Efficacy and Safety of Troglitazone in the Treatment of Lipodystrophy Syndromes

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Background: **Troglitazone promotes adipocyte differentiation in vitro and increases insulin sensitivity in vivo. Therefore, troglitazone may have therapeutic benefit in lipoatrophic diabetes.**

Objective: **To determine whether troglitazone ameliorates hyperglycemia and hypertriglyceridemia or increases fat mass in lipoatrophic patients.**

Design: **Open-labeled prospective study.**

Setting: **United States and Canada.**

Patients: **20 patients with various syndromes associated with lipoatrophy or lipodystrophy.**

Intervention: **6 months of therapy with troglitazone, 200 to 600 mg/d.**

Measurements: **Levels of hemoglobin A_{1c}, triglycerides, free fatty acids, and insulin; respiratory quotient; percentage of body fat; liver volume; and regional fat mass.**

Results: **In the 13 patients with diabetes who completed 6 months of troglitazone therapy, hemoglobin A_{1c} levels decreased by a mean of 2.8% (95% CI, 1.9% to 3.7%; $P < 0.001$). In all 19 study patients, fasting triglyceride levels decreased by 2.6 mmol/L (230 mg/dL) (CI, 0.7 to 4.5 mmol/L [62 to 398 mg/dL]; $P = 0.019$) and free fatty acid levels decreased by 325 μmol/L (CI, 135 to 515 μmol/L; $P = 0.035$). The respiratory quotient decreased by a mean of 0.12 (CI, 0.08 to 0.16; $P < 0.001$), suggesting that troglitazone promoted oxidation of fat. Body fat increased by a mean of 2.4 percentage points (CI, 1.3 to 4.5 percentage points; $P = 0.044$). Magnetic resonance imaging showed an increase in subcutaneous adipose tissue but not in visceral fat. In one patient, the serum alanine aminotransferase level increased eightfold during the 10th months of troglitazone treatment but normalized 3 months after discontinuation of treatment. Liver biopsy revealed an eosinophilic infiltrate, suggesting hypersensitivity reaction as a cause of hepatotoxicity.**

Conclusion: **Troglitazone therapy improved metabolic control and increased body fat in patients with lipoatrophic diabetes. The substantial benefits of troglitazone must be balanced against the risk for hepatotoxicity, which can occur relatively late in the treatment course.**

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See editorial comment on pp 304-306.

Obesity causes insulin resistance, a central feature in the pathogenesis of type 2 diabetes (1). Paradoxically, the absence of adipose tissue also causes insulin resistance and diabetes in humans (2, 3) and genetically engineered animal models (4–6). Lipoatrophy and lipodystrophy are features of a group of heterogeneous syndromes characterized by a paucity of fat, insulin resistance, and hypertriglyceridemia (7). If patients develop diabetes, the syndrome is referred to as *lipoatrophic diabetes*. The disease has several genetic forms, including face-sparing partial lipoatrophy (the Dunnigan syndrome or the Koberling–Dunnigan syndrome, OMIM [Online Mendelian Inheritance in Man] 308980), an autosomal dominant form caused by mutations in the lamin A/C gene (8), and congenital generalized lipoatrophy (the Seip–Berardinelli syndrome, OMIM 269700), an autosomal recessive form mapping to chromosome 9q34 in some pedigrees (9). These diseases are rare; reported estimated prevalences are less than 1 in 10 million (10), although our experience suggests that the actual prevalences may be somewhat higher. An association between lipoatrophy and autoimmune disease, such as juvenile dermatomyositis, has also been described (11), suggesting that autoimmune destruction of adipose tissue results in a form of lipoatrophy.

Thiazolidinediones, a new class of antidiabetic drugs (12), are ligands for peroxisome proliferator–activated receptor-γ (PPAR-γ), a nuclear receptor expressed predominantly in adipose tissue (13). Thiazolidinediones are believed to exert their primary actions in adipose tissue and to indirectly increase insulin sensitivity in other tissues (14). Because thiazolidinediones have been reported to both increase insulin sensitivity (15, 16) and promote adipocyte development (17), these drugs seemed ideally suited to treat lipoatrophic diabetes. Troglitazone, the first thiazolidinedione to be approved for therapeutic use in the United States, has been shown to improve glycemic control

and ameliorate hypertriglyceridemia in patients with type 2 diabetes (18). However, the use of troglitazone is complicated by a rare form of severe, irreversible hepatotoxicity. Two additional thiazolidinediones, rosiglitazone and pioglitazone, were recently approved for use. These drugs are also effective in improving glycemic control in patients with type 2 diabetes (19). Although initial studies of rosiglitazone and pioglitazone suggested that they might not be toxic to the liver, recent reports have raised the possibility that rosiglitazone may rarely cause hepatotoxicity (19, 20).

Because PPAR-γ ligands promote adipocyte differentiation in vitro (13), we hypothesized that troglitazone would promote adipocyte development in patients with various forms of lipoatrophy. This hypothesis implicitly assumes that some lipoatrophic patients possess pre-adipocytes that could be stimulated by troglitazone to complete adipocyte differentiation. In addition, we sought to determine whether troglitazone therapy would improve metabolic control in patients with various forms of lipoatrophy. In light of data suggesting that troglitazone exerts its primary effects on adipocytes, it was uncertain whether the drug would be effective in such patients.

Methods

Patients

Potential study participants were referred by multiple physicians in the United States and Canada in response to advertisements placed in medical journals, notices on the Internet, or word-of-mouth. Some patients had been followed at the National Institutes of Health for varying periods of time (up to 20 years). Because of the rarity of the syndrome, it was not practical to conduct population-based recruitment.

