Metabolic Effects of Rosiglitazone in HIV Lipodystrophy

A Randomized, Controlled Trial

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Background: **Patients with HIV infection who are treated with antiretroviral agents often lose subcutaneous fat and have metabolic abnormalities, including insulin resistance and reduced adiponectin levels, which may be related to disrupted subcutaneous adipogenesis and altered peroxisome proliferator–activated receptor-γ signaling.**

Objective: **To investigate the effects of rosiglitazone (4 mg/d), a peroxisome proliferator–activated receptor-γ agonist, in HIV-infected men and women with hyperinsulinemia and lipoatrophy.**

Design: **A randomized, double-blind, placebo-controlled, 3-month study.**

Setting: **University hospital.**

Patients: **28 HIV-infected men and women with hyperinsulinemia and lipoatrophy.**

Measurements: **Insulin sensitivity measured by euglycemic hyperinsulinemic clamp testing; subcutaneous leg fat area measured by computed tomography; adiponectin, free fatty acid, and lipid levels; and safety variables.**

Results: **Rosiglitazone, when compared with placebo, improved insulin sensitivity (mean [±SD] change, 1.5 ± 2.1 mg of glucose/kg of lean body mass per minute vs. −0.4 ± 1.6 mg/kg per minute; $P = 0.02$), increased adiponectin levels (mean [±SD], 2.2 ± 2.2 μg/mL vs. 0.1 ± 1.1 μg/mL; $P = 0.006$), and reduced free fatty acid levels (mean [±SD], −0.09 ± 0.1 mmol/L vs. 0.01 ± 0.1 mmol/L; $P = 0.02$). Mean percentage (±SD) of body fat (1.38% ± 3.03% vs. −0.83% ± 2.76%; $P = 0.03$) and subcubaneous leg fat area (2.3 ± 8.4 cm^2 vs. −0.9 ± 1.9 cm^2; $P = 0.02$) increased significantly with rosiglitazone compared with placebo. Mean total cholesterol levels (±SD) also increased with rosiglitazone compared with placebo (0.6 ± 1.0 mmol/L [25 ± 37 mg/dL] vs. −0.4 ± 0.6 mmol/L [−15 ± 25 mg/dL]; $P = 0.007$).**

Limitations: **The study was relatively small and of short duration.**

Conclusions: **The authors demonstrated positive effects of rosiglitazone on lipoatrophy; insulin sensitivity; and metabolic indices, including adiponectin levels, in HIV-infected patients with lipoatrophy and insulin resistance. Peroxisome proliferator–activated receptor-γ agonists may correct the metabolic abnormalities associated with disrupted adipogenesis in this population. Further studies must determine the clinical utility of such agents in HIV-infected patients.**

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Treating HIV-infected patients with combination antiretroviral therapy is often associated with metabolic abnormalities, including insulin resistance, hypertriglyceridemia, and loss of subcutaneous fat (1–8). Because of the combined use of antiretroviral medications, identifying exact mechanisms responsible for these metabolic disturbances has been difficult, but increasing evidence supports direct metabolic toxicity from each class of antiretroviral agents. For example, exposure to protease inhibitors impairs glucose uptake by cultured adipocytes (9) and indinavir administration decreases glucose utilization in healthy volunteers (10, 11). Nucleoside reverse transcriptase inhibitors are implicated in the development of lipoatrophy (12–14) and are associated with increased basal lipolysis among HIV-infected individuals (15, 16). Furthermore, nucleoside reverse transcriptase inhibitors may also affect fat-cell differentiation and apoptosis rates through mitochondrial DNA depletion (17). While several studies show increased lipid levels in association with protease inhibitor use (18, 19), protease inhibitors, as well as non-nucleoside reverse transcriptase inhibitors, reduce fractional clearance of very-low-density lipoproteins, thereby contributing to hyperlipidemia (20). Direct effects of antiretroviral medications, as well as their indirect effects through altered fat distribution, contribute to metabolic abnormalities that may increase patients' risk for cardiovascular disease (4, 21).

Loss of subcutaneous fat may be an important mechanism that contributes to the metabolic abnormalities in these patients (22–24). Furthermore, obvious loss of subcutaneous fat is an important cosmetic concern for HIV-infected patients. Recent studies suggest that potential disruption of adipogenesis in the subcutaneous fat occurs through altered sterol regulatory element-binding protein-1 and the peroxisome proliferator–activated receptor-γ (PPAR-γ) signaling cascade (25). Adiponectin levels are reduced in association with decreased subcutaneous fat in HIV-infected patients with lipodystrophy, and this may be one mechanism that mediates altered insulin sensitivity in these patients (26–31). In addition, previous studies found increased lipolysis and free fatty acid levels in patients with HIV lipodystrophy and suggest effects of increased free fatty acid levels on insulin sensitivity in these patients (15, 16, 32).

