Nocturnal and Postprandial Free Fatty Acid Kinetics in Normal and Type 2 Diabetic Subjects

Effects of Insulin Sensitization Therapy

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Whether free fatty acid (FFA) rate of appearance (R_a) is increased in type 2 diabetes is controversial. To characterize nocturnal and postprandial abnormalities in FFA kinetics and to determine the effects of treatment with insulin sensitizers on lipolysis, we measured palmitate R_a in control subjects ($n = 6$) and individuals with poorly controlled, sulfonylurea-treated type 2 diabetes ($HbA_{1c} = 8.7 \pm 0.2\%$, $n = 20$), the latter before and at the end of 12 weeks of treatment with troglitazone (600 mg/day, $n = 4$), metformin (~2,000 mg/day, $n = 8$), or placebo ($n = 8$). Subjects consumed a standard breakfast at 0800 h. Results in control subjects and type 2 diabetic subjects were compared at baseline. Integrated nocturnal FFA R_a ($AUC_{1:00–8:00\ A.M.}$) was ~50% higher in type 2 diabetic subjects than in control subjects (29.4 ± 3.0 vs. 19.4 ± 3.9 mmol · m^{-2} · 7 h^{-1}, respectively, $P < 0.05$), whereas postprandial palmitate R_a ($AUC_{0–240\ min}$) was almost threefold higher in type 2 diabetic subjects than in control subjects (14.2 ± 1.7 vs. 5.3 ± 1.0 mmol · m^{-2} · 4 h^{-1}, respectively, $P < 0.01$). After troglitazone treatment, nocturnal palmitate R_a did not change, but postprandial palmitate R_a decreased by ~30% ($P < 0.05$). Palmitate kinetics did not change with metformin or placebo treatment. In summary, nocturnal and postprandial FFA R_a is increased in type 2 diabetes. Postprandial lipolysis appears to be preferentially improved by thiazolidinediones compared with nocturnal lipolysis. *Diabetes* 52:675–681, 2003

Patients with type 2 diabetes have resistance to the antilipolytic effects of insulin on adipose tissue (1,2). This dysregulation of adipose tissue lipolysis has been implicated as a major cause of the abnormalities in lipoprotein and glucose metabolism that are characteristic of type 2 diabetes (3). However, plasma free fatty acid (FFA) turnover has been reported to be both increased (4) and normal (5–8) in type 2 diabetes. FFA tracer studies in patients with type 2 diabetes have generally been performed under postabsorptive conditions (4,5,7) or during a hyperinsulinemic-euglycemic clamp (1,2); little information is available regarding nocturnal and postprandial FFA metabolism. In fact, patients with poorly controlled type 2 diabetes exhibit an increase in plasma FFA concentrations during the night (9), but it is not known whether this is the result of increased release of FFA into the systemic circulation or decreased plasma FFA clearance. An understanding of fatty acid metabolism during nocturnal and absorptive conditions is important because postabsorptive measurements may not necessarily reflect conditions at other times of the day.

The treatment of type 2 diabetes has been revolutionized by the availability of medications, including biguanides and thiazolidinediones, which improve insulin action on glucose metabolism. In addition, some (10,11) but not all (12) studies suggest that these agents may improve abnormalities in FFA metabolism in the postabsorptive state and during hyperinsulinemia. However, it is not known whether insulin sensitizers affect nocturnal and postprandial FFA kinetics.

The present studies were undertaken to *1*) characterize nocturnal and postprandial FFA kinetics in poorly controlled type 2 diabetic subjects and to *2*) investigate the effects of two insulin sensitizers, metformin and troglitazone, on FFA metabolism. We hypothesized that FFA release into plasma is increased during the night and during meal absorption in subjects with type 2 diabetes and that treatment with insulin sensitizers decreases the rate of FFA appearance.

