

Dose-Dependent Effect of Rosuvastatin on VLDL-Apolipoprotein C-III Kinetics in the Metabolic Syndrome

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OBJECTIVE — Dysregulated apolipoprotein (apo)C-III metabolism may account for hypertriglyceridemia and increased cardiovascular risk in the metabolic syndrome. This study investigated the dose-dependent effect of rosuvastatin on VLDL apoC-III transport in men with the metabolic syndrome.

RESEARCH DESIGN AND METHODS — Twelve men with the metabolic syndrome were studied in a randomized double-blind crossover trial of 5-week intervention periods with placebo, 10 mg rosuvastatin, or 40 mg rosuvastatin, with 2-week placebo washouts between each period. VLDL apoC-III kinetics were examined using a stable isotope method and compartmental modeling at the end of each intervention period.

RESULTS — Compared with placebo, there was a significant dose-dependent reduction with rosuvastatin in plasma triglyceride and VLDL apoC-III concentrations. Rosuvastatin significantly ($P < 0.05$) increased VLDL apoC-III fractional catabolic rate (FCR) and decreased its production rate, with a significant ($P < 0.05$) dose-related effect. With 40 mg rosuvastatin, changes in VLDL apoC-III concentration were inversely associated with changes in VLDL apoC-III FCR and positively associated with VLDL apoC-III production rate ($P < 0.05$). Changes in VLDL apoC-III concentration and production rate were positively correlated with changes in VLDL apoB concentration and production rate and inversely correlated with VLDL apoB FCR ($P < 0.05$). Similar associations were observed with 10 mg rosuvastatin but were either less or not statistically significant.

CONCLUSIONS — In this study, rosuvastatin decreased the production and increased the catabolism of VLDL apoC-III, a mechanism that accounted for the significant reduction in VLDL apoC-III and triglyceride concentrations. This has implications for the management of cardiovascular metabolic risk in obese subjects with the metabolic syndrome.

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Hypertriglyceridemia, a key feature of the metabolic syndrome, is associated with increased risk of cardiovascular disease (1). It is the most consistent lipid disorder in subjects with obesity and type 2 diabetes. Hypertriglyceridemia is primarily related to dysregulated triglyceride-rich lipoprotein (TRL) metabolism, including overproduction of VLDL particles and delayed catabolism of TRLs

and their remnants (2). These abnormalities are a collective consequence of insulin resistance and increased lipid substrate availability in the liver, as well as depressed activities of lipoprotein lipase (LPL) and hepatic clearance receptors (3).

Apolipoprotein (apo)C-III is an 8.8-kDa glycoprotein synthesized by the liver and intestines. ApoC-III is highly associated with hypertriglyceridemia and is a

powerful independent predictor of cardiovascular disease risk (4). In circulation, apoC-III is associated with TRL and HDL, exchanging rapidly between these particles (5). In normolipidemic subjects, the majority of plasma apoC-III is bound to HDL, while in hypertriglyceridemic subjects, the majority is bound to TRL (4). ApoC-III inhibits LPL activity and TRL remnant uptake by hepatic lipoprotein receptors (4). Elevated plasma apoC-III concentration, and specifically its accumulation in TRL and their remnants, is causally related to hypertriglyceridemia in the metabolic syndrome (6). Furthermore, insulin resistance is associated with elevated plasma apoC-III concentrations (7). Hence, interventions that target apoC-III metabolism are clinically important.

Statins decrease de novo cholesterol synthesis, thereby upregulating LDL receptor activity. This enhances the uptake of both hepatic and intestinal-derived TRLs, thereby decreasing their concentrations in the circulation (8). Animal studies suggest that statins decrease apoC-III hepatic mRNA expression and plasma concentrations via the peroxisome proliferator-activated receptor- α pathway (9,10). However, their effect on apoC-III metabolism in vivo is not known.

