Rosiglitazone Improves Postprandial Triglyceride and Free Fatty Acid Metabolism in Type 2 Diabetes

JEROEN P.H. VAN WIJK, MD[1]
EELCO J.P. DE KONING, PHD[2]
MANUEL CASTRO CABEZAS, PHD[1,3]
TON J. RABELINK, PHD[4]

OBJECTIVE — Increased postprandial lipemia is part of diabetic dyslipidemia and is associated with accelerated atherosclerosis. We investigated the effects of the peroxisome proliferator–activated receptor-γ agonist rosiglitazone on postprandial lipemia in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — A randomized, 8-week, crossover, placebo-controlled, double-blind trial was performed in which rosiglitazone at 4 mg was administrated twice daily in 19 patients with type 2 diabetes. Standardized 6-h oral fat-loading tests were performed after each treatment period. Postprandial curves were calculated as the total area under the curve (AUC) and the incremental area under the curve (dAUC).

RESULTS — Rosiglitazone did not change fasting plasma triglycerides compared with placebo (1.97 ± 0.22 vs. 1.88 ± 0.20 mmol/l, respectively) but decreased postprandial triglyceride levels, leading to significantly lower triglyceride dAUC (−37%, $P < 0.05$), without changing total triglyceride AUC. Significant postprandial triglyceride reductions in the chylomicron fraction (Svedberg flotation rate [Sf] >400) were achieved with rosiglitazone, which resulted in a significant lower triglyceride AUC (−22%) in this fraction. The postprandial triglyceride increase in VLDL1 (Sf 60–400) was also lower after rosiglitazone (−27%), but this did not result in a significant lower triglyceride AUC. In VLDL2 (Sf 20–60), there were no significant differences in triglyceride AUC and triglyceride dAUC between rosiglitazone and placebo. Rosiglitazone decreased free fatty acid (FFA) AUC (−12%) and FFA dAUC (−18%) compared with placebo.

CONCLUSIONS — Rosiglitazone improves the metabolism of large triglyceride-rich lipoproteins and decreases postprandial FFA concentrations in type 2 diabetes. This may have clinical implications, as these effects may contribute to cardiovascular risk reduction.

Diabetes Care **28:844–849, 2005**

Dyslipidemia is one of the main cardiovascular risk factors in type 2 diabetes (1). An increased hepatic free fatty acid (FFA) flux has been postulated as a major contributor of diabetic dyslipidemia because it could lead to hepatic overproduction of triglyceride-rich lipoproteins (TRLs) (1). It is important to realize that humans are nonfasting most of the day and that nonfasting triglycerides are also predictors of atherosclerosis (2). Exaggerated and prolonged postprandial hyperlipidemia is an important characteristic of diabetic dyslipidemia (1–3). Several studies have shown that, even in fasting normolipidemic subjects, impaired clearance of TRL and their remnants is linked to atherosclerosis (4–9). Therefore, therapeutic modulation of postprandial lipemia may convey increased protection from atherosclerosis.

Thiazolidinediones (TZDs) are oral antihyperglycemic agents that reduce insulin resistance in peripheral tissues and decrease hepatic glucose production (10). TZDs are potent synthetic ligands for peroxisome proliferator–activated receptor-γ (PPAR-γ) activation, thereby directly influencing the transcription of genes that regulate insulin sensitivity (11). In addition to glucose lowering, TZDs modulate lipid metabolism most likely by directing a PPAR-γ–mediated change in adipocyte metabolism. Rosiglitazone, a PPAR-γ agonist, generally increases LDL and HDL cholesterol (12). Rosiglitazone decreases fasting plasma FFA levels (13), probably due to improved peripheral fat storage, but it has only minor effects on fasting plasma triglycerides (12). Nevertheless, rosiglitazone may improve postprandial triglyceride clearance by stimulating lipoprotein lipase (LPL)-mediated lipolysis (14,15). We conducted a double-blind, placebo-controlled, crossover trial to investigate the effects of rosiglitazone on postprandial lipemia in type 2 diabetes.

RESEARCH DESIGN AND METHODS

— Nonsmoking men and nonfertile women aged 35–70 years with documented type 2 diabetes were considered eligible. Patients on insulin treatment were excluded. All patients were treated with oral antihyperglycemic agents, which continued during the study. Exclusion criteria were current or previous treatment with TZD, HbA_{1c}

From the [1]Department of Internal Medicine, University Medical Center Utrecht, Utrecht, The Netherlands; the [2]Department of Endocrinology and Metabolism, Leiden University Medical Center, Leiden, The Netherlands; the [3]Department of Internal Medicine, St. Franciscus Gasthuis, Rotterdam, The Netherlands; and the [4]Department of Nephrology and Hypertension, Leiden University Medical Center, Leiden, The Netherlands.