RESEARCH DESIGN AND METHODS

Subjects. Six healthy, nondiabetic subjects (three men and three women; age 27 ± 2 years; BMI 21.4 ± 0.8 kg/m^2) and 20 patients with type 2 diabetes (11 men and 9 women; age 56 ± 3 years; BMI 33.3 ± 1.3 kg/m^2) participated in the study. Of the 20 diabetic subjects, 10 were on stable antihypertensive medication and 6 were on stable lipid-lowering medication throughout the study. Individuals with serum creatinine >1.5 mg/dl, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2× the upper limit of normal, blood pressure >170 mmHg systolic or >110 mmHg diastolic, recent (within 3 months) cardiovascular event, or symptomatic cardiac disease were excluded. All diabetic subjects were being treated with sulfonylurea monotherapy; HbA_{1c} concentrations were 8.7 ± 0.2%. During a 6-week prestudy baseline period, the diabetic subjects were started on micronized glyburide in place of their usual sulfonylurea, 3 mg daily for 2 weeks and then 6 mg daily for the final 4 weeks. Subjects who continued to have a fasting plasma glucose >126 mg/dl at the end of the baseline period were randomized to receive troglitazone (600 mg/day, $n = 4$), metformin (starting dose of 500 mg/day and increased by 500 mg/day as tolerated every 5–7 days in divided doses to a maximum of 2,500

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AUC, area under the curve; FFA, free fatty acid; LPL, lipoprotein lipase; MCR, metabolic clearance rate; R_a, rate of appearance; SNS, sympathetic nervous system.

mg/day, $n = 8$), or placebo ($n = 8$) for 12 weeks. The protocol was approved by the Saint Luke's Hospital Institutional Review Board. Consent was obtained from the subjects after the nature of the study was explained.

Experimental protocol. Diabetic subjects were studied on two occasions: once at the end of the baseline period before randomization (week 0) and a second time at the end of the study period (week 12). Control subjects were studied on one occasion only. Subjects were admitted to the inpatient Clinical Study Unit at 4:00 P.M. the day before the study. At 1800 h, a mixed meal (50% carbohydrate, 30% fat, and 20% protein) was given containing calories equal to one-third of energy requirements for weight maintenance, estimated at 1.3 × basal energy expenditure (Harris-Benedict equation). At 2000 h, 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. Room lights were turned off at 2200 h. Beginning at midnight, [9,10-^{3}H]palmitate was infused at 0.3 μCi/min. At 0800 h (0 min), a mixed breakfast with a macronutrient content identical to the previous evening's meal was given. Blood samples were taken hourly from −420 min (0100 h) through −60 min and at −30, −20, −10, 0, 30, 60, 120, 180, and 240 min for determination of palmitate concentration and specific activity and determination of plasma glucose, insulin, and growth hormone concentrations. Care was taken to avoid disturbance of sleep during blood sampling.

Analyses. [9,10-^{3}H]palmitate (specific activity 60 Ci/mmol; American Radiolabeled Chemicals, St. Louis, MO) was prepared for infusion as previously described (13,14). Plasma palmitate specific activity was measured by high-performance liquid chromatography (13); [$^2H_{31}$]palmitate was used as an internal standard for determination of palmitate and total FFA concentrations (15). Standard radioimmunoassays were used to measure plasma insulin (16) and growth hormone (17). 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, CA).

Calculations and statistical analysis. Palmitate rate of appearance (R_a) in plasma was calculated using Steele's equations for non–steady-state conditions with an effective palmitate volume of distribution of 90 ml/kg (18). Total nocturnal (1:00 A.M. to 8:00 A.M.) and postprandial (8:00 A.M. to noon) lipolytic rate was calculated for each subject on each study day, using area-under-the-curve (AUC) analysis. The metabolic clearance rate (MCR) of palmitate was calculated by dividing palmitate R_a by plasma palmitate concentration. The statistical significance of comparisons between diabetic subjects and normal control subjects were determined by using Student's t test for independent samples. Posttreatment values were compared with baseline values in the diabetic subjects by using Student's t test for paired samples.

RESULTS

There were no adverse events in the study. No subject failed to qualify on glycemic grounds at the end of the baseline period. Six of the eight metformin subjects reached a maintenance metformin dose of 2,500 mg/day without difficulty. Two of the subjects took a lower maintenance dose (1,250 and 2,000 mg/day) because of gastrointestinal side effects at higher doses. The four subjects who took troglitazone tolerated it well.

Baseline hormone concentrations. Nocturnal and prebreakfast plasma insulin and C-peptide concentrations during the baseline study are shown in Fig. 1. Insulin and C-peptide levels were higher throughout in type 2 diabetic subjects than in control subjects. In the diabetic subjects, insulin and C-peptide decreased between 0100 and 0400 h and were stable thereafter. Insulin and C-peptide were unchanged in the control subjects. Plasma growth hormone concentrations were significantly lower in the diabetic subjects compared with control subjects (Table 1). There was no change in growth hormone during the night in either group of subjects.