Rosuvastatin is a highly efficacious statin recently shown to decrease the progression of atherosclerosis in high-risk subjects (11). In a dose range between 10 and 40 mg, rosuvastatin significantly reduced plasma LDL cholesterol and triglyceride and increased HDL cholesterol concentrations in the metabolic syndrome (12). We recently reported that rosuvastatin dose-dependently increased TRLs and decreased fractional catabolic rates of HDL particles that contain only apoA-I (LpA-I), consistent with parallel reduction in plasma triglycerides and an increase in HDL cholesterol concentrations (13,14). The triglyceride-lowering effect of rosuvastatin may, in part, be regulated by the reduction of plasma apoC-III concentrations (13). However, the precise mechanism of action of this agent on VLDL-apoC-III kinetics in the meta-

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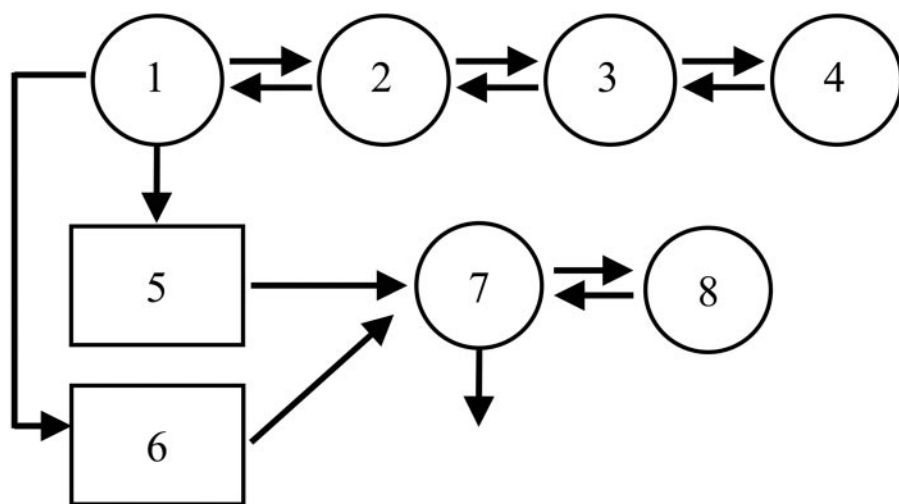


Figure 1—Compartment model describing apoC-III tracer kinetics. Leucine tracer is injected into plasma (compartment 2) and distributes to extravascular compartments 1, 3, and 4. Compartments 1–4 are required to describe leucine tracer kinetics observed in plasma. Compartment 1 is connected to two intracellular delay compartments (compartment 5 and 6) that account for the assembly, synthesis, and secretion of apoC-III. Compartment 7 describes the kinetics of VLDL apoC-III and compartment 8 is an extravascular exchange compartment.

bolic syndrome subjects has not been examined.

In the present study, we investigated the dose-related effect of rosuvastatin on VLDL apoC-III transport in the metabolic syndrome. We hypothesized that a higher dose of rosuvastatin would reduce VLDL apoC-III concentration by a mechanism that primarily involves decreasing the production of apoC-III. We also explored the dose-dependent effect of rosuvastatin on other markers of TRL metabolism, including apoB-48 and apoA-V.

RESEARCH DESIGN AND METHODS

Twelve Caucasian men with the metabolic syndrome by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) definition (15) were recruited. Upper limits for HDL cholesterol ≤ 1.2 mmol/l, LDL cholesterol ≤ 6 mmol/l, and triglycerides ≤ 4.5 mmol/l were stipulated to exclude subjects with genetic hyperlipidemia including familial hypercholesterolemia and familial hypertriglyceridemia and other secondary causes of severe dyslipidemia. Subjects with diabetes (fasting glucose >7 mmol/l), cardiovascular disease, renal dysfunction (macroproteinuria and/or serum creatinine >150 $\mu\text{mol/l}$), apoE2/E2 genotype, hypothyroidism, or abnormal liver or muscle enzymes; who consumed >30 g alcohol/day; or who used lipid-modifying agents were excluded. All were nonsmokers and were consuming ad libitum weight-mainte-

nance diets. Participants provided informed written consent, and the study was approved by the Ethics Committee of Royal Perth Hospital.

Study design and clinical protocols

This was a randomized double-blind three-way crossover trial. Eligible patients entered a 4-week run-in diet-stabilizing period, at the end of which they were randomized to a 5-week intervention period of 40 mg rosuvastatin, 10 mg rosuvastatin, or placebo. Rosuvastatin was provided by AstraZeneca (London, U.K.). Advice was given to continue isocaloric diets and to maintain a physical activity constant. Compliance with study medication was assessed by tablet count.