To be eligible for the study, patients had to have both insulin resistance and lipoatrophy. For our purposes, insulin resistance was defined as either a fasting plasma insulin level greater than 143 pmol/L or impaired response to intravenous insulin (0.15 U/kg). The latter criterion was defined as a decrease in plasma glucose of less than 50% in patients with fasting glucose levels of 11 mmol/L or less ($\leq$200 mg/dL) or a decrease of 5.5 mmol/L or less ($<$100 mg/dL) in patients with fasting glucose levels greater than 11.1 mmol/L ($>$200 mg/dL).

Of 33 patients screened for this study, 8 were excluded because serum aminotransferase concentrations were abnormal (range, 833 to 6666 nkat/L) and liver biopsies showed steatohepatitis with varying degrees of fibrosis. Five patients were excluded for various reasons, such as the inability to give informed consent or adhere to the study follow-up schedule. The remaining 20 patients were recruited into the study (**Table**).

Fat distribution was assessed by physical examination and magnetic resonance imaging (MRI). A region of the body was defined as affected if MRI showed a marked decrease in fat in that region. Four patients had generalized lipoatrophy, defined as involvement of the following nine regions: face, neck, upper trunk, abdominal subcutaneous fat, visceral fat, and all four extremities. Two of these patients (U1 and P1) had near-total absence of fat throughout their bodies; the other two (A1 and A2) had a generalized decrease in fat but retained some fat in their visceral abdomen. Sixteen patients, including 7 patients with the Dunnigan syndrome, had partial lipoatrophy affecting five to eight fat depots.

Six patients had accompanying autoimmune disease or results on three or more laboratory tests that suggested autoimmunity (for example, antinuclear antibody, rheumatoid factor, and elevated erythrocyte sedimentation rate); these patients therefore were presumed to have an autoimmune cause of their lipoatrophy. The cause of lipoatrophy appeared to be genetic in 10 patients; lipoatrophy appeared shortly after birth in 1 patient, and 9 patients had several affected relatives. Seven of these 9 patients had Dunnigan partial lipodystrophy (21) (**Table**); the 7 patients were members of three pedigrees. After completion of the study, the diagnosis of the Dunnigan syndrome was confirmed by identifying the R482Q mutation in the lamin A/C gene in all three pedigrees (22). In 4 patients, the cause of disease was unknown.

Of the 20 study patients (**Table**), 14 had diabetes and 2 had impaired glucose tolerance according to the 1997 American Diabetes Association criteria (23). Most diabetic patients were receiving pharmacotherapy before study entry. Five patients were receiving insulin (0.5 to 2 U/kg of body weight per day) and 5 were receiving sulfonylureas; patients continued to receive these therapies during the study. Two patients were receiving metformin, but this therapy was discontinued 6 weeks before initiation of troglitazone treatment.

Syndromes of lipoatrophy are associated with substantial comorbid conditions. Of the 8 patients with triglyceride levels greater than 4.5 mmol/L (400 mg/dL), 6 had a

Table. **Characteristics of the Study Patients***

Condition and Patient	Age	Sex	Diabetes	Diabetes Therapy	Dyslipidemia	Antilipid Therapy	Fasting Insulin Level	Leptin Level	ALT Level	Respiratory Quotient	Total Fat†
	y						*pmol/L*	*μg/L*	*nkat/L*		*%*
Generalized lipoatrophy											
Congenital‡											
P1	27	Female	Yes	Insulin	Yes	None	NA§	<1.0	383	1.14	7
Autoimmune cause											
A1	6	Female	No	None	Yes	None	146	1.4	300	0.98	9
A2	19	Female	Yes	Metformin	Yes	None	167	<1.0	583	0.91	10
Unknown cause											
U1	26	Female	Yes	Insulin	Yes	None	NA§	<1.0	533	0.94	12
Partial lipoatrophy											
Dunnigan sydrome											
D1P2	65	Female	Yes	Glyburide	Yes	Gemfibrozil, atorvastatin	49	8.8	300	0.90	20
D2P2	38	Female	Yes	Glipizide	Yes	None	83	4.1	267	0.92	18
D3P2	62	Female	Yes	Glyburide	Yes	Gemfibrozil, atorvastatin	90	4.9	250	0.90	24
D4P3	27	Female	No	None	Yes	None	402	8.2	633	0.98	27
D5P4	29	Female	Yes	None	Yes	Fenofibrate, atorvastatin	153	3.7	550	0.94	25
D6P4	49	Female	Yes	Metformin	Yes	Fenofibrate, atorvastatin	215	3.6	583	0.88	21
D7P4	40	Female	No	None	Yes	None	132	2.4	233	0.91	21
Other familial											
F1P5	30	Female	No	None	Yes	None	271	9.8	283	0.97	26
F2P5	57	Male	Yes	None	Yes	None	146	9	217	1.01	26
Autoimmune cause											
A3	59	Female	Yes	Glyburide	Yes	Gemfibrozil	153	10.4	333	0.88	22
A4	28	Female	No	None	Yes	None	194	6.5	283	1.00	24
A5	64	Male	Yes	U-500 insulin	Yes	Gemfibrozil, atorvastatin	NA§	18.6	417	0.90	37
A6	51	Female	No	None	Yes	Atorvastatin	153	23.1	267	1.02	36
Unknown cause											
U2	51	Female	Yes	Insulin	Yes	Gemfibrozil, atorvastatin	NA§	23.3	483	0.84	43
U3	33	Female	Yes	Glyburide	Yes	None	167	17.2	467	0.85	43.6
U4	47	Female	Yes	U-500 insulin	No	None	NA§	5.6	233	0.95	20

* ALT = alanine aminotransferase; NA = not applicable.
† Measured by using dual-energy x-ray absorptiometry.
‡ All patients with a genetic form of lipoatrophy belong to a pedigree. Patients with the same "P" number belong to the same pedigree.
§ Patient was receiving insulin.

history of pancreatitis. Seventeen patients had acanthosis nigricans, a dermatologic condition associated with insulin resistance. Twelve of the 18 female participants had histories of irregular menses and polycystic ovaries as documented by ultrasonography; 6 of these women had hirsutism. Of the 6 remaining female participants, 4 were postmenopausal, 1 was perimenopausal, and 1 was prepubertal.

