002
Phospholipid	518 ± 267	205 ± 94‡	464 ± 292	<.03
VLDL				
Apo B48	8 ± 9	9 ± 4	8 ± 5	NS
Apo B100	188 ± 143	110.8 ± 62	223 ± 204	NS
Triglyceride	1,733 ± 833	857 ± 468†	608 ± 491‡	<.0002
Cholesterol	316 ± 228	171 ± 78*	123 ± 69†	<.01
Phospholipid	472 ± 338	326 ± 179	199 ± 110†	<.05

NOTE. Results are the mean ± SD.
*$P < .05$, †$P < .02$, ‡$P < .005$ *v* baseline.

tes[2-5,18] and experimentally in diabetic animals.[22] Curtin et al,[2-4] in a series of experiments, showed increased levels of apo B48, apo B100, and lipids in triglyceride-rich lipoproteins from diabetic patients compared with nondiabetic subjects following a high-fat meal. Taggart et al[5] separated the TRL into chylomicron and VLDL fractions and showed that in response to a high-cholesterol meal, diabetic patients produced large amounts of small apo B48–containing particles that were isolated in the VLDL fraction after ultracentrifugation. More recently, Phillips et al[18] have shown that an improvement in diabetic control reduced the number of postprandial apo B48 and apo B100 particles found in the chylomicron fraction. The chylomicron fraction consists of both intestinally derived apo B48–containing particles and a larger number of hepatically derived apo B100–containing particles. The present study demonstrated that inhibition of HMGCoA reductase, the rate-limiting enzyme for cholesterol synthesis, resulted in potentially important alterations in both the chylomicron and VLDL fractions in the postprandial phase. These changes were unrelated to an alteration in weight or diabetic control.

The significant decrease in cholesterol in the chylomicron fraction may reflect a reduction in either absorption or synthesis but could also be related to increased clearance. HMGCoA reductase inhibitors have been shown to have an effect on cholesterol absorption perhaps related to a reduction in acyl coenzyme A:cholesterol acyltransferase activity in the intestine.[23] The fact that triglyceride and phospholipid were also significantly decreased suggests that cholesterol absorption inhibition per se was not a major cause of our findings. Chylomicron apo B48 decreased significantly, suggesting that the production of intestinally derived particles may be altered by statin therapy. The significant reduction in chylomicron fraction apo B100 demonstrates a major statin effect on large hepatically derived particles. Some years ago, it was suggested that the clearance of chylomicrons (Svedberg flotation units [sf] > 1,000) did not change with statin treatment in hypercholesterolemia but the clearance of chylomicron remnants (sf < 1,000) improved after treatment.[24] A study by Burnett et al[25] using atorvastatin in miniature pigs led to the conclusion, using a multicompartmental model, that atorvastatin has no significant effect on the postprandial intestinal assembly or secretion of triglyceride-rich lipoprotein. Both of the abovementioned studies used retinyl palmitate, which some studies have shown to have deficiencies as a marker of apo B48 intestinally derived particles.[26,27]

The regulation of apo B assembly into lipoproteins and their secretion from the liver is complex. In vivo studies in the past few years have demonstrated the importance of cholesterologenesis in controlling the hepatic secretion of apo B100.[28] It is apparent that peroxisome proliferation–activated receptor-α also controls apo B100 secretion through its effect on de novo fatty acid synthesis, increasing β-oxidation and decreasing apo B and VLDL production and secretion.[29] Insulin also has many effects on VLDL metabolism. Hormone-sensitive lipase is suppressed, inhibiting the release of fatty acids from adipose tissue.[30] Hepatic lipase is stimulated by insulin, leading to the catabolism of both chylomicrons and VLDL remnants,[31] and insulin stimulates lipoprotein lipase, increasing chylomicron uptake by the liver and VLDL turnover to LDL.[32]

In hyperlipidemic patients, the major effect of statins is to increase the clearance of apo B–containing particles, but studies have also demonstrated reductions in apo B secretion from the liver.[33,34] Our study demonstrates a considerable alteration in the particle number, as shown by the 55% reduction in total apo B, and also in particle composition, with a greater than 80% reduction in cholesterol, 65% reduction in triglyceride, and 60% reduction in phospholipid. An alteration in the composition of the particle may effect receptor uptake and alter the rate of clearance. This has recently been demonstrated in LDL by Bergland et al,[34] who showed that compositional changes on statin treatment led to an alteration in particle affinity for the LDL receptor which negated, to some extent, the expected effect of upregulation of LDL receptors on LDL clearance.