All subjects were admitted to the metabolic ward in the morning after a minimum of a 12-h fast. They were studied semi-recumbent and allowed water only for the initial 10 h of the study. Venous blood was collected for biochemical measurements. Body weight and height were measured and arterial blood pressure was recorded using a Dinamap1846 SX/P monitor (Critikon, Tampa, FL). Dietary intake was assessed using 24-h dietary diaries and DIET 4 Nutrient Calculation Software (Xyris Software, Queensland, Australia).

A single bolus of D₃-leucine (5 mg/kg) was administered intravenously into an antecubital vein via a Teflon cannula. Blood samples were taken at baseline and at 5, 10, 20, 30, and 40 min and 1, 1.5, 2,

2.5, 3, 4, 5, 6, 8, and 10 h after isotope injection. Additional blood samples were collected in the morning on the 4 following days (24, 48, 72, and 96 h) after a minimum 12-h fast. All the procedures were repeated at the end of each treatment period.

Biochemical analyses

Laboratory methods for measurements of lipids, lipoproteins, and other biochemical analytes have been previously detailed (13,14). Insulin resistance was calculated using a homeostasis model assessment score. VLDL apoC-III values were determined by electro-immunodiffusion using a Hydrigel LP CIII Electro-immunodiffusion kit (Sebia, France); interassay coefficients of variations (CVs) were $<5.0\%$ (5). Plasma apoB-48 concentrations were measured by a sandwich enzyme-linked immunoassay using anti-human apoB-48 monoclonal antibodies (interassay CV $<5\%$). Plasma apoA-V concentration was determined using a dual-antibody sandwich enzyme-linked immunosorbent assay (Linco Diagnostic Services).

Isolation of VLDL apoC-III

The methods for the isolation of lipoproteins and apoC-III have been previously described (5). In brief, 3 ml plasma was used for isolation of 1 ml VLDL (<1.006 kg/l) fraction by sequential ultracentrifugation at 40,000 rpm in a Ti 50.4 rotor (Optima LE-80K; Beckman Coulter, Australia). The VLDL samples were then prepared for isoelectric focusing gel electrophoresis. VLDL (200 μl) from each time point was delipidated and reconstituted in 50 μl isoelectric focusing sample buffer (8 M urea; 0.001% wt/vol bromophenol blue). ApoC-III was isolated by preparative isoelectric focusing gel electrophoresis (8 M urea; 7.5% acrylamide; 1.5% ampholytes pH 4–6; 16 h; 200 V; 4°C). Gels were electro-blotted onto polyvinylidene fluoride membranes (Immobilon; Millipore) at 700 mA for 1 h using a Hoefer TE 42 transfer unit (Amersham Biosciences, Australia) and stained with Coomassie Brilliant Blue R 250 (5).

Measurement of D₃-leucine enrichment in apoC-III₁

Isoelectric focusing resolves apoC-III into three isoforms: apoC-III₀, apoC-III₁, and apoC-III₂. ApoC-III₁ was investigated in this study because of its greater concentration in plasma and observations from previous studies that the kinetics of apoC-III isoforms was similar (16). All refer-

Table 1—Lipid, lipoprotein, and apolipoprotein concentrations on placebo, 10 mg rosuvastatin, and 40 mg rosuvastatin