Fatty liver is another important feature sometimes associated with lipoatrophy. To be included in the study, patients had to have normal biochemical function of the liver (**Table**). Nevertheless, results of ultrasonography in 12 patients suggested fatty infiltration of the liver.

Lipoatrophic diabetes was associated with chronic complications of diabetes in some patients. Six patients had albuminuria, seven had diabetic polyneuropathy, and three had diabetic retinopathy (one of whom had proliferative retinopathy). One patient had three-vessel coronary artery disease.

Design

Patients were treated with troglitazone in an open-label prospective trial in which each patient was compared with his or her own baseline state. Because of the rarity of lipoatrophy syndromes and the variability of the clinical features, it was not feasible to use a randomized, placebo-controlled design. The study was approved by the institutional review board of the National Institute of Diabetes and Digestive and Kidney Diseases. Informed consent was obtained from the patient or his or her legal guardian. The decision to analyze the data after 6 months of therapy was made before the study was begun.

Patients were evaluated as inpatients at the Clinical Center of the National Institutes of Health before treat-

ment with troglitazone was initiated. They were admitted again after 6 weeks, 3 months, and 6 months of treatment. Before starting troglitazone therapy, diabetic patients were followed for at least 6 weeks while receiving stable doses of medication. Patients receiving insulin or sulfonylureas continued therapy with these drugs; however, metformin therapy was discontinued before troglitazone therapy was initiated.

In diabetic patients, troglitazone therapy was started at a dosage of 200 mg/d and was increased to 400 to 600 mg/d over the course of 6 to 12 weeks, with the goal of optimizing glycemic control. The slow titration was chosen to minimize the risk for hypoglycemia. Doses of insulin or sulfonylureas were decreased if this was necessary to prevent hypoglycemia. Patients received stable doses of lipid-lowering medication for at least 6 weeks before starting troglitazone therapy.

In nondiabetic adult participants, troglitazone was prescribed at a dosage of 400 mg/d. In one 6-year-old child weighing 15 to 18 kg, the dosage was 100 mg/d. Liver function tests and blood counts were performed every 3 to 4 weeks. Patients completed weekly questionnaires about their symptoms to identify potential side effects.

Patients were instructed not to change their diet and exercise habits during this study. Information about dietary habits was collected by using a validated questionnaire (25) that was evaluated by a blinded grader. In addition, during each visit, patients were asked to recall the type, frequency, intensity, and duration of physical activity since the last visit.

Laboratory Tests

Glucose and triglyceride levels were determined by using standard methods with automated Hitachi equipment (Boehringer Mannheim, Indianapolis, Indiana). Hemoglobin A_{1c} was measured by using high-pressure liquid chromatography (Bio-Rad, Hercules, California). Insulin and leptin levels were measured by using immunoassays with reagents from Abbott Imx Instrument (Abbott Park, Illinois) and Linco (St. Charles, Missouri), respectively. Free fatty acid levels were measured by using a commercially available kit (Wako, Richmond, Virginia). Suppression of free fatty acid levels in response to oral glucose (75 g) was calculated as follows (26): $100\% \times [(\text{fasting free fatty acid level}) - (\text{2-hour suppressed free fatty acid level})]/[\text{fasting free fatty acid level}]$.

Oxygen consumption and CO_2 production were measured by using Deltatrac equipment (Sensormedics, Yorba Linda, California) while patients were breathing 21% O_2: 0.4% CO_2. The test was performed in resting patients on awakening at 6 a.m. after an overnight ($\geq$8 hours) fast. The respiratory quotient was calculated as [CO_2 generated]/[O_2 consumed]. The nonprotein respiratory quotient was estimated by correcting for 24-hour urea nitrogen excretion, and the ratio of free fatty acid oxidation to carbohydrate oxidation was calculated (27).

Body Fat Distribution

Skinfolds (triceps, biceps, subscapular, and suprailiac) were measured on the side of the dominant arm by using Lange skinfold calipers (Cambridge Scientific Industries, London, United Kingdom) according to techniques described elsewhere (28). The mean of three measurements was used in analyses. A nonstretch tape measure was used to measure circumferences to the nearest mm; the mean of three measurements was used. Body fat percentage was calculated from the sum of four skinfold measurements (29, 30).

Whole-body composition measurements were made by using a Hologic QDR 2000 dual-energy x-ray absorptiometer (Hologic, Inc., Bedford, Massachusetts) in the "enhanced array beam whole body" mode with software version 5.71A. Scans of the entire body included the Hologic three-step acrylic/acrylic-aluminum wedge standard that simulates lean and fat soft tissue. Mass (in grams) of total body and regional fat and bone mineral content were determined. The percentage of fat was then calculated (31). Daily scans of a lumbar spine tissue–equivalent phantom obtained over 6 months yielded a 0.40% coefficient of variation for the array mode.