Address correspondence and reprint requests to Jeroen P.H. van Wijk, MD, Department of Internal Medicine, University Medical Center Utrecht, Room G02.402, P.O. Box 85500, 3508 GA Utrecht, The Netherlands. E-mail: j.p.h.vanwijk@azu.nl.

Received for publication 6 August 2004 and accepted in revised form 21 December 2004.

Abbreviations: ALT, alanine transferase; apoB, apolipoprotein B; AST, aspartate aminotransferase; AUC, area under the curve; dAUC, incremental AUC; FFA, free fatty acid; LPL, lipoprotein lipase; PPAR-γ, peroxisome proliferator–activated receptor-γ; TRL, triglyceride-rich lipoprotein; TZD, thiazolidinedione.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*General characteristics and baseline fasting metabolic profile of the study group (n = 19)*

Men/women	14/5
Age (years)	60 ± 1
BMI (kg/m^2)	29.2 ± 1.1
Waist circumference (cm)	101 ± 2
Systolic blood pressure (mmHg)	144 ± 3
Diastolic blood pressure (mmHg)	86 ± 2
Glucose (mmol/l)	7.8 ± 0.4
HbA_{1c} (%)	6.2 ± 0.2
Antihyperglycemic therapy	
SU only	6 (32%)
Metformin only	5 (26%)
Combination metformin + SU	8 (42%)
Total cholesterol (mmol/l)	4.9 ± 0.2
HDL cholesterol (mmol/l)	0.99 ± 0.08
LDL cholesterol (mmol/l)	2.99 ± 0.16
Triglycerides (mmol/l)	1.95 ± 0.22

Data are given as means ± SE. SU, sulfonylureum derivative.

>9%, serum creatinin >200 μmol/l, abnormal thyrotropin, aspartate aminotransferase (AST), or alanine aminotransferase (ALT) ≥2 times the upper limit of normal, congestive cardiac failure, blood pressure >160/>95 mmHg, total cholesterol >8 mmol/l and/or triglycerides >5 mmol/l, and an alcohol intake >3 units/day. The study protocol was approved by the local research ethics committee of the University Medical Center Utrecht. All participants gave written informed consent.

The study was designed as a randomized, crossover, placebo-controlled, double-blind trial. Eligible patients were randomly assigned to receive rosiglitazone 4 mg b.i.d. or placebo in addition to their current oral antihyperglycemic agents for 8 weeks. A 6-week wash-out period was included between the two treatment periods. At the end of each treatment period, a standardized 6-h oral fat-loading test was carried out. At the beginning and at the end of each 8-week treatment period, anthropometric and fasting laboratory parameters were determined. Patients were instructed to fast at least 12 h before each visit. No study medication or other medication was used on the morning of the study days.

Oral fat loading test and separation of lipoproteins

After placing a cannula for venous blood sampling, subjects rested for 30 min before administration of the fat load. Fresh cream (a 40% weight/volume fat emulsion representing a total energy content of 3,700 kcal/l) was ingested within 5 min at a dose of 50 g fat and 3.75 g glucose/m^2 body surface (9,16). Participants remained supine during each test and were only allowed to drink mineral water. Peripheral blood samples were obtained in sodium EDTA (2 mg/ml), kept on ice, and centrifuged immediately for 15 min at 800*g* at 4°C, then plasma was stored at −80°C. Lipoproteins were subfractionated by ultracentrifugation as described previously in detail (16,17). Consecutive runs were carried out to float Svedberg flotation rate (Sf) >400 (chylomicrons), 60–400 (VLDL1), 20–60 (VLDL2), 12–20 (IDL), and 2–12 (LDL).