	Placebo (P)	10 mg rosuvastatin (R10)	40 mg rosuvastatin (R40)	Group difference (P)			
				P vs. R10	P vs. R40	R10 vs. R40	Dose effect (P)
Total cholesterol (mmol/l)	5.52 ± 0.25	3.64 ± 0.16	3.20 ± 0.13	<0.001	<0.001	0.024	<0.001
Triglycerides (mmol/l)	2.47 ± 0.32	1.88 ± 0.21	1.44 ± 0.13	0.027	<0.001	0.063	<0.001
LDL cholesterol (mmol/l)	3.50 ± 0.22	1.78 ± 0.12	1.51 ± 0.10	<0.001	<0.001	0.063	<0.001
HDL cholesterol (mmol/l)	0.94 ± 0.04	0.98 ± 0.05	1.03 ± 0.04	0.227	0.011	0.129	0.011
ApoB (g/l)	1.19 ± 0.05	0.74 ± 0.03	0.65 ± 0.03	<0.001	<0.001	0.009	<0.001
ApoA-I (g/l)	1.22 ± 0.04	1.27 ± 0.04	1.25 ± 0.03	0.090	0.086	0.566	0.276
ApoB/ApoA-I ratio	0.98 ± 0.02	0.58 ± 0.02	0.51 ± 0.03	<0.001	<0.001	0.006	<0.001
ApoC-III (mg/l)	139 ± 9.85	122 ± 8.98	107 ± 4.55	0.045	<0.001	0.047	0.011
Lathosterol (μmol/l)	24.0 ± 2.64	6.33 ± 0.80	3.42 ± 0.35	<0.001	<0.001	0.145	<0.001
Lathosterol-to-cholesterol ratio	4.36 ± 0.42	1.73 ± 0.19	1.08 ± 0.11	<0.001	<0.001	0.031	<0.001
Campesterol (μmol/l)	11.8 ± 1.73	9.84 ± 1.36	10.1 ± 1.30	0.005	0.015	0.609	0.113
Campesterol-to-cholesterol ratio	2.11 ± 0.28	2.74 ± 0.38	3.12 ± 0.36	<0.001	<0.001	0.016	<0.001

Data are means ± SE or P.

ences to apoC-III kinetics will correspond to the kinetics of apoC-III₁. The apoC-III₁ protein bands were excised from the polyvinylidene fluoride and hydrolyzed in 200 μl 6 M HCl overnight at 110°C in pyrolysis-cleaned half-dram vials. Samples are dried at 110°C and derivatized using a modified oxazolinone method. The oxazolinone derivatives are analyzed by negative ion chemical ionization gas chromatography–mass spectrometry. The isotopic enrichment is determined as the tracer-to-tracee ratio of monitored selected ions at a mass to charge (m/z) ratio of 212/209. The average coefficient of variation of apoC-III tracer measurement, including processes associated with isolation of apoC-III from plasma through to the measurement of isotopic enrichment, is 5.4% (5).

Kinetic analyses

A model of VLDL apoC-III metabolism was developed using the SAAM II program (SAAM Institute, Seattle, WA) (Fig. 1; 17). The model consists of a four-compartment subsystem (compartments 1–4) that describes plasma leucine kinetics. This subsystem is connected to two intrahepatic delay compartments (compartments 5 and 6) that account for the time required for the assembly, synthesis, and secretion of apoC-III into plasma. The kinetics of VLDL apoC-III is described by a plasma compartment (compartment 7) and an extravascular exchange compartment (compartment 8). The time for delay compartment 5 (mean ± SE 0.52 ± 0.04 h) was shorter than compartment 6 (1.98 ± 0.25 h); however, this did not affect estimates of

VLDL apoC-III fractional catabolic rate (FCR), nor was there any effect of treatment on delay times. FCR of VLDL apoC-III, equivalent to the irreversible loss from compartment 7, was estimated after fitting the model to the VLDL apoC-III tracer data. The production rate (PR), the transport rate of apoC-III through the VLDL pool, was calculated as the product of FCR and pool size, which equals the plasma concentration multiplied by plasma volume; plasma volume was estimated as 4.5% of body weight, with adjustment made to account for the decrease in relative plasma volume with body weights in the obese range.

Statistical analysis

Skewed variables were logarithmically transformed where appropriate. Data at the end of the three treatment periods were compared using a mixed-effect model (SAS Proc Mixed; SAS Institute), which also tested for carry-over, treatment sequence, and time-dependent effects. There were no significant carry-over, treatment-sequence, or time-dependent effects. A mixed-effect model was also used to examine the dose-related effect of rosuvastatin on study variables. The P values are reported, with statistical significance set at the 5% level. Statistical associations between changes in variables were also examined on both doses of rosuvastatin using simple, stepwise, and multiple linear regression methods.