To evaluate body composition, axial T1-weighted MRI scans were obtained from the dome of the diaphragm to the patella on a 1.5-Tesla magnet (32). Fat volumes were calculated by using a three-dimensional analysis software package on a General Electric Advantage (Milwaukee, Wisconsin) workstation. Manual tracings were used to divide each slice into subcutaneous and visceral compartments. The pixel intensity thresholds of MRI were then applied by visually selecting intensity levels that best delineated between fat and nonfat tissue. Subcutaneous and visceral adipose tissue volumes were computed automatically as the product of the pixel area and slice thickness.

Statistical Analysis

Baseline values and those obtained after 6 months of troglitazone therapy are given as the mean ± SD. Changes from baseline were evaluated by using the Wilcoxon signed-rank test and are reported as mean change from baseline (95% CI). We used *t*-tests for paired samples wherever applicable. A *P* value less than 0.05 was considered statistically significant.

The primary end points—hemoglobin A_{1c} level, plasma triglyceride level, and percentage of body fat—were defined before initiation of the study, and troglitazone had a statistically significant effect on all of these variables. Because the statistical analyses were tests of a priori hypotheses rather than random screening of variables for statistically significant differences, we did not adjust for simultaneous comparisons. Moreover, many of the differences were significant at the $P < 0.001$ level (for example, hemoglobin A_{1c}, high-density lipoprotein (HDL) cholesterol, respiratory quotient, and thigh fat content) and would have remained significant at the $P < 0.05$ level after correction for simultaneous comparisons.

Role of the Funding Source

The study was supported by funding from the Division of Intramural Research of the National Institute of Diabetes and Digestive and Kidney Diseases. All of the researchers of this study were employed by the funding source or by other components of the National Institutes of Health.

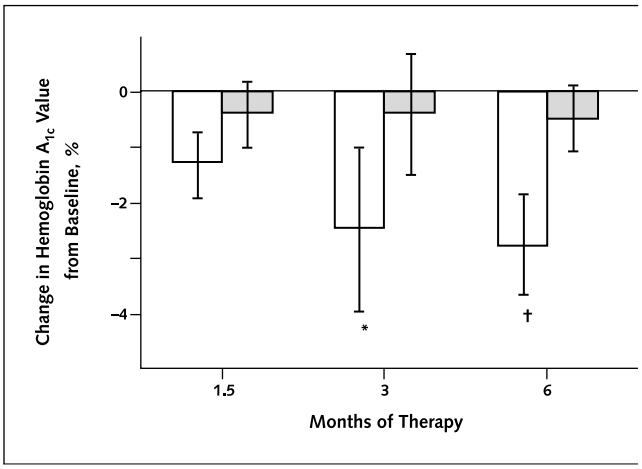
Results

Baseline Laboratory Data

The average hemoglobin A_{1c} value was 10.2% ± 2.9% (normal value < 6.6%) in the 14 study patients with diabetes. In the 20 patients who entered the study, mean triglyceride levels were elevated (5.8 ± 5.6 mmol/L [513 ± 495 mg/dL]; normal range, 0.4 to 1.7 mmol/L [35 to 150 mg/dL]) and HDL cholesterol levels were decreased (0.7 ± 0.2 mmol/L [27 ± 9 mg/dL]; normal range, 0.9 to 1.7 mmol/L [35 to 66 mg/dL]). Free fatty acid levels were also elevated (877 ± 344 μmol/L [normal range, 350 to 500 μmol/L]).

The fasting respiratory quotient was elevated in lipoatrophic patients compared with age- and sex-matched controls (0.95 ± 0.07 vs. 0.77 ± 0.09; $P = 0.008$), suggesting that lipoatrophic patients oxidize carbohydrates as their primary fuel despite elevated levels of free fatty acids in the fasting state. This contrasts with the case in patients with type 2 diabetes, who oxidize fat as their primary fuel in the fasting state (24).

Figure 1. **Decrease in mean hemoglobin A_{1c} values in 13 diabetic (*white bars*) and 6 nondiabetic (*gray bars*) patients after 6 months of therapy with troglitazone.**



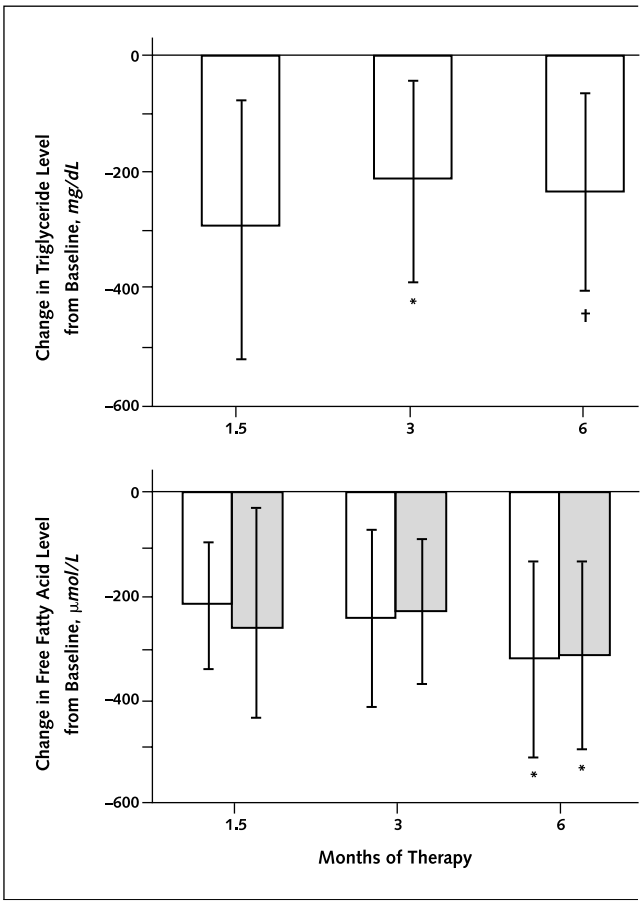
Error bars represent 95% CIs. Baseline hemoglobin A_{1c} values were 10.5% ± 2.7% in diabetic patients and 5.9% ± 0.6% in nondiabetic patients (normal range, 4.2% to 6.6%). Baseline data differ slightly from the data presented in the Results section because the figures exclude data from patient A2, in whom troglitazone therapy was discontinued before 6 months of treatment was completed. *$P < 0.002$; †$P < 0.001$.