Analytical methods

Total cholesterol, HDL cholesterol obtained after precipitation with phosphotungstate/$MgCl_2$, and triglycerides were measured in duplicate by colorimetric assay with the CHOD-PAP and GPO-PAP kits, respectively (Roche Diagnostics, Mannheim, Germany). FFAs were measured by an enzymatic colorimetric method (Wako Chemicals, Neuss, Germany). For FFA measurement, a lipase inhibitor was added to the plasma in order to block ex vivo lipolysis. Total plasma apolipoprotein B (apoB) was measured by nephelometry using apoB monoclonal antibodies. Glucose, creatinin, serum ALT, and AST were measured by standard enzymatical laboratory methods. Insulin was measured by enzyme-linked immunosorbent assay (Mercodia, Uppsala, Sweden). For estimation of insulin sensitivity, the homeostasis model assessment (HOMA) (glucose × insulin/22.5) was calculated.

Statistical analysis

All values are expressed as the mean ± SE in the text, tables, and figures. The area under the curve (AUC) for triglycerides and FFAs was calculated by the trapezoidal rule using GraphPad Prism version 4.0. Incremental integrated AUCs (dAUC) were also calculated after correction for baseline values. Differences between rosiglitazone and placebo were analyzed by paired *t* test. During serial measurements, time effects when compared with $t = 0$ were tested using repeated-measures ANOVA with Bonferroni correction for multiple comparisons. Bivariate correlations were calculated using Spearman's correlation coefficients. Calculations were performed using SPSS/PC +11.5 (SPSS, Chicago, IL). Statistical significance was taken at the 5% level. A reduction in triglyceride dAUC of 20% was considered clinically relevant. Power analysis with $\beta = 0.10$ and $\alpha = 0.05$ revealed that 15 patients had to be included to find such a reduction. Since a small drop-out rate was expected, we aimed to include 20 patients.

RESULTS

General characteristics

In total, 22 diabetic patients were screened. Two patients were excluded after the screening visit because of abnormal thyrotropin and HbA_{1c} >9%. One patient withdrew informed consent during the study. General characteristics of the 19 remaining participants are listed in Table 1. All patients were using oral antihyperglycemic agents, which was unchanged during the study. Eight patients were treated for dyslipidemia with statins (four with simvastatin and four with atorvastatin). ACE inhibitors ($n = 3$), a β-blocking agent ($n = 1$), a calcium antagonist ($n = 1$), and a diuretic ($n = 1$) were used in six patients with hypertension. Rosiglitazone was well tolerated, and no patient showed significant side effects other than headache, dizziness, and gastrointestinal complaints ($n = 3$). Rosiglitazone significantly reduced ALT compared with placebo (36 ± 2 vs. 42 ± 4 units/l, $P < 0.05$). Significant decreases in hemoglobin and hematocrit were also observed after treatment with rosiglitazone (data not shown).

Table 2—*Effects of rosiglitazone and placebo on fasting and postprandial lipids*

	Rosiglitazone	Placebo
Fasting cholesterol (mmol/l)		
Plasma	5.39 ± 0.24*	4.96 ± 0.20
Sf >400 (chylomicron)	0.03 ± 0.01	0.02 ± 0.01
Sf 60–400 (VLDL1)	0.25 ± 0.04	0.24 ± 0.04
Sf 20–60 (VLDL2)	0.26 ± 0.04	0.23 ± 0.03
Sf 12–20 (IDL)	0.42 ± 0.06	0.37 ± 0.05
Sf 2–12 (LDL)	3.45 ± 0.20*	3.14 ± 0.15
HDL cholesterol	1.05 ± 0.21	0.98 ± 0.09
Fasting plasma TG (mmol/l)	1.97 ± 0.22	1.88 ± 0.20
ApoB (g/l)	0.90 ± 0.05	0.86 ± 0.04
Total cholesterol–to–HDL cholesterol ratio	5.63 ± 0.40	5.54 ± 0.34
Non-HDL cholesterol (mmol/l)	4.34 ± 0.23*	3.98 ± 0.17
Plasma TG AUC (mmol · h^{-1} · l^{-1})	14.7 ± 1.7	16.0 ± 1.8
Plasma TG dAUC (mmol · h^{-1} · l^{-1})	3.04 ± 0.65*	4.82 ± 0.77
Sf >400 TG AUC (mmol · h^{-1} · l^{-1})	2.01 ± 0.50*	2.59 ± 0.54
Sf >400 TG dAUC (mmol · h^{-1} · l^{-1})	1.83 ± 0.38*	2.28 ± 0.44
Sf 60–400 TG AUC (mmol · h^{-1} · l^{-1})	5.18 ± 0.81	5.74 ± 0.70
Sf 60–400 TG dAUC (mmol · h^{-1} · l^{-1})	1.25 ± 0.20*	1.73 ± 0.29
Sf 20–60 TG AUC (mmol · h^{-1} · l^{-1})	1.52 ± 0.25	1.64 ± 0.21
Sf 20–60 TG dAUC (mmol · h^{-1} · l^{-1})	−0.11 ± 0.11	0.05 ± 0.08
FFA AUC (mmol · h^{-1} · l^{-1})	3.80 ± 0.22*	4.36 ± 0.30
FFA dAUC (mmol · h^{-1} · l^{-1})	1.80 ± 0.20*	2.24 ± 0.27

Data are given as means ± SE. Sf, Svedberg flotation rate. *$P < 0.05$ compared with placebo. TG, triglycerides.

