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The effect of high-dose simvastatin on free fatty acid metabolism in patients with type 2 diabetes mellitus

William L. Isley[a,*], William S. Harris[b], John M. Miles[a]

[a]Endocrine Research Unit, Division of Endocrinology, Nutrition, and Metabolism, Mayo Clinic, Rochester, MN 55905, USA
[b]Saint Luke's Lipid and Diabetes Research Center, Mid-America Heart Institute, Kansas City, MI, USA

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Abstract

Statins improve all major lipid fractions, reduce coronary heart disease risk, and may have a minor effect on glucose tolerance. A reduction in free fatty acid flux and concentrations could be partly responsible for these effects. We measured nocturnal and postprandial plasma palmitate concentrations and rate of appearance (R_a) on 2 occasions in 12 obese dyslipidemic subjects with type 2 diabetes mellitus, using a single-blind, crossover format (placebo followed by simvastatin, 80 mg/d), and also on 1 occasion in 6 untreated control subjects. The diabetic subjects had increased average nocturnal (127 ± 13 vs 80 ± 10 μmol/L, $P < .05$) and 2-hour postprandial (49 ± 6 vs 17 ± 2 μmol/L, $P < .001$) palmitate concentrations, as well as increased nocturnal (31.6 ± 3.7 vs 19.5 ± 3.7 mmol/m^2 over 9 hours, $P < .05$) and postprandial (11.5 ± 3.7 vs 5.5 ± 3.7 mmol/m^2 over 4 hours, $P < .005$) integrated palmitate R_a compared to normal controls. High-dose simvastatin reduced serum triglycerides by 35% but had no effect on plasma palmitate concentrations or R_a. These results suggest that the triglyceride-lowering effect of statins is not mediated through an effect on FFA metabolism.

1. Introduction

Disordered lipid metabolism is a hallmark of type 2 diabetes mellitus [1]. Increased delivery of free fatty acids (FFA) to the liver leads to an overproduction of very low density lipoprotein (VLDL) triglyceride [2,3] that contributes to the characteristic dyslipidemia (high triglycerides and low high-density lipoprotein cholesterol [HDL-C]) of type 2 diabetes mellitus [4]. Hydroxymethyl glutaryl CoA reductase inhibitors, or statins, are widely used in type 2 diabetic patients and have been shown to decrease cardiovascular events in individuals with this condition [5,6]. Whereas the primary effect of statins is a reduction in circulating low-density lipoprotein cholesterol (LDL-C), these agents also affect other lipid fractions. Statins are known to reduce triglycerides and increase HDL-C [7,8]. The molecular mechanism responsible for the triglyceride-lowering effect of statins is not precisely known. It is possible that these agents could reduce hepatic FFA delivery. Reports which suggest that statin treatment may prevent type 2 diabetes mellitus [9] and improve insulin sensitivity in patients with known diabetes [10,11] are consistent with such a mechanism, as lowering of plasma FFA is thought to improve insulin sensitivity [12]. However, available data concerning direct effects of statins on plasma FFAs in humans are contradictory [13-15]. To our knowledge, the effect of statin agents on plasma FFA kinetics and postprandial FFA metabolism has not been previously investigated. We therefore undertook the present study to assess the effect of high-dose simvastatin therapy on FFA metabolism in patients with type 2 diabetes mellitus.

2. Research design and methods

2.1. Study subjects

All procedures involving human subjects were reviewed and approved by the Institutional Review Board of Saint Luke's Hospital of Kansas City. Informed, written consent was obtained from the subjects after the nature of the study was explained.

Six healthy normal subjects with body mass index of 29 kg/m^2 or lower (fasting triglycerides <150 mg/dL in 5 subjects, fasting triglycerides 203 mg/dL in 1 subject) and

* Corresponding author. Tel.: +1 507 284 3289; fax: +1 507 284 5745.
E-mail address: isley.william@mayo.edu (W.L. Isley).