Baseline FFA metabolism. Palmitate R_a at baseline in the 20 diabetic subjects and 6 control subjects is shown in Fig. 2. In the diabetic subjects, palmitate R_a was ~85 μmol · m^{-2} · min^{-1} during the night, with a slight decrease to ~75 μmol · m^{-2} · min^{-1} at 0500 h and a subsequent increase to ~85 μmol · m^{-2} · min^{-1} at 0730 h. In contrast,

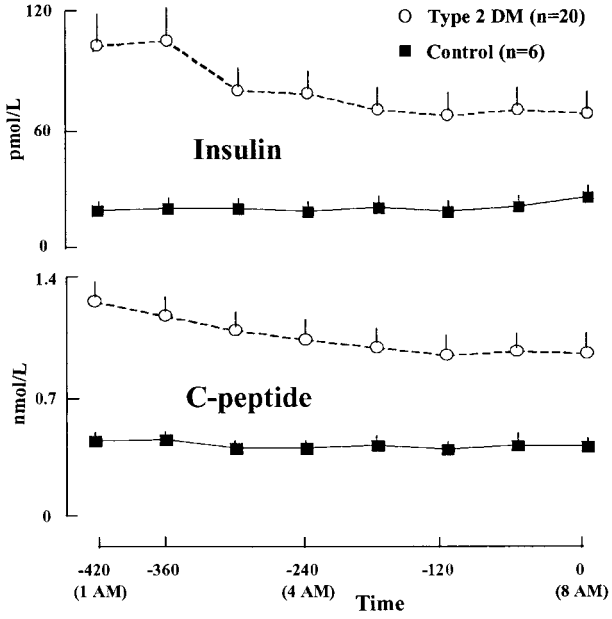

FIG. 1. Plasma insulin and C-peptide concentrations in healthy volunteers and type 2 diabetic subjects at baseline, from 1:00 A.M. (0100 h) to 8:00 A.M. (0 min).

palmitate R_a decreased in the control subjects from ~65 μmol · m^{-2} · min^{-1} at 0100 h to ~40 μmol · m^{-2} · min^{-1} by 0500 h and remained at that level until 0800 h. Changes in palmitate R_a were mirrored by changes in total plasma FFA concentrations (Fig. 3). In the diabetic subjects, FFA concentrations increased between 0100 h and ,800 from ~510 to ~625 μmol/l. In the control subjects, FFA concentrations decreased from ~470 to ~305 μmol/l. The MCR of palmitate decreased slightly during the night in the diabetic subjects (from 663 ± 66 ml · m^{-2} · min^{-1} at 2:00–4:00 A.M. to 563 ± 55 ml · m^{-2} · min^{-1} at 5:00–7:00 A.M., $P < 0.005$) but increased postprandially (from 606 ± 85 ml · m^{-2} · min^{-1} for the 7:30–8:00 A.M. interval to 1,195 ± 165 ml · m^{-2} · min^{-1} for the 9:00–11:00 A.M. interval, $P < 0.0001$; data not shown). In the control subjects, palmitate MCR remained constant during the night and increased postprandially (532 ± 91 ml · m^{-2} · min^{-1} for the 7:30–8:00 A.M. interval to 1,101 ± 198 ml · m^{-2} · min^{-1} for the 9:00–11:00 A.M. interval, $P < 0.02$; data not shown). There was no difference in either nocturnal or postprandial palmitate MCR between diabetic subjects and control subjects. Values for nocturnal and postprandial lipolysis are shown in Table 2. Nocturnal integrated palmitate R_a was ~50% greater at baseline in the diabetic subjects compared with control subjects, whereas postprandial R_a was nearly 200% higher in the diabetic subjects compared with control subjects.

Baseline nocturnal glucose concentrations. Nocturnal plasma glucose concentrations are shown in Fig. 4. In control subjects, glucose concentrations were 4.9 ± 0.1 mmol/l at 0100 h and did not change during the night. In diabetic subjects at baseline, plasma glucose concentrations were 8.7 ± 0.4 mmol/l at 0100, decreased slightly to 8.1 ± 0.4 mmol/l by 0400 h, then increased to 9.5 ± 0.4 mmol/l by 0800 h. There was an increase in plasma glucose between 0400 and 0800 h in 17 of 20 diabetic subjects (85%). When data from 0400 to 0800 h were analyzed, there

TABLE 1
Plasma growth hormone concentrations (μg/l) in control and type 2 diabetic subjects during the baseline study

	Time (min)							
	−420	−360	−300	−240	−180	−120	−60	0
Control subjects (n = 6)	2.9 ± 0.8	2.6 ± 0.5	1.3 ± 0.3	0.8 ± 0.3	1.8 ± 0.6	2.1 ± 0.6	2.1 ± 0.9	0.7 ± 0.2
*All diabetic subjects (n = 20)	0.7 ± 0.08	0.9 ± 0.13	0.8 ± 0.14	0.8 ± 0.08	0.7 ± 0.06	0.9 ± 0.14	0.7 ± 0.09	0.8 ± 0.10

Data are means ± SD. *P < 0.001 vs. control subjects.

was no correlation between Δ palmitate R_a and Δ plasma glucose concentration.