RESULTS— The clinical and biochemical characteristics of the 12 subjects were reported previously (13,14). They were centrally obese, insulin resistant,

and dyslipidemic. There were no significant treatment effects on body weight, blood pressure, insulin, glucose, fatty acids, and homeostasis model assessment score. Both 10 and 40 mg rosuvastatin were well tolerated. There were no significant changes in liver and muscle enzymes or serum creatinine, and no subjects developed dipstick-positive proteinuria. Mean daily dietary intake was as follows: energy (10,245 ± 575 kJ), total fat (90.9 ± 6.3g), total carbohydrate (256 ± 15 g), protein (123 ± 7 g), cholesterol (385 ± 46 mg), and alcohol (6.5 ± 2.9 g) and did not differ significantly between treatment phases.

Table 1 gives the plasma concentrations of lipids, lipoproteins, and apolipoproteins on placebo, 10 mg rosuvastatin, and 40 mg rosuvastatin. Compared with placebo, rosuvastatin significantly decreased plasma cholesterol, triglycerides, LDL cholesterol, and apoB and apoC-III concentrations and the apoB/apoA-I and lathosterol-to-cholesterol ratios, with a significant increase in HDL cholesterol concentration and campesterol-to-cholesterol ratio. These changes were greater with 40 mg than with 10 mg rosuvastatin, with a statistically significant dose-dependent effect.

Table 2 gives the plasma concentrations and kinetics of VLDL apoC-III on placebo and on 10 and 40 mg rosuvastatin. Compared with placebo, rosuvastatin decreased VLDL apoC-III concentration (10 mg rosuvastatin –22%, 40 mg rosuvastatin –45%) and production rate (10 mg rosuvastatin –15%, 40 mg rosuvastatin –25%) and increased VLDL apoC-III FCR (10 mg rosuvastatin +17%, 40 mg

Table 2—Concentrations, FCRs, and PRs for VLDL apoC-III during placebo, 10 mg rosuvastatin, and 40 mg rosuvastatin treatments

	Placebo (P)	10 mg rosuvastatin (R10)	40 mg rosuvastatin (R40)	Group difference (P)			
				P vs. R10	P vs. R40	R10 vs. R40	Dose effect (P)
Concentration (mg/l)	84.6 ± 12.0	64.1 ± 8.9	46.4 ± 4.5	0.041	<0.001	0.036	<0.001
FCR (pools/day)	0.96 ± 0.06	1.09 ± 0.07	1.28 ± 0.06	0.027	<0.001	0.002	<0.001
PR (mg · kg ⁻¹ · day ⁻¹)	2.86 ± 0.42	2.42 ± 0.29	2.14 ± 0.19	0.145	0.018	0.298	0.029

Data are means ± SE or P.

rosuvastatin +36%). There was a statistically significant dose-dependent effect of rosuvastatin on VLDL apoC-III concentration, FCR, and PR (Table 1). Rosuvastatin dose-dependently lowered plasma apoB-48 (placebo 4.46 ± 0.25 ; 10 mg rosuvastatin 4.12 ± 0.31 ; 40 mg rosuvastatin 3.54 ± 0.19 ; $P_{\text{value}_{\text{dose}}} = 0.002$). There was no significant effect of rosuvastatin on apoA-V concentration (placebo 132 ± 28 ; 10 mg rosuvastatin 155 ± 34 ; 40 mg rosuvastatin 103 ± 17 ; $P_{\text{value}_{\text{dose}}} = 0.107$).

With 40 mg rosuvastatin, the reduction in VLDL apoC-III concentration was significantly associated with an increase in VLDL apoC-III FCR ($r = -0.710$, $P = 0.01$) and a fall in VLDL apoC-III PR ($r = 0.939$, $P < 0.01$). The changes in VLDL apoC-III PR and FCR were independent determinants of change in VLDL apoC-III concentration (adjusted $r^2 = 98\%$, $P < 0.01$). With 10 mg rosuvastatin, the decrease in VLDL apoC-III concentration was significantly associated with the reduction in VLDL apoC-III PR ($r = 0.752$, $P < 0.01$). The fall in VLDL apoC-III concentration was associated with the increase in VLDL apoC-III FCR, but this failed to reach statistical significance ($r = -0.511$, $P = 0.08$). The changes in VLDL apoC-III PR and FCR were independent determinants of change in VLDL apoC-III concentration (adjusted $r^2 = 97\%$, $P < 0.01$).