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Table 1
Baseline characteristics (mean ± SD) of 6 (4 men, 2 women) nondiabetic control subjects and 12 (7 men, 5 women) subjects with type 2 diabetes mellitus

	Control subjects	Diabetic subjects
Age (y)*	39 ± 14.9	55.7 ± 7.6
Weight (kg)*	85.8 ± 5.9	103.9 ± 19.2
BMI (kg/m^2)**	26.7 ± 2.2	35.8 ± 5.7
HbA_{1c} (%)	–	8.3 ± 1.5
Cholesterol (mg/dL)**	177 ± 24	242 ± 38
Triglycerides (mg/dL)**	129 ± 47	274 ± 58
HDL-C (mg/dL)	36 ± 12	40 ± 9
VLDL-C (mg/dL)**	26 ± 9	50 ± 18
LDL-C (mg/dL)	115 ± 19	148 ± 38

BMI indicates body mass index.
* $P < .04$ control subjects vs diabetic subjects.
** $P < .002$ control subjects vs diabetic subjects.

12 obese subjects with type 2 diabetes mellitus and fasting hypertriglyceridemia (200-500 mg/dL) were recruited for these investigations. Baseline characteristics of the study subjects are given in Table 1. Screening tests were generally determined before a 4-week placebo run-in period. Mean fasting plasma glucose concentrations in the control subjects were 84 ± 9 mg/dL (mean ± SD). Individuals with serum creatinine of more than 1.5 mg/dL, alanine aminotransferase, or aspartate aminotransferase 2× or higher than the upper limit of normal, blood pressure higher than 170 mm Hg systolic, or higher than 110 mm Hg diastolic, a recent (within 3 months) cardiovascular event, or symptomatic cardiac disease were excluded. The antihyperglycemic therapies of the diabetic subjects were maintained without change in dosing throughout the study and included diet (2), sulfonylurea (1), sulfonylurea plus metformin (2), sulfonylurea plus glitazone (3), metformin plus glitazone (2), sulfonylurea plus metformin plus glitazone (1), and insulin plus glitazone (1).

Only 1 diabetic subject was taking prescription lipid-lowering medication (atorvastatin, 40 mg BID) at the time of study recruitment. The medication was discontinued 4 weeks before beginning the study. Of the 12 diabetic subjects, 10 were on stable antihypertensive medication throughout the study. Three of the female diabetic subjects were taking oral estrogens and one was taking an estrogen-progestin combination. Two diabetic subjects were taking thyroid hormone replacement. One of the female control subjects took oral estrogen (prescribed for premature menopause) and replacement thyroid hormone throughout the study.

2.2. Experimental protocol

After a 4-week placebo run-in period, diabetic subjects received placebo (identical in appearance to simvastatin) for 12 weeks, followed by simvastatin 80 mg daily taken at bedtime for 12 weeks, in a single-blind, crossover fashion, each subject serving as his/her own control. The study subjects were blinded to the statin or placebo treatment. In the diabetic subjects, FFA turnover studies were performed at the end of each treatment period. The normal subjects were studied on 1 occasion only. Subjects were instructed to refrain from alcohol consumption and vigorous exercise for 48 hours before the study.

Subjects were admitted to the inpatient Clinical Study Unit at 4:00 PM the day before the study. At 6:00 PM, a mixed meal (50% carbohydrate, 30% fat, and 20% protein) was given containing calories equal to 45% of basal energy expenditure, one third of the estimated energy requirements for weight maintenance. At 8:00 PM, an infusion cannula was placed in a forearm vein and a retrograde cannula in a contralateral hand vein; the hand was heated for sampling of arterialized venous blood [16]. The 3 catheters were kept patent by controlled (15 mL/h each) infusions of 0.9% NaCl. Room lights were turned off at 10:00 PM. Beginning at 10:00 PM (−600 min), an infusion of [9,10-^{3}H] palmitate (~0.3 μCi/min) was started and continued to the end of the study (12:00 PM, or +240 min). At 8:00 AM (0 min), a mixed breakfast with macronutrient content identical to the previous evening's meal was given. Blood samples were taken hourly from −540 minutes (11:00 PM) through −60 minutes and at −30, −20, −10, 0, 30, 60, 120, 180, and 240 minutes for determination of plasma palmitate concentration and specific activity as well as plasma glucose concentration. Care was taken to minimize sleep disturbance during blood sampling.