Effects of rosiglitazone on fasting metabolic parameters

Rosiglitazone significantly decreased fasting plasma glucose (6.2 ± 0.3 vs. 7.2 ± 0.5, $P < 0.01$) and HOMA (2.06 ± 0.35 vs. 3.76 ± 0.50, $P < 0.01$) compared with placebo but did not change HbA_{1c} (6.2 ± 0.6 vs. 6.3 ± 0.7%). The effects of rosiglitazone and placebo on fasting lipoprotein profile are listed in Table 2. Rosiglitazone increased total cholesterol due to a significant increase in LDL cholesterol, leading to an increased non-HDL cholesterol compared with placebo.

Effects of rosiglitazone on postprandial triglycerides and FFAs

Rosiglitzone did not change fasting triglycerides in plasma or in the chylomicron VLDL1 and VLDL2 fractions compared with placebo. After rosiglitazone, the postprandial triglyceride increase in plasma was lower compared with placebo (Fig. 1), which resulted in a significant lower triglyceride dAUC (Table 2). Total plasma triglyceride AUC was not different between rosiglitazone and placebo. A significant reduction in the postprandial triglycerides content of the chylomicron fraction was achieved with rosiglitazone, which resulted in a significant lower triglyceride AUC (−22%, $P < 0.05$) in this fraction. The postprandial triglycerides rise in VLDL1 was also lower after rosiglitazone (−27%, $P < 0.05$), but this did not result in a significant lower triglyceride AUC. In VLDL2, there were no significant differences in triglyceride AUC and triglyceride dAUC between rosiglitazone and placebo. Fasting FFA levels tended to be lower after treatment with rosiglitazone compared with placebo (0.35 ± 0.03 vs. 0.41 ± 0.03 mmol/l, respectively, $P = 0.06$). Rosiglitazone significantly decreased FFA dAUC (−18%, $P < 0.05$) compared with placebo, leading to significantly lower FFA AUC (−12%, $P < 0.05$). The reductions in FFA AUC and triglyceride dAUC upon treatment with rosiglitazone were not related to the reduction of fasting plasma glucose ($r = 0.14$ and $r = 0.07$, respectively), but they were significantly related to the reduction of ALT ($r = 0.53$ and $r = 0.42$, respectively, $P < 0.05$). A subgroup analysis of subjects on ($n = 8$) and off ($n = 11$) statin treatment showed similar effects of rosiglitazone on plasma triglyceride dAUC (−42 and −34%, respectively) and FFA AUC (−14 and −11%, respectively).

CONCLUSIONS — The main finding of the present study is that rosiglitazone improves postprandial triglyceride metabolism in patients with type 2 diabetes. Because humans are nonfasting most of the day and nonfasting triglycerides are strong predictors of atherosclerosis (2–9), this may convey increased protection from cardiovascular disease in these patients. Significant effects on triglyceride clearance were found in the chylomicron and VLDL1 fractions, suggesting a preferential action of rosiglitazone on large TRL. Finally, rosiglitazone significantly decreased postprandial FFA concentrations.

Increased postprandial lipemia is a common feature of diabetic dyslipidemia and is associated with accelerated atherosclerosis, even in fasting normolipidemic subjects (1–9). The increase of large VLDL1 particles, in particular, is associated with the generation of atherogenic remnants (1). In one study (2), postprandial triglycerides levels distinguished between case subjects with future myocardial infarction and control subjects even better than fasting plasma triglycerides levels. The data from the present study show that rosiglitazone does not change fasting triglycerides but decreases the postprandial triglyceride increase in plasma (−37%), chylomicrons (−20%), and VLDL1 (−27%). Although this did not lead to a significantly lower total triglyceride AUC in plasma, the total triglyceride AUC in the chylomicron fraction significantly decreased by 22%. Whether these effects are sufficient to produce clinical benefit is an open issue. However, it is tempting to hypothesize that the antiatherosclerotic effects observed with TZDs may involve the improvement of postprandial lipemia (18–20). Another interesting aspect of the study is the fact that the effects of rosiglitazone were found on top of statin treatment. In our opinion, this is of interest because statins are used by a majority of patients with type 2 diabetes, and they have been shown to improve postprandial triglyceride metabolism. Whether further improvement of triglyceride metabolism by rosiglitazone exerts additional vascular benefit in diabetic patients on statin treatment remains to be shown.