Given the role of apoC-III in regulating TRL metabolism, associations between VLDL apoC-III and VLDL apoB kinetic parameters were explored. Both VLDL apoC-III and VLDL apoB kinetic parameters were derived from the same subjects. The dose-dependent effect of rosuvastatin on apoB-containing lipoproteins in these subjects was reported earlier (13). Changes in VLDL apoC-III concentration were significantly associated with changes in VLDL apoB concentration ($r = 0.901$, $P < 0.01$), FCR ($r = -0.791$, $P = 0.002$), and PR ($r = 0.642$, $P = 0.024$). Similar associations were observed be-

tween plasma total apoC-III concentration and the corresponding VLDL apoB FCR. Changes in VLDL apoC-III PR were significantly associated with changes in VLDL apoB concentration ($r = 0.934$, $P < 0.01$), FCR ($r = -0.897$, $P < 0.01$), and PR ($r = 0.639$, $P = 0.025$). The above associations between VLDL apoC-III and VLDL apoB kinetic parameters were also seen with 10 mg rosuvastatin but were not as significant.

Additional analysis revealed that changes in plasma triglycerides were associated with changes in VLDL apoC-III concentration, FCR, and PR ($r = 0.958$, $P < 0.01$; $r = -0.653$, $P = 0.021$; and $r = 0.932$, $P < 0.01$, respectively); VLDL apoB concentration, FCR, and PR ($r = 0.879$, $P < 0.01$; $r = -0.860$, $P < 0.01$; and $r = 0.570$, $P = 0.053$, respectively); and plasma apoB-48 concentration ($r = 0.586$, $P = 0.045$). In a stepwise regression model that included plasma apoB-48 and VLDL apoB concentrations, VLDL apoC-III concentration was an independent predictor of changes in plasma triglycerides (adjusted $r^2 = 93\%$, $P < 0.01$). Furthermore, changes in VLDL apoC-III FCR and PR were independent determinants for changes in plasma triglyceride concentrations in a stepwise regression model that included VLDL apoB FCR and PR (adjusted $r^2 = 94\%$, $P < 0.01$).

CONCLUSIONS— We provide new information on the dose-ranging effect of rosuvastatin, a potent HMG-CoA (or 3-hydroxy-3-methyl-glutaryl-CoA) reductase inhibitor, on VLDL apoC-III metabolism in subjects with the metabolic syndrome. We demonstrated that rosuvastatin dose-dependently decreased VLDL apoC-III concentrations by increasing the FCR and decreasing the PR of VLDL apoC-III. These results add further to our work on the dose-dependent effect of rosuvastatin on apoB-containing lipoproteins and HDL particle kinetics in the same subjects (13,14).

Hypertriglyceridemia in insulin-

resistant states, including the metabolic syndrome, results from overproduction and reduced catabolism of TRL and their remnants. These kinetic aberrations may be related to altered VLDL apoC-III metabolism. Previous studies demonstrated that overproduction of VLDL apoC-III explained the higher VLDL apoC-III concentration in these subjects (17). The increased VLDL apoC-III concentration and production rate were associated with elevated VLDL triglycerides, oversecretion of VLDL apoB, and reduced VLDL apoB catabolism (17,18). Statins have been shown to effectively reduce plasma and VLDL apoC-III concentrations (4). The effect of statin therapy on VLDL apoC-III transport, however, has not been examined. We extend these reports by examining the dose-related effect of rosuvastatin on VLDL apoC-III kinetics in the metabolic syndrome using a three-way crossover study design.

Consistent with larger clinical trials, rosuvastatin dose-dependently reduced plasma triglyceride concentrations in subjects with the metabolic syndrome (12). The reduction in plasma triglyceride concentrations was chiefly explained by the decrease in VLDL apoC-III concentrations. This is consistent with previous observations that reduced apoC-III in TRL enhances LPL-mediated lipolysis and receptor-mediated clearance of TRL, thereby lowering plasma triglyceride levels (4).