2.3. Analyses

[9,10-^{3}H] Palmitate (specific activity 60 Ci/mmol; American Radiolabeled Chemicals, St Louis, Mo) was prepared for infusion as previously described [17]. Plasma palmitate specific activity was measured by high-performance liquid chromatography [18], using [$^2H_{31}$] palmitate as an internal standard for determination of palmitate concentrations [19]. All FFA analyses were done on samples collected in EDTA and paraoxon, the latter to inhibit lipoprotein lipase and thus prevent ex vivo triglyceride hydrolysis [20].

Plasma glucose concentrations were determined on a centrifugal analyzer using a glucose oxidase method. HbA_{1c} was determined by high-performance liquid chromatography on a BioRad Variant instrument (Hercules, Calif).

For determination of lipids and lipoproteins, blood was drawn into serum separator tubes. Serum total cholesterol, triglyceride, and HDL-C were measured enzymatically on a Cobras Fara II (Roche) using enzymatic reagents and procedures standardized by the Lipid Standardization Program of the CDC/NIH and Pacific Biometrics Foundation (Seattle, Wash) proficiency surveys. High-density lipoprotein cholesterol was determined in the serum supernate after precipitation of VLDL and LDL with dextran sulfate–magnesium chloride as described by Warnick et al [21]. Very low density lipoprotein cholesterol and LDL-C concentrations were determined by the Friedewald equation [22], or if triglycerides were greater than 400 mg/dL, by β-quantitation. In this procedure, the VLDL fraction

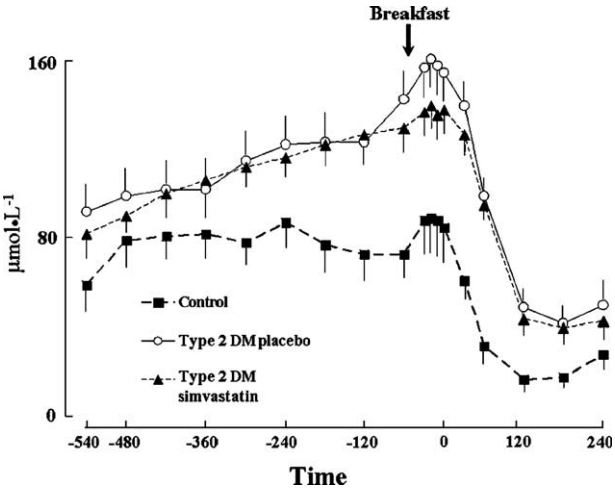

Fig. 1. Plasma palmitate concentrations (mean ± SE) in controls and diabetic subjects on placebo.

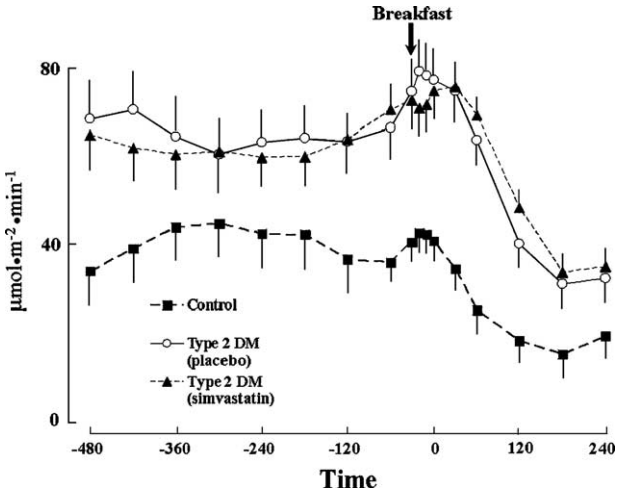

Fig. 2. Plasma palmitate appearance (R_a) (mean ± SE) in controls and diabetic subjects treated with placebo.