Data on the effects of TZDs on postprandial lipemia are scarce. In one study

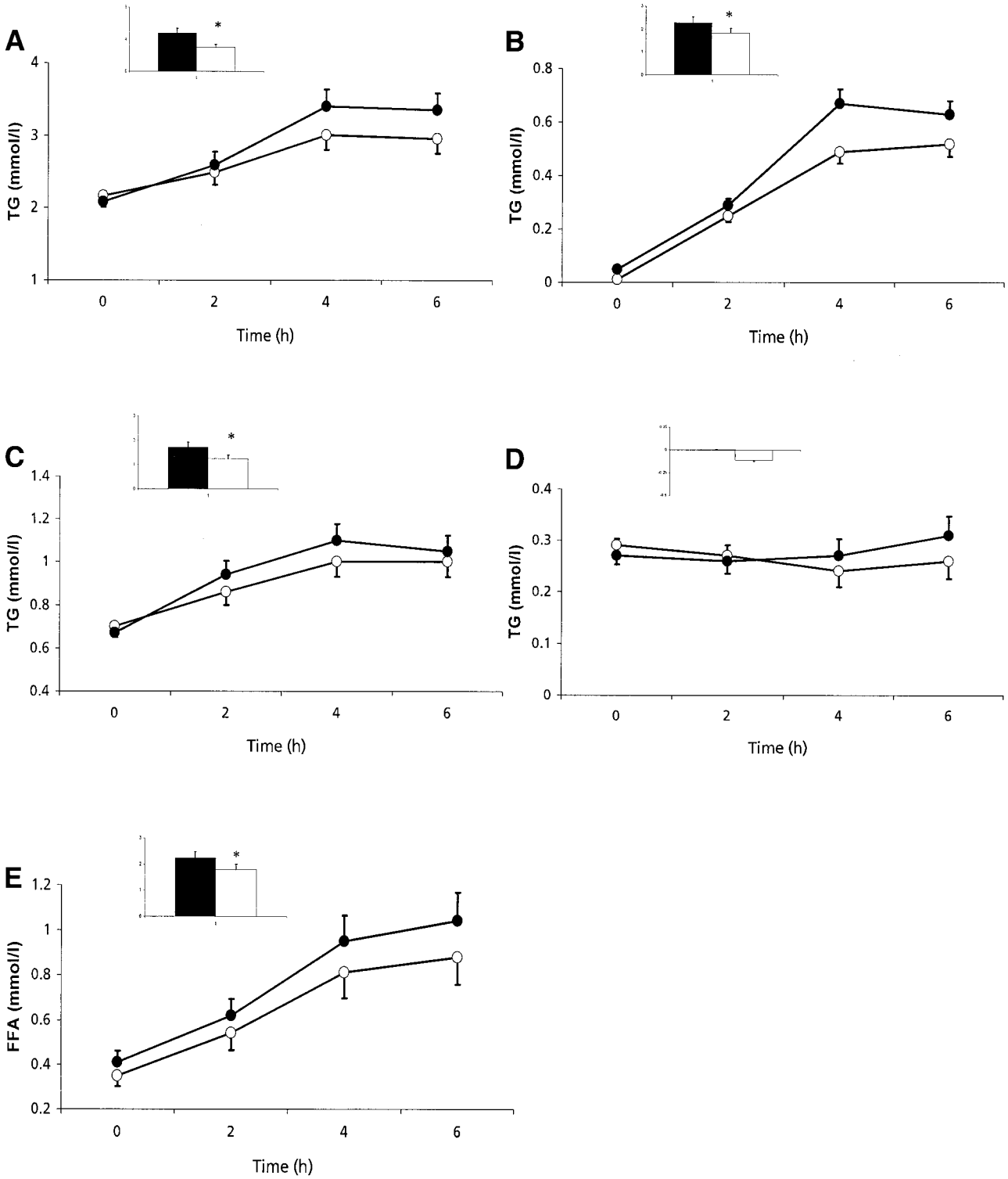

Figure 1—*Mean triglyceride (TG) concentrations during the oral fat-loading test in plasma* (A)*, Sf >400* (B)*, Sf 60–400* (C)*, and Sf 20–60* (D) *and mean plasma FFA concentrations* (E) *after treatment with rosiglitazone* (○) *and placebo* (●)*. Data are means ± SE. Sf, Svedberg flotation rate. Mean dAUCs after treatment with rosiglitazone* (□) *and placebo* (■) *are shown as inserts.* *$P < 0.05$ *vs. placebo.*

(21), there was a lack of effect of pioglitazone on postprandial triglyceride levels. However, in that study, the postprandial triglyceride level was measured only 2 h after a conventional breakfast. Our study was performed in a metabolic ward setting using an oral fat load, and triglyceride levels were measured at 2-h intervals up to 6 h postprandially. The present study is

the first to show improved postprandial triglyceride metabolism by rosiglitazone. Whether rosiglitazone also improves postprandial lipemia during insulin action, such as after a mixed meal, remains to be investigated in future studies.

In most intervention studies with lipid-lowering drugs, the reduction in postprandial lipemia is more or less similar to the reduction in fasting plasma triglycerides, which are the main determinants of postprandial lipemia (22). To the best of our knowledge, this is the first study to describe improved postprandial triglyceride metabolism without lowering fasting triglyceride levels. These results suggest other mechanisms for improved postprandial lipemia than reduced competition for the common lipolytic pathway. First, TZDs are able to upregulate adipocyte LPL production through activation of PPAR-γ (14,15), which could have contributed to the improved incremental triglyceride response after rosiglitazone. Unfortunately, LPL mass and activity were not measured in the present study. Second, it has been demonstrated that rosiglitazone directly stimulates the expression and function of lipoprotein receptor–related protein in vitro (23). Third, rosiglitazone significantly decreased postprandial FFA concentrations, probably by increasing adipocyte FFA trapping, thereby decreasing the source of hepatic VLDL production (12,24–26). Finally, improvement of glycemic control may translate into improvement of postprandial