Thiazolidinediones, which are PPAR-γ agonists, improved insulin sensitivity and stimulated adipogenesis in individuals with congenital lipodystrophy (33) and may therefore be useful for HIV-infected patients with lipodystrophy. In a previous 6- to 12-week open trial of rosiglitazone in 8 HIV-infected patients with fat redistribution, Gelato and colleagues (34) observed increased subcutane-

ous adipose tissue in conjunction with improved glucose disposal. Yki-Järvinen and colleagues (35) completed a 24-week randomized, controlled trial of rosiglitazone (8 mg/d) in 30 HIV-infected patients with fat redistribution and did not observe a statistically significant effect on body fat, although liver fat and aminotransferase levels improved. We report what we believe to be the first randomized, placebo-controlled trial to demonstrate a statistically significant benefit of PPAR-γ–agonist therapy for lipoatrophy in a sample of HIV-infected patients with insulin resistance.

Context

Antiretroviral therapy often causes metabolic abnormalities characterized by lipoatrophy and HIV lipodystrophy. Thiazolidinediones (such as rosiglitazone) are peroxisome proliferator–activated receptor-γ agonists that improve insulin sensitivity and stimulate adipogenesis.

Contribution

In a randomized, double-blind, placebo-controlled study of HIV-infected individuals, rosiglitazone improved insulin sensitivity, increased adiponectin levels, decreased free fatty acid levels, and improved peripheral fat deposition during 3 months of treatment with antiretroviral agents.

Implications

Rosiglitazone seems to reverse some of the metabolic abnormalities that accompany antiretroviral therapy and may help prevent or moderate HIV lipodystrophy.

Cautions

The small sample size and short duration of treatment limit the generalizability of the findings.

–The Editors

METHODS

Patients

A total of 72 HIV-infected men and women were screened to determine eligibility for a 3-month randomized, double-blind, placebo-controlled trial of rosiglitazone (4 mg once daily) for treating hyperinsulinemia and fat redistribution between March 2001 and December 2002. Eligibility requirements included previously documented HIV infection; hyperinsulinemia (fasting insulin level $\geq$ 104 pmol/L, or $>$ 521 pmol/L after a 2-hour glucose challenge); evidence of fat redistribution, including lipoatrophy in the face, arms, hips, or legs, by patient self-report and confirmed on physical examination by an investigator; and stable antiretroviral regimen for more than 3 months. Patients were excluded if they had a previous diagnosis of kidney or heart failure or diabetes, current or previous use of a thiazolidinedione or other antidiabetic agents, fasting glucose level greater than 7.0 mmol/L (>126 mg/dL), liver aminotransferase levels at least 2.5 times the upper limit of normal, creatinine level greater than 176.8 μmol/L (>2.0 mg/dL), hemoglobin level less than 90 g/L, current use or use within the past 12 weeks of anabolic therapies (except physiologic testosterone replacement in men or estrogen replacement in women), active drug or alcohol abuse, or pregnancy. Patients were recruited through the multidisciplinary HIV clinics at the Massachusetts General Hospital and the Brigham and Women's Hospital, Boston, Massachusetts, and through advertisements in the greater Boston region. Twenty-eight of 29 patients who were eligible for enrollment entered the study. Patients provided informed written consent, and the Massachusetts General Hospital Human Research Committee and the Massachusetts Institute of Technology Committee on the Use of Humans as Experimental Subjects approved the study protocol.