was isolated from whole serum by ultracentrifugation at 100 000 rpm for 2 hours in a Beckman TL-100 using a TLA100.3 rotor. The VLDL layer was removed by aspiration, and the cholesterol content of the infranatant containing HDL and LDL was determined as described above. The LDL-C value was calculated by subtraction of the HDL-C previously measured, and the VLDL-C was calculated as the total cholesterol minus the infranatant cholesterol.

2.4. Calculations and statistical analysis

Palmitate rate of appearance (R_a) was calculated using Steele's equations [23] for non–steady-state conditions assuming an effective palmitate volume of distribution of 90 mL/kg. Integrated nocturnal (−540 to 0 minutes) and postprandial (0 to 240 minutes) R_a were calculated for each subject on each study day, using area under the curve analysis. Mean nocturnal (average of values from −540 to 0 minutes) and 2-hour postprandial plasma palmitate concentrations were also calculated.

Using similar techniques in assessing the effect of insulin sensitizers on FFA metabolism, we were able to show ~25% reduction in postprandial FFA concentrations [24]. Given our study population, we would have had at least 90% power to detect a 25% reduction in FFA at the 95% confidence level.

The statistical significance of comparisons between diabetic subjects at baseline and normal control subjects was determined by using Student *t* test for independent samples. In the diabetic subjects, post-simvastatin values were compared with placebo values using a paired Student *t* test.

3. Results

Total cholesterol, VLDL cholesterol, and triglycerides were greater in the diabetic subjects than in the controls ($P < .002$; Table 1). Simvastatin therapy was tolerated well by all diabetic subjects with no major side effects. There was no significant change in glycemic control (HbA_{1c} 8.3% ± 1.4% on placebo, 8.6% ± 1.5% on simvastatin). Serum LDL-C was reduced by 49%, whereas VLDL-C and triglycerides were reduced by 33% and 35%, respectively, by simvastatin compared to placebo ($P < .01$; data not shown). Serum HDL-C increased by 6% with high-dose simvastatin compared to placebo ($P = .056$, data not shown).

Table 2
Integrated rates of palmitate rate of appearance (area under the curve analysis) and plasma concentration in normal subjects and in diabetic subjects after treatment with placebo or simvastatin

Subject group	Rate of appearance		Plasma concentration	
	Nocturnal (mmol/m^2 per 9 h)	Postprandial (mmol/m^2 per 4 h)	Nocturnal mean (μmol/L)	Two-hour postprandial (μmol/L)
Control	19.5 ± 3.7	5.5 ± 1.1	80 ± 10	17 ± 2
Type 2 diabetes mellitus				
Placebo	31.6 ± 3.7*	11.5 ± 1.5**	127 ± 13*	49 ± 6***
Simvastatin	30.3 ± 4.0*	12.5 ± 1.7**	118 ± 9*	44 ± 5***

* $P < .05$, diabetic subjects vs control.
** $P < .005$, diabetic subjects vs control.
*** $P < .001$, diabetic subjects vs control.

Palmitate concentrations are shown in Fig. 1. Mean nocturnal and 2-hour postprandial concentrations were higher in diabetic subjects than in controls ($P < .05$ and $P < .001$, respectively; Table 2). Palmitate R_a is shown in Fig. 2. Integrated R_a was higher in diabetic subjects than in controls during the night ($P < .05$) and during the postprandial period ($P < .005$) (Table 2). Simvastatin had no effect on integrated nocturnal or postprandial palmitate R_a (Table 2, Fig. 2).