lipemia, especially in patients with poor glycemic control. For example, in patients with poor glycemic control, it has been shown that metformin (27) and glipizide (28) improve postprandial lipemia. In contrast, in diabetic patients with good glycemic control, nateglinide and glibenclamide attenuated hyperglycemia, but they did not improve postprandial lipemia (29). Patients in our study had good glycemic control (HbA_{1c} 6.2%). Rosiglitazone decreased fasting plasma glucose, but not HbA_{1c}, and improved postprandial triglyceride metabolism. Improvement of postprandial lipemia upon treatment with rosiglitazone was not related to the decrease in fasting plasma glucose. Therefore, we propose that it is unlikely that the beneficial effects of rosiglitazone on postprandial lipemia are due solely to improved glycemic control, although it may have contributed.

It has been shown that in the postprandial phase, when chylomicrons and VLDL compete for clearance by LPL, the former are hydrolyzed preferentially (30). This could partly explain the greater beneficial effects of rosiglitazone on postprandial triglyceride clearance in large TRL (chylomicrons and VLDL1) compared with small TRL (VLDL2). Alternatively or additionally, it has been suggested that hepatic VLDL1 and VLDL2 production are independently regulated (31,32). Acute insulin administration suppresses the rates of VLDL1 apoB production but has no effect on VLDL2 apoB production (31). Hence, increased insulin sensitivity by rosiglitazone may have resulted in the suppressed postprandial production of VLDL1 compared with VLDL2, as suggested by our results.

Insulin resistance is commonly associated with biochemical evidence of nonalcoholic steatohepatitis, such as increases in ALT (33). Treatment with rosiglitazone improved insulin sensitivity and significantly reduced ALT. Interestingly, the reduction of ALT upon treatment with rosiglitazone was related to the decreases in FFA AUC and triglyceride dAUC, suggesting reduced liver fat content due to preferential adipocyte FFA storage (33,34).

In conclusion, rosiglitazone improves the metabolism of large TRL and decreases postprandial FFA concentrations in type 2 diabetes. This may have clinical implications, as these effects may contribute to cardiovascular risk reduction.

Acknowledgments— This study was financially supported by a grant from GlaxoSmithKline.