Design

All study participants completed a detailed metabolic assessment before randomization and again after 3 months of therapy with rosiglitazone, 4 mg/d, or placebo. After baseline assessment, patients were randomly assigned to treatment stratified by age (<45 years vs. $\geq$45 years) and sex by using a computer-generated list. A member of the Massachusetts General Hospital research pharmacy prepared and labeled the rosiglitazone and placebo in identical capsules. The research physicians, nurses, and patients were blinded to treatment assignment during the entire study. Testing included a 75-g oral glucose tolerance test and fasting determination of blood lipid, hemoglobin, liver aminotransferase, nonesterified free fatty acid, and adiponectin levels, as well as $CD4^+$ cell count and HIV viral load. On a separate day, insulin sensitivity was determined by hyperinsulinemic euglycemic clamp testing (36). Clamp testing was completed after a 12-hour overnight fast, and patients received a primed infusion of regular insulin, 40 mU/m^2 per minute (Humulin, Eli Lilly and Co., Indianapolis, Indiana; or Novolin, Novo Nordisk, Inc., Bagsværd, Denmark), for 2 hours. A variable rate of dextrose was administered to maintain blood glucose levels at 5.0 mmol/L (90 mg/dL). Retrograde intravenous blood samples obtained from a heated hand were used to approximate arterialized blood for determining blood glucose level (37). Insulin sensitivity was assessed as the glucose disposal rate (mg/kg of lean body mass per minute), and the ratio of the glucose disposal rate to mean serum insulin level at steady state (glucose disposal rate/mean serum insulin $\times$ 100) was obtained during the final 20 minutes of the clamping procedure. Two patients (one in each treatment group) did not undergo clamp testing because of limited intravenous access.

Computed tomography was used to measure the subcutaneous fat area of the midthigh and abdomen, as well as the visceral abdominal fat area (38). To assess subcutaneous leg fat area, we obtained an image at midpoint between the articular surface of the femoral head and medial femoral condyle by using the following scan variables: 120 kV,

170 mA, 2 seconds, 1-cm slice thickness, and a 36-cm field of view. To assess abdominal visceral and subcutaneous adipose tissue areas, we obtained a computed tomography scan at the level of the L4 pedicle. Scan variables were 144-cm table height, 80 kV, 70 mA, 2 seconds, 1-cm slice thickness, and a 48-cm field of view. Fat attenuation coefficients were set at −50 to −250 HU, as described by Borkan and colleagues (39). Subcutaneous tissue area was measured by using graphical analysis software (Alice, Parexel, Waltham, Massachusetts). Bioelectrical impedance analysis was used to measure the percentage of body fat by using Model BIA 101 (RJL Systems, Clinton Township, Michigan). Dual-energy x-ray absorptiometry was used to measure lean body mass for clamp calculations and regional fat mass (Hologic QDR 4500A, Hologic Inc., Bedford, Massachusetts). Patients also rated the severity of their lipoatrophy at baseline and 3 months (0- to 12-point scale), including subjective assessment of fat atrophy of the face, arms, and legs and presence of prominent veins. Patients were asked to rate their lipoatrophy in each of these 4 regions (absent = 0, mild = 1, moderate = 2, or severe = 3), and the sum of these scores was used as a lipoatrophy self-rated score. There was a significant positive correlation between lipoatrophy self-rated score and the physician rating of lipoatrophy severity using the same scale ($r = 0.49$; $P = 0.009$).

Patients completed 4-day food records (Minnesota Data Nutrition Systems, Minneapolis, Minnesota) and underwent indirect calorimetry (Deltatrac II, Sensormedics, Yorba Linda, California) to determine their overall nutritional status at baseline and 3 months. Weight, height, waist-to-hip ratio, and resting blood pressure were measured at each visit.

In addition to the baseline and 3-month assessments, patients completed brief safety visits at 2 weeks, 1 month, and 2 months after randomization. Patients were evaluated for potential side effects, and blood samples were obtained for whole blood count, creatinine concentration, and liver aminotransferase level. Adherence to study medication was determined by pill count at each visit.

Bioassays

Serum insulin levels were measured by using radioimmunoassay (Diagnostic Products Corp., Los Angeles, California). Intra-assay and interassay coefficients of variation ranged from 3.1% to 9.3% and 4.9% to 10.0%, respectively. The $CD4^+$ cell count was determined by flow cytometry (Becton Dickinson Biosciences, San Jose, California), and HIV viral load was determined by ultrasensitive assay (Amplicor HIV-1 Monitor Assay, Roche Molecular Systems, Branchburg, New Jersey) with limits of detection of 50 000 to 75 000 copies/mL. Adiponectin levels were measured by using radioimmunoassay (LINCO Research, Inc., St. Charles, Missouri). Intra-assay and interassay coefficients of variation ranged from 1.78% to 6.21% and 6.90% to 9.25%, respectively. Nonesterified free fatty acid levels were measured with an in vitro enzymatic colorimetric assay kit (Wako Chemicals USA, Richmond, Virginia). The intra-assay coefficients of variation for free fatty acids levels ranged from 1.1% to 2.7%. Low-density lipoprotein cholesterol level was measured directly (Genzyme Diagnostics, Cambridge, Massachusetts). Other laboratory measurements, including total cholesterol, high-density lipoprotein cholesterol, triglyceride, glucose, and alanine aminotransferase levels, were obtained by using standard techniques.