We demonstrated, for the first time, that rosuvastatin dose-dependently increased VLDL apoC-III fractional catabolism and reduced VLDL apoC-III production. Both VLDL apoC-III FCR and PR were independent determinants of VLDL apoC-III concentration. The increase in VLDL apoC-III FCR may be explained, in part, by direct removal of VLDL apoC-III from circulation and/or its redistribution to other lipoproteins, specifically HDL. The redistribution of apoC-III from VLDL to HDL during LPL-mediated hydrolysis of VLDL tri-

glycerides and its subsequent transfer back to triglyceride-rich particles are well established (19). The precise mechanism of action of rosuvastatin on VLDL apoC-III PR is unclear. Statins have been shown to activate the peroxisome proliferator-activated receptor- α pathway via inhibition of ρ -signaling, thereby repressing apoC-III mRNA expression and reducing apoC-III synthesis in human HepG2 hepatoma cells (9). To date, no studies have examined the effect of statins on apoC-III synthesis in humans. Further analysis of total plasma apoC-III kinetics in the same subjects showed that rosuvastatin reduced total plasma apoC-III concentration by dose-dependently increasing total plasma apoC-III FCR, with no significant changes to total plasma apoC-III PR (total plasma apoC-III PR is synonymous with the amount of apoC-III secreted into plasma by both the liver and intestine) (E.M.M.O., G.F.W., D.C.C., P.H.R.B., unpublished data). We propose that the reduction in VLDL apoC-III PR may be a function of altered distribution of apoC-III between VLDL and HDL particles with rosuvastatin treatment, rather than an effect on apoC-III gene expression and hence hepatic or intestinal apoC-III synthesis.

The reduction in CETP mass and activity with rosuvastatin may also contribute to an altered distribution of apoC-III between VLDL and HDL particles and, hence, changes to its kinetics by favoring the formation of smaller VLDL and larger HDL species (20) with different thermodynamic stability and composition.

The reduction in VLDL apoC-III production with rosuvastatin was associated with the decrease in VLDL apoB concentration and PR and increase in VLDL apoB FCR. The precise reason for a potential coupling of VLDL apoC-III and VLDL apoB metabolism remains unclear, but is consistent with the role of apoC-III as a regulator of apoB transport. Sundaram et al. (21) demonstrated that overexpression and hence oversecretion of apoC-III stimulated apoB synthesis, VLDL assembly, and secretion in McARH7777 cells. Although rosuvastatin significantly reduced VLDL apoC-III PR, there was no impact on VLDL apoB PR (13), suggesting an uncoupling of this association. This observation further reinforces that the persistent state of insulin resistance in metabolic syndrome subjects is a powerful promoter of apoB secretion (3).

ApoA-V may regulate triglyceride me-

tabolism, including VLDL assembly, LPL activity, and VLDL receptor binding (22). However, the association between apoA-V and plasma triglycerides remains contentious (22). To date, no studies have examined the effect of statin therapy on apoA-V levels. Rosuvastatin, while significantly reducing plasma triglycerides, did not alter apoA-V concentrations in our study. This may be explained, in part, by recent evidence suggesting that the primary metabolic role of apoA-V is intracellular rather than extracellular (23). Consistent with this notion, apoA-V was shown to reduce the lipidation of VLDL without altering apoB secretion (23). Future studies using VLDL triglyceride kinetics, coupled with cellular studies, are warranted to better understand the role of apoA-V in vivo.

Our study was restricted to men, and we did not study type 2 diabetic subjects. Our findings may apply to women, type 2 diabetic patients, and subjects of different ethnicity, although this requires further investigation. Measurements of lipases in postheparin plasma may have corroborated our findings. The effects of rosuvastatin on apoC-II, a cofactor for LPL, should also be examined. ApoC-III displays noncompetitive inhibitory properties against apoC-II, indicating the opposing regulatory effects of these two apolipoproteins on TRL metabolism (24). The ratio of apoC-III to apoC-II may therefore be a crucial factor in the regulation of triglyceride hydrolysis.

In conclusion, elevated plasma triglycerides are powerful predictors of cardiovascular disease in the metabolic syndrome. ApoC-III may account for this association. Rosuvastatin effectively reduces plasma triglycerides by improving VLDL apoC-III transport in subjects with the metabolic syndrome. Our findings further suggest that these subjects may derive incremental benefit from higher-dose rosuvastatin therapy (12). Future studies should explore whether lifestyle changes and other pharmacotherapies can further reduce apoC-III concentrations against the background of rosuvastatin in the metabolic syndrome.

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