Effects of insulin sensitization therapy. HbA_{1c} values were similar in the three groups of diabetic subjects and decreased significantly with metformin (from 8.9 ± 0.4 to 8.0 ± 0.4%, P < 0.05) and troglitazone (from 8.6 ± 0.3 to 7.4 ± 0.2%, P < 0.05) therapy. HbA_{1c} did not change significantly in the placebo group (from 8.7 ± 0.3 to 9.0 ± 0.4%). There was no change in total serum cholesterol or triglycerides in the three groups. HDL cholesterol did not change in the placebo or metformin groups, but increased significantly after 12 weeks of troglitazone (from 32 ± 6 to 41 ± 5 mg/dl, P < 0.05).

There was no change in nocturnal or postprandial lipolysis after 3 months of placebo or metformin treatment (Table 2). Nocturnal lipolysis did not change after troglitazone treatment, but there was a significant decrease in postprandial lipolysis after troglitazone (P < 0.05). The decrease in postprandial lipolysis, expressed as percentage change from baseline values, was significantly greater with troglitazone than placebo (Δ = −29 ± 4 vs. 5 ± 12%, P < 0.02). Nocturnal and postprandial palmitate R_a before and after troglitazone therapy is shown in Fig. 5. Only four subjects received troglitazone therapy because the drug was voluntarily withdrawn from the market during the course of the study.

DISCUSSION

The results of this study demonstrate that individuals with poorly controlled type 2 diabetes have around-the-clock abnormalities in the regulation of adipose tissue lipolysis, with increased release of FFAs both during the night and during the postprandial period. Our study is the first to report nocturnal FFA kinetics in diabetic subjects; to our knowledge, the only previous study of postprandial FFA kinetics in diabetic individuals was that of Kelley et al. (6), who found impaired suppression of FFA appearance after ingestion of a liquid meal. In the present study, palmitate R_a remained fairly constant during the night in the diabetic subjects at a time when there was an increase in plasma glucose concentrations. In contrast, palmitate R_a decreased during the night in healthy control subjects, and there was no increase in plasma glucose concentrations. In diabetic subjects, there was a decrease in postprandial but not nocturnal lipolysis after treatment with troglitazone, whereas there was no effect of metformin therapy on rates of lipolysis.

Since insulin is the major regulator of basal adipose tissue lipolytic activity (19,20), the higher rates of nocturnal and postprandial lipolysis in our diabetic subjects compared with control subjects were due at least in part to resistance to the antilipolytic effects of insulin in adipose tissue. In fact, the diabetic subjects had higher lipolytic rates in spite of threefold greater plasma insulin concentrations compared with control subjects. Resistance to insulin-mediated suppression of FFA concentrations (21) and kinetics (1) has been observed previously in subjects with type 2 diabetes. Our diabetic subjects were obese, and obesity itself is associated with increased FFA release and a reduced antilipolytic effect of insulin (22). However,