We dedicate this study to the memory of our mentor Prof. Dr. D.W. Erkelens.

References

1. Taskinen MR: Diabetic dyslipidaemia: from basic research to clinical practice. *Diabetologia* 46:733–749, 2003
2. Stampfer MJ, Krauss RM, Ma J, Blanche PJ, Holl LG, Sacks FM, Hennekens CH: A prospective study of triglyceride level, low-density lipoprotein particle diameter, and risk of myocardial infarction. *JAMA* 276:882–888, 1996
3. de Man FH, Castro Cabezas M, van Barlingen HH, Erkelens DW, de Bruin TW: Triglyceride-rich lipoproteins in non-insulin-dependent diabetes mellitus: postprandial metabolism and relation to premature atherosclerosis. *Eur J Clin Invest* 26:89–108, 1996
4. Groot PH, van Stiphout WA, Krauss XH, Jansen H, van Tol A, van Ramshorst E, Chin-On S, Hofman A, Cresswell SR, Havekes L: Postprandial lipoprotein metabolism in normolipidemic men with and without coronary artery disease. *Arterioscler Thromb* 11:653–662, 1991
5. Patsch JR, Miesenbock G, Hopferwieser T, Muhlberger V, Knapp E, Dunn JK, Gotto AM Jr, Patsch W: Relation of triglyceride metabolism and coronary artery disease: studies in the postprandial state. *Arterioscler Thromb* 12:1336–1345, 1992
6. Weintraub MS, Grosskopf I, Rassin T, Miller H, Charach G, Rotmensch HH, Liron M, Rubinstein A, Iaina A: Clearance of chylomicron remnants in normolipidaemic patients with coronary artery disease: case control study over three years. *BMJ* 312:936–939, 1996
7. van Wijk JP, Halkes CJ, De Jaegere PP, Plokker HW, Erkelens DW, Cabezas MC: Normalization of daytime triglyceridemia by simvastatin in fasting normotriglyceridemic patients with premature coronary sclerosis. *Atherosclerosis* 171:109–116, 2003
8. Karpe F, Steiner G, Uffelman K, Olivecrona T, Hamsten A: Postprandial lipoproteins and progression of atherosclerosis. *Atherosclerosis* 106:83–97, 1994
9. Halkes CJ, van Dijk H, de Jaegere PP, Plokker HW, van der Helm Y, Erkelens DW, Cabezas MC: Postprandial increase of complement component 3 in normolipidemic patients with coronary artery disease: effects of expanded-dose simvastatin. *Arterioscler Thromb Vasc Biol* 21:1526–1530, 2001
10. Saltiel AR, Olefsky JM: Thiazolidinediones in the treatment of insulin resistance and type II diabetes. *Diabetes* 45:1661–1669, 1996
11. Lehmann JM, Moore LB, Smith-Oliver TA, Wilkison WO, Willson TM, Kliewer SA: An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma). *J Biol Chem* 270:12953–12956, 1995
12. van Wijk JP, de Koning EJ, Martens EP, Rabelink TJ: Thiazolidinediones and blood lipids in type 2 diabetes. *Arterioscler Thromb Vasc Biol* 23:1744–1749, 2003
13. Miyazaki Y, Glass L, Triplitt C, Matsuda M, Cusi K, Mahankali A, Mahankali S, Mandarino LJ, DeFronzo RA: Effect of rosiglitazone on glucose and non-esterified fatty acid metabolism in type II diabetic patients. *Diabetologia* 44:2210–2219, 2001
14. Shirai K, Itoh Y, Sasaki H, Totsuka M, Murano T, Watanabe H, Miyashita Y: The effect