4. Discussion

Consistent with a previous report from our laboratory which compared obese subjects with poorly controlled type 2 diabetes to lean nondiabetic controls [24], nocturnal and postprandial palmitate concentrations and R_a were higher in obese subjects with poorly controlled type 2 diabetes compared to nonobese (but overweight) controls. Simvastatin had no effect on nocturnal or postprandial palmitate concentrations or kinetics in the diabetic subjects, but it reduced triglycerides by 35%. Simvastatin had no effect on glycemic control in the diabetic subjects either.

A suppressive effect of statins on plasma FFA, if it were to occur, would most likely be mediated at the level of the fat cell, as adipose tissue lipolysis is the major source of plasma FFA [25]. Previous studies have reported conflicting results regarding the effect of statins on FFA metabolism. Atorvastatin has been shown to decrease hepatic [26] and plasma [27] FFA in rats. The implications of observations in rodents are uncertain, however, considering known species differences in FFA and triglyceride metabolism [28]. Five small studies in diabetic and nondiabetic humans have failed to demonstrate an effect of statins (pravastatin, simvastatin, and fluvastatin) on FFA [13,29-31]. A large multicenter trial, the Diabetes Atorvastatin Lipid Intervention (DALI) study, randomized 217 dyslipidemic subjects with type 2 diabetes to placebo, 10-mg atorvastatin or 80-mg atorvastatin for 30 weeks [15]. The investigators observed a 35% and 45% reduction in triglycerides at the low and high atorvastatin doses compared with placebo ($P < .001$), and a 20% to 25% reduction in fasting FFA in the 2 atorvastatin groups compared with placebo ($P < .05$) [15]. A possible explanation for the discrepancy between this and our study could relate to an analytical artifact. Triglyceride-rich lipoproteins can undergo ex vivo hydrolysis unless tubes containing an inhibitor of lipoprotein lipase are used for blood collection; this phenomenon occurs in proportion to the triglyceride content in the blood sample [32]. Because atorvastatin markedly lowered plasma triglyceride concentrations in the DALI study, the amount of FFA generated by the ex vivo hydrolysis of triglycerides might likewise have been reduced, resulting in lower apparent FFA concentrations on atorvastatin. It is not stated in the DALI report if an inhibitor of lipolysis was used. In our study, paraoxon, an inhibitor of lipoprotein lipase, was used to prevent such an artifactual rise in FFA.

Our study is the first to investigate the possible effects of statins on FFA kinetics, and the first to report postprandial FFA data. The results of the present study indicate that the magnitude of postprandial abnormalities in FFA metabolism is also greater than nocturnal/fasting abnormalities when overweight control subjects are studied. Our failure to observe an effect of high-dose simvastatin on postprandial palmitate concentrations and kinetics in diabetic subjects is strong evidence against an important effect of simvastatin on FFA metabolism.

In the liver, fatty acids are potentially available from several sources, including de novo lipogenesis, direct hepatic uptake of triglycerides from lipoprotein triglycerides and cholesterol esters, and plasma FFA. Of these, the one that is best established for an effect on hepatic VLDL production in humans is FFA [2]. We observed neither a change in plasma FFA concentrations nor a change in FFA flux in diabetic patients treated with high-dose simvastatin. Hence our results indicate that statins influence VLDL synthesis and secretion via a mechanism other than through an effect on FFA availability. The most likely alternative mechanism is an effect on the intrahepatic cholesterol pool [33,34] or increased delipidation of VLDL [35].

In conclusion, although statins have multiple beneficial effects on plasma lipid levels, their effects appear to be independent of an effect on FFA metabolism. Pharmacological agents that target lipolytic dysregulation in insulin-resistant states as well as lower atherogenic lipoproteins are in development and may be beneficial in treating the multiple metabolic abnormalities in patients with type 2 diabetes mellitus [36].

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