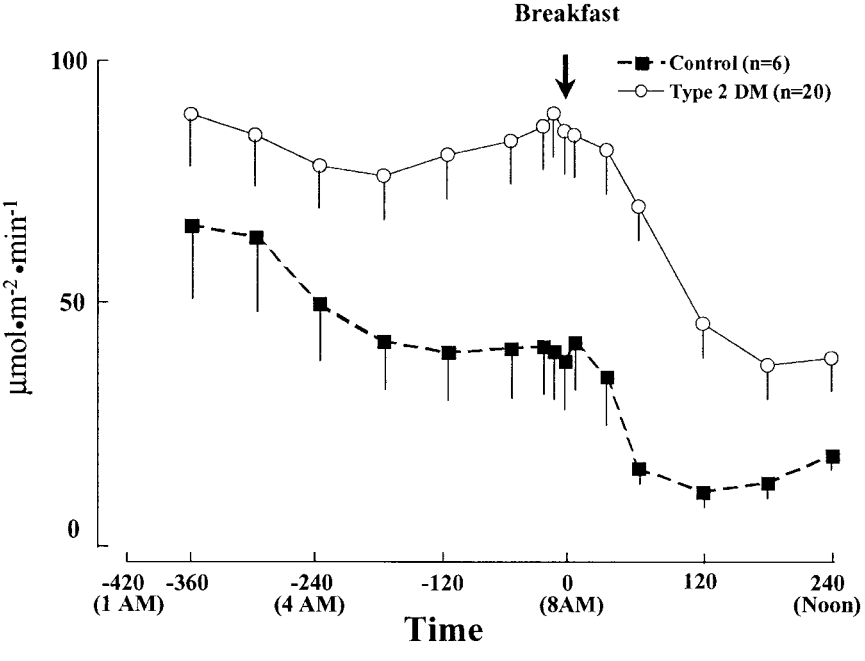

FIG. 2. Palmitate rate of appearance in healthy control subjects and type 2 diabetic subjects at baseline, from 0100 h (−420 min) to noon (240 min).

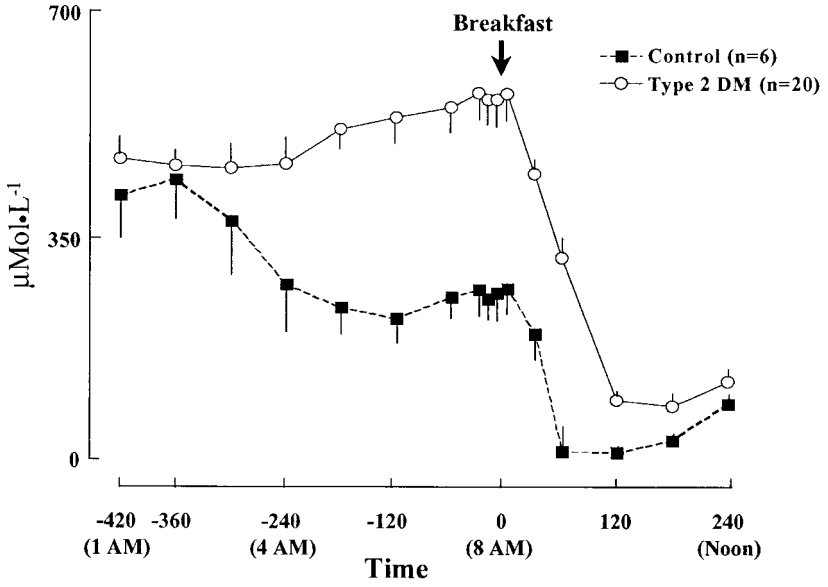

FIG. 3. Plasma FFA concentrations in healthy control subjects and type 2 diabetic subjects at baseline, from 0100 h (−420 min) to noon (240 min).

a recent study found that insulin-mediated suppression of lipolysis was more impaired in obese type 2 diabetic subjects than in nondiabetic, obese control subjects under insulin clamp conditions, and that systemic palmitate release correlated with visceral fat area (2).

In the present study, fatty acid kinetics were expressed in relationship to body surface area. The method used to express FFA kinetics can have a considerable effect on the interpretation of the results when there are differences in body composition between groups. When FFA turnover is expressed per unit of total body weight or per unit of fat mass, obese subjects routinely have lower flux rates than lean subjects, whereas when FFA turnover is expressed per kilogram of fat-free mass, obese subjects have the same or greater flux rates (23). Therefore, expressing FFA kinetics per unit of fat-free mass or body surface area (as in the present study), which correlates closely with energy requirements (24), may provide the best index to determine whether rates of FFA appearance are normal or abnormal.