A major abnormality in diabetes is the postprandial elevation of triglyceride, and statins are most effective in decreasing triglyceride in hypertriglyceridemic subjects. It has been suggested that a reduction in triglyceride production in the liver may be associated with a reduction in apo B100 due to increased apo B100 catabolism prior to secretion.[35,36] The association between triglyceride and apo B100 in the liver is complex. For example, in the rat model, Carrella et al[37] have shown an increase in fatty acid synthesis and a slight increase in hepatic triglyceride on pravastatin treatment, even though this led to a greater than 50% decrease in serum triglycerides. A strong correlation between changes in the triglyceride and apo B production rate on lovastatin in patients with combined hyperlipidemia[38] led the investigators to support the hypothesis that the overall hypolipidemic effect of lovastatin is due to a decreased assembly and secretion of apo B–containing lipoproteins. Statins may have an effect on microsomal triglyceride transfer protein,[35] supporting the theory that the reduction by statins of postprandial particles is due to a decreased production of hepatically derived postprandial particles rather than increased turnover. In our study, serum triglyceride decreased from a mean of 2.4 to 1.7 mmol/L, and this was reflected in the 67% reduction in the chylomicron triglyceride AUC and 50% reduction in triglyceride in VLDL. Since the ratio of triglyceride to apo B was significantly reduced (18.1 to 8.8, $P < .05$), statins may have a beneficial effect by producing a triglyceride-poor postprandial lipoprotein particle in diabetes. A reduction in

lipoprotein triglyceride might also decrease the risk of coronary artery disease through a pathway such as fibrinolysis, known to be influenced by plasma triglyceride levels.[39]

This study has allowed us to investigate the relationship between apo B100 and hepatically derived triglyceride. We found that the major changes were in the hepatically derived apo B100–containing particles in both the chylomicron and VLDL fractions. Apo B100 increased to baseline 1 month after statin therapy, with a continuing reduction in triglyceride. This dissociation between apo B and triglyceride suggests that triglyceride may not have a regulatory effect on apo B secretion from the liver, and apo B100 secretion may be independent of triglyceride. The prolonged effect on hepatically derived triglyceride may be explained by the induction of peroxisomes which regulate the expression of genes responsible for triglyceride metabolism in the liver.[40] Although HMGCoA reductase resides mainly in the endoplasmic reticulum, peroxisomes have also been shown to contain HMGCoA reductase, which might explain the effect of statins on the assembly of the triglyceride-rich particle in the liver.[40,41]

Our results suggest that statins, by reducing cellular cholesterol synthesis, decrease the production particularly of the larger hepatically derived apo B100 particles found in the chylomicron fraction. Large remnant particles may be particularly atherogenic since they are cleared more slowly,[42] so the benefits of statin therapy may be related, in part, to a reduction in the size of these postprandial particles. It is interesting that in the present study fasting chylomicron cholesterol and triglyceride did not reflect the postprandial levels, confirming our previous studies suggesting that major abnormalities in chylomicrons are to be found in the postprandial state.[5,18] These results again suggest that more attention should be given to investigating the relationship between atherosclerosis and the postprandial state, particularly in diabetes. Our results suggest that since good glycemic control is a difficult goal to achieve,[43,44] treatment of lipoprotein abnormalities merits further research in a bid to prevent atherosclerosis. Just recently, we have demonstrated that an improvement in diabetic control per se did not reduce postprandial chylomicron triglyceride or VLDL cholesterol even though there was a significant reduction in chylomicron apo B48 and apo B100.[18] The present study suggests that cerivastatin is very effective as an agent to normalize postprandial lipoproteins.

In conclusion, this study in type 2 diabetic patients demonstrates that cerivastatin reduces the lipid content and number of large postprandial chylomicron particles. These changes were independent of glycemic control and suggest a mechanism that could account for the beneficial effect of statins in the secondary prevention of myocardial infarction.

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