Metabolic Control

Before initiation of troglitazone therapy, the 14 diabetic patients had poor metabolic control. In the 13 diabetic patients who completed 6 months of troglitazone treatment, hemoglobin A_{1c} levels decreased by a mean of 2.8 percentage points (95% CI, 1.9 to 3.7 percentage points; $P < 0.001$) (**Figure 1**). One patient (U1) was able to discontinue insulin therapy while achieving significant improvement in hemoglobin A_{1c} values (11.7% at baseline compared with 7.3% after therapy). Troglitazone therapy enabled another patient (A3) to discontinue glyburide therapy while improving hemoglobin A_{1c} values (8.7% at baseline compared with 6.4% after therapy). In contrast, troglitazone therapy did not change hemoglobin A_{1c} values (**Figure 1**) or fasting insulin levels in nondiabetic patients. Mean insulin levels in nondiabetic patients decreased by 42 pmol/L (CI, −12 to 95 pmol/L), but this change was not statistically significant ($P = 0.18$).

Troglitazone therapy significantly decreased average fasting triglyceride levels in the 19 patients who completed

Figure 2. **Decreases in mean levels of triglycerides and free fatty acids in 19 patients after 6 months of therapy with troglitazone.**



Top. Decrease in mean levels of triglycerides. The mean triglyceride level at baseline was 6.0 ± 5.7 mmol/L (530 ± 504 mg/dL) (normal value, 0.4 to 1.7 mmol/L [35 to 150 mg/dL]). **Bottom.** Decrease in mean levels of free fatty acids in the fasting state (*white bars*) and 2 hours after oral administration of glucose, 75 g (*gray bars*). Mean levels at baseline were 899 μmol/L ± 338 μmol/L and 566 μmol/L ± 377 μmol/L, respectively (normal range, 350 to 500 μmol/L and <50 μmol/L). Error bars represent 95% CIs. *$P < 0.05$; †$P < 0.02$. To convert triglyceride values to mmol/L, multiply by 0.0113.

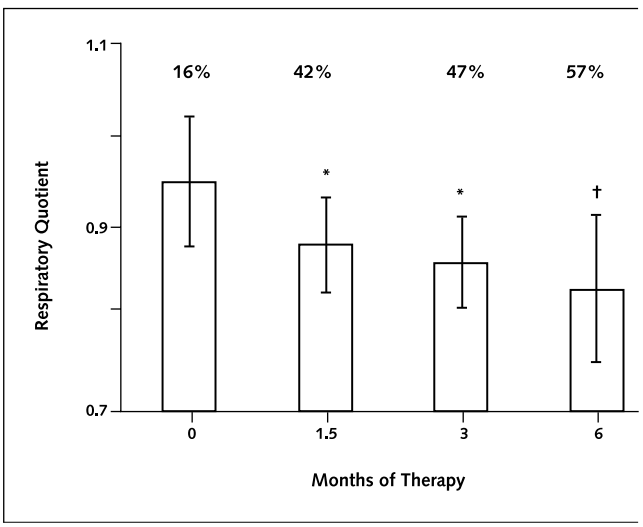
the study (mean decrease, 2.6 mmol/L [CI, 0.7 to 4.5 mmol/L]; 230 mg/dL [CI, 62 to 398 mg/dL]) ($P = 0.019$) (**Figure 2**, *top*). Troglitazone also increased mean levels of HDL cholesterol ($P < 0.001$) by 0.22 mmol/L (CI, 0.15 to 0.29 mmol/L) (8 mg/dL [CI, 5 to 11 mg/dL]). Fasting free fatty acid levels decreased significantly (mean decrease, 325 μmol/L [CI, 135 to 515 μmol/L]; $P = 0.035$) (**Figure 2**, *bottom*). Suppressed levels of free fatty acids (those obtained 2 hours after a 75-g oral glucose load) decreased by a similar percentage ($P = 0.039$) (**Figure 2**, *bottom*).

Troglitazone therapy significantly decreased the fasting respiratory quotient from 0.95 ± 0.07 to 0.83 ± 0.07 (change, 0.12 [CI, 0.08 to 0.16]; $P < 0.001$) (**Figure 3**). Because the amount of CO_2 generated varied depending on the nature of the fuel source, measurement of respiratory quotient provides an estimate of the fractional oxidation of fat and carbohydrates. Thus, the change in respiratory quotient suggests that troglitazone therapy markedly increased calculated fractional fat oxidation (16% at baseline compared with 57% after 6 months of therapy) and simultaneously decreased oxidation of carbohydrates (84% at baseline compared with 43% after 6 months of therapy). However, because the rate of lipogenesis also contributes to the respiratory quotient, inhibition of lipogenesis by troglitazone might also explain these findings.