The effect of type 2 diabetes on basal FFA kinetics is unclear because of conflicting results from different studies. Previous studies have reported that basal, postabsorptive FFA turnover rates are either increased (4) or not increased (1,5–8) in type 2 diabetic subjects compared with control subjects. The explanation for these apparent divergent results may be related to differences in study subjects, experimental design, and data presentation. In studies conducted in lean diabetic and nondiabetic subjects, Hall et al. (4) found increased FFA turnover, expressed per kilogram of body weight, in untreated diabetic subjects compared with control subjects. Groop et al. (1) found no difference in FFA R_a, expressed per unit of body surface area, between treated diabetic and control subjects. In studies conducted in overweight and obese diabetic and nondiabetic subjects, FFA flux, expressed per kilogram of fat-free mass or kilogram of body weight, was the same in diabetic and nondiabetic obese subjects (5–7). Available data thus indicate that lean untreated diabetic subjects have greater FFA R_a than lean nondiabetic subjects, whereas FFA R_a is similar in treated diabetic and BMI-matched nondiabetic subjects, whether lean or obese. In the only previous study that compared FFA kinetics in overweight diabetic and lean control subjects, no difference in FFA R_a, expressed per kilogram of body weight, was detected between groups (8). In contrast, our study found that FFA R_a is greater in obese diabetic subjects than in lean control subjects when kinetic data are expressed per unit of body surface area to help correct for the confounding effect of differences in body composition between groups.

Several investigators have reported that FFA MCR is reduced in type 2 diabetic subjects compared with BMI-matched control subjects (5–7). In contrast, we found no differences in FFA MCR between obese diabetic subjects

TABLE 2
Integrated rates of palmitate rate of appearance (AUC analysis) in normal subjects and in diabetic patients before and after treatment with placebo, metformin, or troglitazone.

	Integrated palmitate R_a			
	Nocturnal (mmol · m^{-2} · 7 h^{-1})		Postprandial (mmol · m^{-2} · 4 h^{-1})	
Subject group	Baseline	3 months	Baseline	3 months
Control (n = 6)	19.4 ± 3.9	—	5.3 ± 1.01	—
All diabetic (n = 20)	29.4 ± 3.0*	—	14.2 ± 1.7†	—
Placebo (n = 8)	31.8 ± 6.0	37.2 ± 5.6	17.7 ± 3.4	17.0 ± 3.0
Metformin (n = 8)	31.9 ± 3.3	36.2 ± 4.4	13.7 ± 1.5	16.6 ± 2.2
Troglitazone (n = 4)	19.6 ± 4.7	19.1 ± 5.9	8.0 ± 1.7	5.7 ± 1.4‡

Data are means ± SD. *$P < 0.05$ vs. control; †$P < 0.01$ vs. control; ‡$P < 0.05$ vs. baseline.

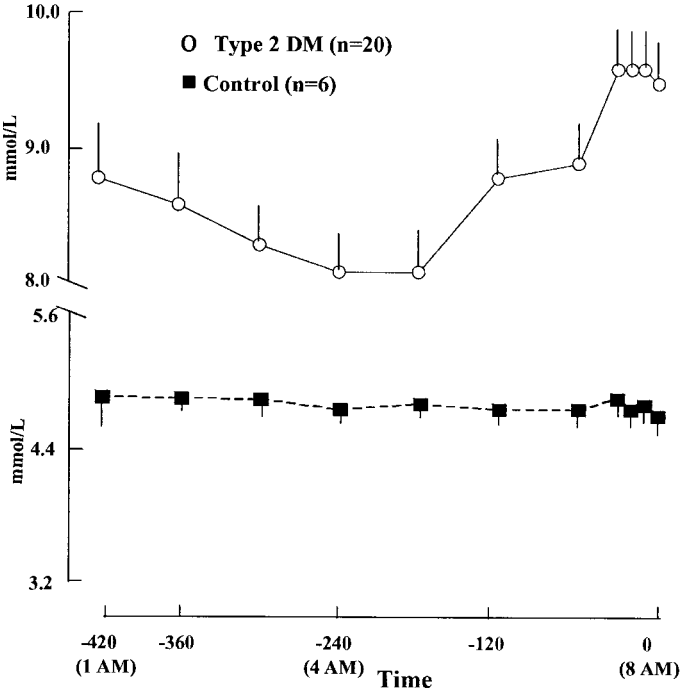

FIG. 4. Plasma glucose concentrations in healthy control subjects and type 2 diabetic subjects.

and lean control subjects in the present study. However, MCR increased during the postprandial period. This is consistent with an increase in FFA MCR in normal subjects during insulin infusion that we have recently observed (S.K., unpublished observations).