of insulin sensitizer, troglitazone, on lipoprotein lipase mass in preheparin serum. *Diabetes Res Clin Pract* 46:35–41, 1999
15. Schoonjans K, Peinado-Onsurbe J, Lefebvre AM, Heyman RA, Briggs M, Deeb S, Staels B, Auwerx J: PPARalpha and PPARgamma activators direct a distinct tissue-specific transcriptional response via a PPRE in the lipoprotein lipase gene. *EMBO J* 15:5336–5348, 1996
16. Verseyden C, Meijssen S, Castro Cabezas M: Postprandial changes of apoB-100 and apoB-48 in triglycerides rich lipoproteins in familial combined hyperlipidemia. *J Lipid Res* 43:274–280, 2002
17. Karpe F, Hamsten A: Determination of apolipoproteins B-48 and B-100 in triglyceride-rich lipoproteins by analytical SDS-PAGE. *J Lipid Res* 35:1311–1317, 1994
18. Sidhu JS, Kaposzta Z, Markus HS, Kaski JC: Effect of rosiglitazone on common carotid intima-media thickness progression in coronary artery disease patients without diabetes mellitus. *Arterioscler Thromb Vasc Biol* 24:930–934, 2004
19. Minamikawa J, Tanaka S, Yamauchi M, Inoue D, Koshiyama H: Potent inhibitory effect of troglitazone on carotid arterial wall thickness in type 2 diabetes. *J Clin Endocrinol Metab* 83:1818–1820, 1998
20. Koshiyama H, Shimono D, Kuwamura N, Minamikawa J, Nakamura Y: Inhibitory effect of pioglitazone on carotid arterial wall thickness in type 2 diabetes. *J Clin Endocrinol Metab* 86:3452–3456, 2001
21. Shimono D, Kuwamura N, Nakamura Y, Koshiyama H: Lack of effect of pioglitazone on postprandial triglyceride levels in type 2 diabetes. *Diabetes Care* 24:971, 2001
22. Karpe F: Postprandial lipemia: effect of lipid-lowering drugs. *Atheroscler Suppl* 3: 41–46, 2002
23. Gauthier A, Vassiliou G, Benoist F, McPherson R: Adipocyte low density lipoprotein receptor-related protein gene expression and function is regulated by peroxisome proliferator-activated receptor gamma. *J Biol Chem* 278:11945–11953, 2003
24. Rieusset J, Auwerx J, Vidal H: Regulation of gene expression by activation of the peroxisome proliferator-activated receptor gamma with rosiglitazone (BRL 49653) in human adipocytes. *Biochem Biophys Res Commun* 265:265–271, 1999
25. Bogacka I, Xie H, Bray GA, Smith SR: The effect of pioglitazone on peroxisome proliferators–activated receptor-γ target genes related to lipid storage in vivo. *Diabetes Care* 27:1660–1667, 2004
26. Spiegelman BM: PPAR-γ: adipogenic regulator and thiazolidinedione receptor. *Diabetes* 47:507–514, 1998
27. Jeppesen J, Zhou MY, Chen YD, Reaven GM: Effect of metformin on postprandial lipemia in patients with fairly to poorly controlled NIDDM. *Diabetes Care* 17: 1093–1099, 1994
28. Jeppesen J, Zhou MY, Chen YD, Reaven GM: Effect of glipizide treatment on postprandial lipaemia in patients with NIDDM. *Diabetologia* 37:781–787, 1994
29. Vakkilainen J, Mero N, Schweizer A, Foley JE, Taskinen MR: Effects of nateglinide and glibenclamide on postprandial lipid and glucose metabolism in type 2 diabetes. *Diabetes Metab Res Rev* 18:484–490, 2002
30. Karpe F, Hultin M: Endogenous triglyceride-rich lipoproteins accumulate in rat plasma when competing with a chylomicron-like triglyceride emulsion for a common lipolytic pathway. *J Lipid Res* 36: 1557–1566, 1995
31. Malmstrom R, Packard CJ, Watson TD, Rannikko S, Caslake M, Bedford D, Stewart P, Yki-Jarvinen H, Shepherd J, Taskinen MR: Metabolic basis of hypotriglyceridemic effects of insulin in normal men. *Arterioscler Thromb Vasc Biol* 17: 1454–1464, 1997
32. Prinsen BH, Romijn JA, Bisschop PH, de Barse MM, Barrett PH, Ackermans M, Berger R, Rabelink TJ, de Sain-van der Velden MG: Endogenous cholesterol synthesis is associated with VLDL-2 apoB-100 production in healthy humans. *J Lipid Res* 44:1341–1348, 2003
33. Pagano G, Pacini G, Musso G, Gambino R, Mecca F, Depetris N, Cassader M, David E, Cavallo-Perin P, Rizzetto M: Nonalcoholic steatohepatitis, insulin resistance, and metabolic syndrome: further evidence for an etiologic association. *Hepatology* 35:367–372, 2002
34. Neuschwander-Tetri BA, Brunt EM, Wehmeier KR, Oliver D, Bacon BR: Improved nonalcoholic steatohepatitis after 48 weeks of treatment with the PPAR-gamma ligand rosiglitazone. *Hepatology* 38:1008–1017, 2003