Body Composition and Liver Size

The body weight of 19 patients treated with troglitazone did not significantly change with therapy. At baseline, the mean body weight was 70.1 ± 25.0 kg. After 6 months of therapy with troglitazone, body weight increased by a mean of 2.4 kg (CI, −2.0 to 6.8 kg; $P > 0.2$). Likewise, circulating leptin concentrations did not change signifi-

Figure 3. **Decrease in mean respiratory quotient after 6 months of therapy with troglitazone.**



At each time point, the percentage contribution of fat oxidation to total-body nonprotein oxygen consumption is indicated. In the calculation of fractional oxidation of carbohydrate and fat, the contribution of fatty acid biosynthesis to the measured value of respiratory quotient was not included. However, because the process of lipogenesis is associated with an estimated respiratory quotient of 1.48 to 9.6 (33) (whereas oxidation of carbohydrate and fat yield respiratory quotients of 1.0 and 0.7, respectively), an increased rate of fatty acid biosynthesis may have contributed to the elevated respiratory quotient. The values on the y-axis begin at 0.7 because this is the lowest observable value for the respiratory quotient. Error bars represent 95% CIs. *$P < 0.002$; †$P < 0.001$.

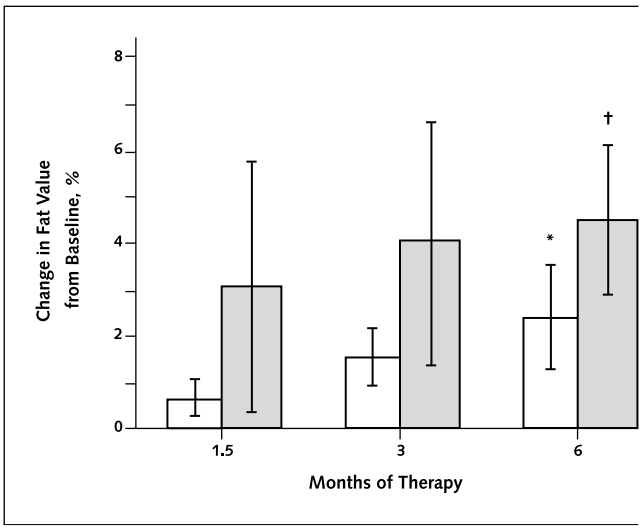
cantly after therapy; the baseline level of 8.7 ± 6.1 μg/L decreased by 0.1 μg/L (CI, −2.6 to 2.8 μg/L; $P > 0.2$).

In contrast, changes in body composition after troglitazone therapy were significant. According to MRI, the volume of subcutaneous fat in the thigh region increased by 771 mL (CI, 405 to 1137 mL) after therapy from a baseline value of 4013 ± 2980 mL ($P < 0.001$). Subcutaneous fat in the abdominal region (2487 ± 2407 mL at baseline) increased by 837 mL (CI, 209 to 1465 mL; $P = 0.025$). Visceral abdominal fat decreased by a mean of 358 mL ([CI, −17 to 697 mL) from baseline values (2149 ± 1907 mL), but this change was not statistically significant ($P = 0.065$). According to dual-energy x-ray absorptiometry (**Figure 4**), total-body fat increased from 24.4% ± 9.9% to 26.8% ± 10.6% (mean increase, 2.4 percentage points [CI, 1.3 to 4.5 percentage points]; $P = 0.044$).

Magnetic resonance imaging indicated that troglitazone decreased the volume of the liver from 1954 ± 675 mL to 1709 ± 512 mL (mean decrease, 246 mL [CI, 78 to 414 mL]; $P = 0.015$).

Changes in body composition and liver size appeared not to have resulted from changes in diet or exercise (data not shown). According to questionnaire responses, patients changed neither their diets nor their exercise habits during the study.

Figure 4. **Increase in mean body fat values after 6 months of troglitazone therapy.**



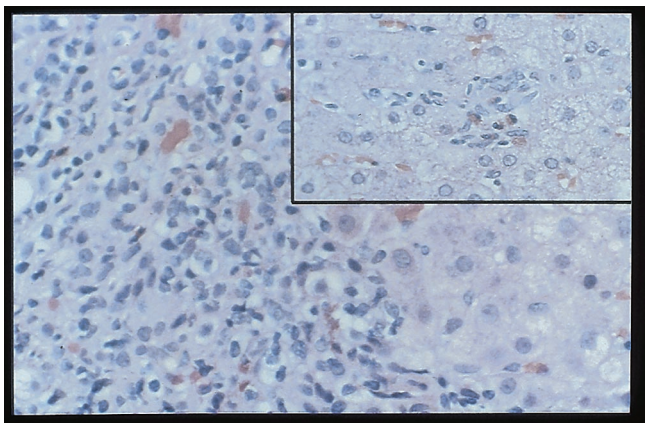
Dual-energy x-ray absorptiometry was used to measure body fat. Mean values at baseline were 19.2% ± 12.8% for right-arm fat (*gray bars*) and 24.4% ± 10.1% for total-body fat (*white bars*). Error bars represent 95% CIs. *$P < 0.05$; †$P < 0.02$.

Liver Function Abnormalities

During the study, troglitazone therapy was discontinued in one patient (A2) because of abnormal results on liver function tests. In this patient, the alanine aminotransferase (ALT) concentration increased from 583 nkat/L to 1100 nkat/L (normal value, <668 nkat/L) after 6 weeks of therapy. Findings on liver biopsy performed 1 month after discontinuation of troglitazone therapy was consistent with nonalcoholic steatohepatitis, a form of liver disease commonly seen in lipoatrophy. Because glycemic control deteriorated and triglyceride levels increased after troglitazone therapy was discontinued, metformin therapy was initiated. Metabolic control then improved and the serum ALT concentration normalized. The increase in ALT concentration in this patient may have been caused by a predisposition to steatohepatitis in association with lipoatrophy.