We found impaired postprandial suppression of FFA appearance in diabetic subjects compared with lean control subjects, concordant with the data of Kelley et al. (6) in diabetic subjects after ingestion of a liquid meal. The majority of FFA appearance derives from the activity of hormone-sensitive lipase in adipose tissue (25), although lipoprotein lipase (LPL) may also contribute to the FFA pool. Available evidence suggests that VLDL is not an important source of FFA, but that significant amounts of FFA derive from chylomicrons during meal absorption. In dogs, >95% of LPL-generated FFAs are taken up directly into tissues and, thus, are not released into the circulation (26). However, Roust and Jensen (27) reported that approximately one-third of chylomicron triglyceride fatty acids are released into plasma during meal absorption, with no apparent difference between lean control subjects and hyperinsulinemic, obese nondiabetic subjects. To our knowledge, comparable data in diabetic individuals are not available. Since chylomicrons are a source of FFAs during meal absorption, increased release of FFAs from chylomicron triglyceride may have contributed to increased postprandial FFA appearance in our study.

Previous studies have found that plasma FFA concentrations increase during the night in subjects with type 2 diabetes (9). Our results indicate that the increase in FFA concentrations that occurs between 4:00 and 8:00 A.M. in type 2 diabetic subjects is the result of a slight increase in FFA flux and perhaps a modest decrease in FFA MCR. The increase in plasma FFA concentrations that we observed was accompanied by an increase in palmitate flux between 4:00 and 8:00 A.M., and may have been due in part to waning of insulin concentrations. It is also possible that a decrease in sensitivity to the antilipolytic action of insulin occurred during the night. Boden et al. (28) found a decrease in insulin sensitivity with respect to glucose metabolism between midnight and 6:00 A.M that correlated with an increase in plasma FFA concentrations.

Although physiological increases in growth hormone have potent lipolytic effects (29), it is unlikely that growth hormone contributed to the differences in lipolytic rates between diabetic and control subjects in our study. The diabetic subjects in our study had significantly lower growth hormone concentrations than the control subjects, consistent with a previous study that found blunted nocturnal growth hormone release in a similar group of diabetic subjects (30). This indicates that growth hormone would be an unlikely mediator of nocturnal "hyperlipolysis" in poorly controlled diabetes. Increased FFA concentrations suppress pituitary growth hormone secretion (31), and suppression of FFA concentrations with acipimox, a

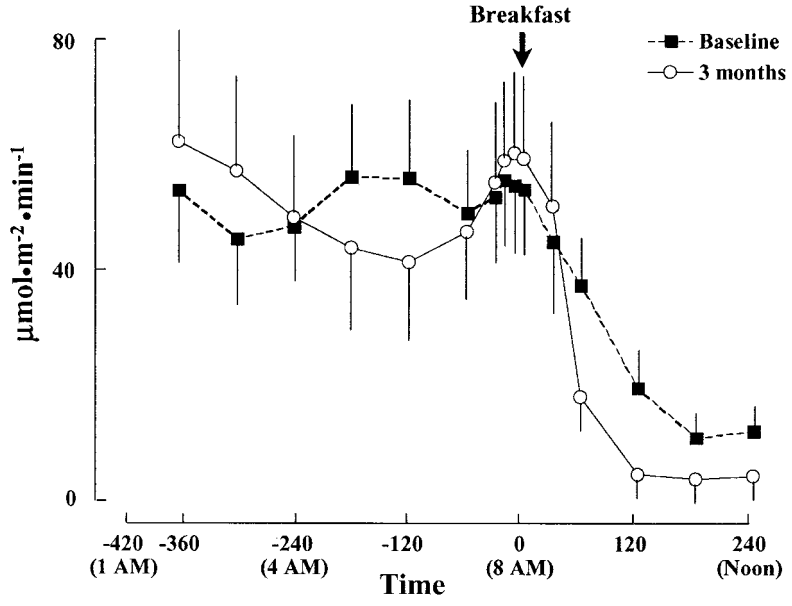

FIG. 5. Palmitate rate of appearance in type 2 diabetic subjects (n = 4) at baseline and after 3 months of troglitazone (600 mg/day), from 0100 h (−420 min) to noon (240 min).

nicotinic acid analog, stimulates growth hormone release (32).