Because troglitazone therapy markedly improved metabolic control, it was continued beyond the study period in the 19 patients who completed the study. One of these patients (U1) developed fatigue and had an eightfold increase in ALT concentration after 10 months of therapy. Three months before troglitazone therapy was started, the ALT concentration transiently increased to 1134 nkat/L (normal, <668 nkat/L), but it spontaneously normalized within 3 weeks. While this patient was receiving troglitazone, aminotransferase concentrations were monitored every 3 to 4 weeks; her ALT concentration was documented to be within the normal range 3 weeks before the increased ALT concentration was detected. The γ-glutamyltransferase level, bilirubin level, and indices of synthetic function remained in the normal range while the patient's ALT concentration was elevated. Tests of serologic markers for viral hepatitis A, B, and C yielded negative results, and autoantibodies were not detected. Ultrasonography revealed a normal liver echo pattern, normal biliary structures, and a slightly enlarged spleen (unchanged from that seen on pretreatment ultrasonography). A liver biopsy performed 3 days after discontinuation of troglitazone therapy showed an eosinophilic infiltrate consistent with toxicity due to hypersensitivity to the drug (**Figure 5**). Troglitazone therapy was discontinued, and aminotransferase concentrations improved slowly, returning to normal 3 months after therapy ended.

Figure 5. **Liver biopsy specimen showing hepatotoxicity due to troglitazone therapy.**



Liver biopsy was performed 4 days after the patient discontinued troglitazone therapy (6 days after the maximum alanine aminotransferase concentration was observed). **Main panel.** A 40× magnification of the liver specimen obtained by percutaneous liver biopsy and stained with hematoxylin–eosin. Hepatic architecture is preserved, and no steatosis is present. However, a chronic inflammatory infiltrate containing many eosinophils associated with moderate piecemeal necrosis along the edge of the portal area can be seen. The hepatic parenchyma contains numerous small foci of lobular inflammation and hepatocellular apoptosis. There are no areas of confluent necrosis or fibrosis. **Inset.** A 60× magnification showing the predominance of eosinophils in the infiltrate. Electron microscopy did not reveal abnormalities in mitochondria or peroxisomes (data not shown)

Discussion

Troglitazone therapy produced clear benefits in patients with lipoatrophic diabetes. In our study, troglitazone therapy decreased hemoglobin A_{1c} levels by 2.8 percentage points; such a decrease is predicted to reduce relative risks for retinopathy by about 48% and nephropathy by about 22% (34, 35). Furthermore, triglyceride levels decreased by 2.6 mmol/L (230 mg/dL), a reduction that is predicted to decrease the relative risk for cardiovascular events by 35% to 65% (36, 37). Troglitazone treatment also caused a small but statistically significant increase in body fat. Magnetic resonance imaging demonstrated a selective increase in subcutaneous adipose tissue and a significant reduction in the size of the liver, suggesting a shift in fat storage from the liver to the periphery. The increase in body fat without a significant change in weight suggests that lean body mass may have decreased slightly.

Troglitazone is generally viewed as an insulin sensitizer, leading to the idea that the effects of troglitazone would resemble those of insulin. However, unlike insulin, which increases the respiratory quotient and fractional oxidation of carbohydrates (38), troglitazone decreased the respiratory quotient and increased fractional oxidation of fat in our study. Alternatively, the decrease in respiratory quotient might be explained by a decrease in lipogenesis. In either case, the effect of troglitazone on the respiratory quotient is the opposite of that of insulin and therefore cannot be attributed to its activity as an insulin sensitizer. Thus, our findings provide a novel insight into the mechanism of action of troglitazone.

The ability of troglitazone to increase fatty acid oxidation may be a direct action of the drug in lipoatrophic patients and may explain the decrease in free fatty acid levels. Furthermore, because elevated levels of free fatty acid can cause insulin resistance, the ability of troglitazone to decrease free fatty acid levels may explain how the drug increases insulin sensitivity. The proposed effect of troglitazone resembles the action of PPAR-α agonists in promoting fatty acid oxidation (39).

Biological Effects of Troglitazone

Various mouse models of lipoatrophy suggested that the absence of adipose tissue per se is the cause of insulin resistance in this syndrome (4–6). The finding that transplantation of adipose tissue into lipoatrophic mice dramatically ameliorates insulin resistance and improves metabolic control strongly supports this idea (40). Thus, we hypothesized that lipoatrophic patients would benefit from a therapy that increased fat mass. Because PPAR-γ agonists promote adipocyte differentiation both in vitro (17) and in vivo (41, 42), we sought to determine whether troglitazone would induce growth of new adipose tissue in lipoatrophic patients. Using dual-energy x-ray absorptiometry, we observed a small but statistically significant increase (2.4 percentage points) in average body fat during 6 months of therapy. Although it is tempting to attribute this increase in body fat to the ability of troglitazone to promote adipocyte differentiation, we cannot rule out the possibility that it resulted from the ability of troglitazone to decrease glucosuria and the associated calorie wasting. Of note, it is controversial whether troglitazone also increases body fat in patients with type 2 diabetes (43). Although weight gain has been observed in some studies (16, 44), most studies did not correct for the predicted weight gain caused by decreased glucosuria in troglitazone-treated patients. In our study, the increase in body fat was not accompanied by statistically significant weight gain, but the small magnitude of the increase in body fat makes it difficult to draw firm conclusions about the mechanism. It will be important to determine whether body fat will continue to increase in response to long-term troglitazone therapy.