Cortisol, which has potent lipolytic properties at physiological concentrations (33), is a possible mediator of the early morning increase in FFA concentrations observed in our diabetic subjects. The nocturnal decrease in insulin sensitivity that occurs in diabetic subjects correlates with an increase in plasma cortisol concentrations (28). In the present study, we found an increase in plasma glucose concentrations in the diabetic subjects between 4:00 and 8:00 A.M., which is consistent with the "dawn phenomenon," as has been previously described in type 2 diabetes (34) and which may be mediated by cortisol (35). Although there appears to be a relationship between FFA release and endogenous glucose production (36), we found no correlation between the early morning change in plasma glucose concentration and changes in palmitate R_a. Norepinephrine could also contribute to the early morning FFA increase in the diabetic subjects. Norepinephrine is released from sympathetic nerve endings in adipose tissue during basal conditions (37) and meal absorption (38). Sympathetic nervous system (SNS) activity is markedly increased in insulin-resistant states such as type 2 diabetes (39), and it is possible that hypoventilation, a common occurrence in type 2 diabetic patients during sleep (40), could have resulted in further SNS activation in some of our subjects. The decrease in lipolysis that occurs during the night in the control subjects could be related to the decrease in SNS activity that occurs during sleep in normal individuals (41). Our study does not address the contribution of cortisol and SNS activity to the regulation of nocturnal lipolysis.

We found a significant decrease in postprandial, but not nocturnal, palmitate R_a after 3 months of troglitazone (600 mg/day, $n = 4$) in type 2 diabetic subjects. Both pioglitazone (42) and rosiglitazone (43) have been reported to decrease fasting plasma FFA concentrations, and 3 months of troglitazone therapy enhances insulin-mediated suppression of palmitate R_a in patients with type 2 diabetes (11). A recent study found a 23% decrease in postprandial, but not fasting, FFA concentrations after 3 months of rosiglitazone therapy (44). These data are similar to our results, which show a 29% decrease in postprandial palmitate R_a after 3 months of troglitazone. Our data should be interpreted with caution, however. We were able to study only a small number of patients before troglitazone was withdrawn from the U.S. market. This likely accounts for the fact that mean palmitate R_a in the troglitazone group was lower than in the diabetic subjects in aggregate; a larger study would be required to more accurately quantify the effects of troglitazone on lipolysis. It cannot be determined from our data whether this effect is mediated by direct sensitization at the level of hormone-sensitive lipase, enhanced intracellular FFA reesterification in adipocytes, more efficient internalization of LPL-generated fatty acids with less systemic "spillover," or a combination of these effects. Whatever the mechanism, lower FFA release may account for increased hepatic and skeletal muscle insulin sensitivity, perhaps mediated by a decrease in intracellular triglyceride in those tissues (43). In the diabetic subjects, the magnitude of the postprandial abnormality in lipolysis was greater than the abnormality in nocturnal lipolysis at baseline, which may explain why an effect of troglitazone on lipolysis was more apparent during the postprandial period.

In contrast to the results with troglitazone treatment, we found no effect of metformin on nocturnal or postprandial lipolysis despite comparable improvement in glycemic control. This observation is consistent with an earlier report in which investigators measured postabsorptive palmitate kinetics before and during metformin treatment in diabetic subjects and found no effect of metformin on lipolysis (12). In contrast, a study in previously drug-naïve patients demonstrated a decrease in FFA turnover during a hyperinsulinemic-euglycemic clamp after 4 weeks of metformin therapy (10).

Our results suggest that strategies to target abnormalities in postprandial and nocturnal adipose tissue lipolysis could be beneficial in the treatment of type 2 diabetes. If nocturnal FFA flux influences postabsorptive gluconeogensis and thus fasting glycemia, therapy designed to suppress lipolysis might improve glycemic control. However, available data on this point are equivocal. Axelsen et al. (45) found that feeding cornstarch at bedtime lowered fasting FFA concentrations and reduced postbreakfast hyperglycemia in subjects with type 2 diabetes; however, overall glycemic control was not affected. In type 2 diabetic subjects, gemfibrozil lowered fasting plasma FFA and glucose concentrations, but did not affect HbA_{1c} (46). A recent study reported improvement in fasting hyperglycemia, glucose tolerance, and insulin sensitivity when acipimox was administered to subjects with type 2 diabetes (47). However, HbA_{1c} values were not reported in that study, and other investigators have found no improvement in glycemic control after acipimox therapy (48,49).

In summary, our study documents the presence of excessive FFA release during the night and after meal ingestion in patients with poorly controlled type 2 diabetes. Therefore, the alterations in adipose tissue lipolysis associated with type 2 diabetes occur on an around-the-clock basis and may be an important continuous contributor to insulin resistance. Troglitazone therapy improved postprandial but not nocturnal hyperlipolysis, whereas metformin had no effect on lipolytic activity. The association between elevated FFAs and various aspects of the insulin resistance syndrome (glucose intolerance and type 2 diabetes, hypertriglyceridemia, etc.) suggests that treatment strategies designed to improve dysregulation in adipose tissue lipolysis could have important therapeutic effects.

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