Like other thiazolidinediones, troglitazone is a ligand for PPAR-γ (13). If the hypothesis that adipose tissue is the site of action of thiazolidinediones is true, it is surprising that this class of drug is effective in patients with lipoatrophy. However, all of the patients in our study had some residual adipose tissue through which the drug might have acted. For safety reasons, we excluded several patients with total lipoatrophy from participating in the study because they had elevated aminotransferase concentrations and abnormal results on liver biopsy. Nevertheless, according to MRI, two patients in our study (P1 and U1) had near-total absence of subcutaneous fat and little or no visceral fat. Despite this near-total absence of adipose tissue, both patients had striking improvement in hemoglobin A_{1c} and triglyceride levels, suggesting that troglitazone may produce beneficial metabolic effects by acting on tissues other than adipose tissue (as observed in a mouse model of lipoatrophy [5]). Furthermore, PPAR-γ was ruled out as a candidate gene for congenital total lipoatrophy (45, 46) and familial partial lipoatrophy (47). Therefore, patients with these diseases are expected to express the PPAR-γ gene.

Study Design

Although we did not use a randomized study design, the weight of evidence suggests that the improved metabolic control was caused by troglitazone rather than improved adherence to therapy associated with participation in a study. First, the magnitude and reproducibility of the improvement of hemoglobin A_{1c} values are more consistent with a drug effect than a placebo effect. Compared to published experience with troglitazone monotherapy in type 2 diabetes (48, 49), our patients demonstrated greater improvement in metabolic variables. Moreover, we instructed patients not to change lifestyle, and questionnaires confirmed that the patients altered neither their diet nor their exercise habits. Finally, patients were maintained on a stable drug regimen for at least 6 weeks before initiation of the study, during which time their metabolic control was stable even though they were being followed in the context of a clinical study.

Although all of the patients had some degree of lipoatrophy, the causes and severity of the syndrome were diverse. Furthermore, because troglitazone is associated with hepatotoxicity, we excluded patients with abnormal liver function values. This policy eliminated most patients with the most severe forms of lipoatrophic diabetes. Despite the heterogeneity of the patients studied, we observed a uniform improvement in metabolic control. Nevertheless, one must be cautious about extrapolating our results to patients with severe lipoatrophy in association with preexisting elevations of ALT concentrations because we are not certain whether the balance of benefit versus risk would be favorable in this group. Moreover, although other thiazolidinediones (such as rosiglitazone and pioglitazone) would probably also be effective in these patients, further studies are needed to confirm this hypothesis.

Risks and Benefits of Troglitazone Therapy

Our study demonstrates the difficulty posed by introduction of new drugs to treat chronic illnesses such as diabetes. Troglitazone clearly produced dramatic benefits to patients with lipoatrophic diabetes despite the risk for serious toxicity. Troglitazone has been reported to cause mild, reversible abnormalities in liver function results in about 2% of patients (50), but the risk for severe, irreversible hepatotoxicity was estimated to be much lower (about 1:50 000) (51). The occurrence of troglitazone-induced hepatotoxicity in one of our patients after 10 months suggests that the risk might not become negligible as therapy progresses. Furthermore, according to the U.S. Food and Drug Administration (FDA), this patient was a "rapid riser," a classification associated with high risk for the irreversible, life-threatening form of hepatotoxicity. This patient's serum ALT concentrations did not return to normal until 3 months after discontinuation of troglitazone therapy, underscoring the severity of hepatitis. In any case, the risk for severe hepatotoxicity led the FDA to recommend withdrawal of troglitazone from the market in March 2000.

It is a crucial question whether the rare, life-threatening form of troglitazone-induced hepatotoxicity is related to the drug's mechanism of action as a PPAR-γ ligand. Because liver biopsies in previous studies were performed at a late stage in the destructive process, their results do not shed light on early injury to the liver (51, 52). In one of our patients, a liver biopsy done 10 days after the first detected abnormality in liver function test results revealed a hepatitic pattern of injury in association with a presence of a prominent eosinophilic infiltrate, compatible with drug-induced hypersensitivity. Histologic findings resembled those seen in other forms of drug-induced hepatitis, such as that produced by isoniazid (53).

If hepatotoxicity is not based on the mechanism of action of troglitazone, it should be possible to produce PPAR-γ ligands that are not hepatotoxic. Rosiglitazone and pioglitazone have been approved by the FDA. Early evidence suggests that unlike troglitazone, these two drugs do not pose a significant risk for the mild form of hepatotoxicity observed with troglitazone (54). Nevertheless, recent reports have suggested that rosiglitazone may rarely cause a severe form of hepatotoxicity (20). Thus, physicians must evaluate on a case-by-case basis the risks and benefits of therapy with each of the drugs in this class and ensure that the patients have been adequately informed of the risks associated with each drug. In the meantime, the FDA recommends measuring ALT concentrations frequently to monitor for possible hepatotoxicity in patients receiving thiazolidinediones.

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Sitting on the U. of Maryland library steps in the sun her pleated, white tennis dress sent retinal micro-shivers cascading through my alerted optic chiasm toward asymmetric area-seventeen sulci, which were then propelled into the nineteens for, so-called, non-humuncular, dispositional representation—ignoring mischievous anti-sense oligonucleotide gene noise, hoping to achieve time-binding(ital) with her flirtatious auditory parcels being sprayed backward from my naive anterior cinguli, prompting my immature, unlocalizeable personhood, i.e., selfness, to say, "Where's your racket?" fifty years ago.

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