Statistical Analyses

Baseline characteristics were compared between randomization groups by using the Student *t*-test and chi-square statistics for noncontinuous variables. The primary outcome variable was insulin sensitivity (measured by hyperinsulinemic euglycemic clamp technique), and the effect of treatment (rosiglitazone vs. placebo) was assessed at 3 months by using analysis of covariance with baseline measures of each variable used as the covariates. Intention-to-treat analyses were performed; for the 1 patient who did not complete the study, the last available observation was carried forward. Values for HIV viral RNA and triglyceride levels were log-transformed before analysis to approximate a normal distribution. All values are presented as means (±SD), unless otherwise indicated. One patient randomly assigned to placebo had an extremely high free fatty acid level at baseline (2.48 mmol/L) and 3 months (3.96 mmol/L). Although this patient's free fatty acid level increased with placebo treatment, similar to those of the remainder of the placebo-treated patients, these values were excluded from the analyses because they were extreme outliers (that is, both baseline and 3-month levels were more than 5 SDs above the group mean).

Power calculations were determined by using the change in insulin-mediated glucose uptake after 3 months of therapy as the primary end point and were based on previously published insulin sensitivity data on HIV-infected patients (22). To detect a clinically relevant 33% improvement in insulin sensitivity, a total of 24 patients would provide 80% power to detect an improvement in glucose uptake of 1.02 mg/kg per minute compared with placebo, assuming an SD of the change of 0.85 mg/kg per minute (22) by using a 2-sided α value of 0.05. We enrolled 28 patients to achieve an evaluable subset of at least 24 patients, assuming a dropout rate of up to 15%. All statistical analyses were performed by using SAS JMP software, version 4.04 (SAS Institute, Inc., Cary, North Carolina).

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The funding source had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

RESULTS

Twenty-seven of the 28 randomly assigned patients completed the study. One patient randomly assigned to

Table 1. **Baseline Demographic Characteristics of Study Sample***

Variable	Both Groups (*n* = 28)	Placebo Group (*n* = 12)	Rosiglitazone Group (*n* = 16)
Age, *y*	45 ± 8	45 ± 8	45 ± 8
Sex, *n*			
Men	21	9	12
Women	7	3	4
Race or ethnicity, *n (%)*			
White	21 (75)	8 (67)	13 (81)
African American	2 (7)	1 (8)	1 (6)
Hispanic	5 (18)	3 (25)	2 (13)
Duration of HIV infection, *y*	9.8 ± 4.5	8.4 ± 4.5	10.8 ± 4.4
Duration of antiretroviral therapy, *y*	7.9 ± 4.0	7.1 ± 3.8	8.5 ± 4.2
$CD4^+$ cell count, $\times 10^9$ *cells/L*	0.469 ± 0.262	0.448 ± 0.285	0.484 ± 0.252
Undetectable HIV RNA level, %†	74	67	80
Antiretroviral use, *n (%)*			
Nucleoside reverse transcriptase inhibitor	28 (100)	12	16
Stavudine	12 (43)	5	7
Non-nucleoside reverse transcriptase inhibitors	13 (46)	7	6
Protease inhibitors	18 (64)	8	10
Other medication use, *n (%)*			
Lipid-lowering agent‡	15 (54)	6	9
Testosterone (*% men*)	11 (52)	6	5
Antihypertensive therapy	6 (21)	5	1
Hormone replacement therapy (*% women*)	2 (29)	1	1

* Values expressed with a plus/minus sign are means ± SD. There were no significant differences between groups for any characteristic except frequency of antihypertensive use ($P = 0.02$ by chi-square test).
† Less than 50 copies/mL of HIV RNA.
‡ 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors or fibric acid inhibitors.

placebo was discontinued from the study after 2 weeks for increased liver aminotransferase level based on predetermined safety criteria. **Table 1** presents the demographic characteristics of the study patients. Overall, waist-to-hip ratio (1.00 ± 0.04 for women and 0.98 ± 0.08 for men) was increased and percentage of leg fat (14.1% ± 8.4%, as measured by dual-energy x-ray absorptiometry) was reduced, consistent with the presence of fat redistribution. Metabolic and body composition variables were similar between the treatment groups at baseline (**Table 2**). One patient assigned to placebo switched from one non-nucleoside reverse transcriptase inhibitor to another; no patient switched nucleoside reverse transcriptase inhibitor or protease inhibitor medications during the study.

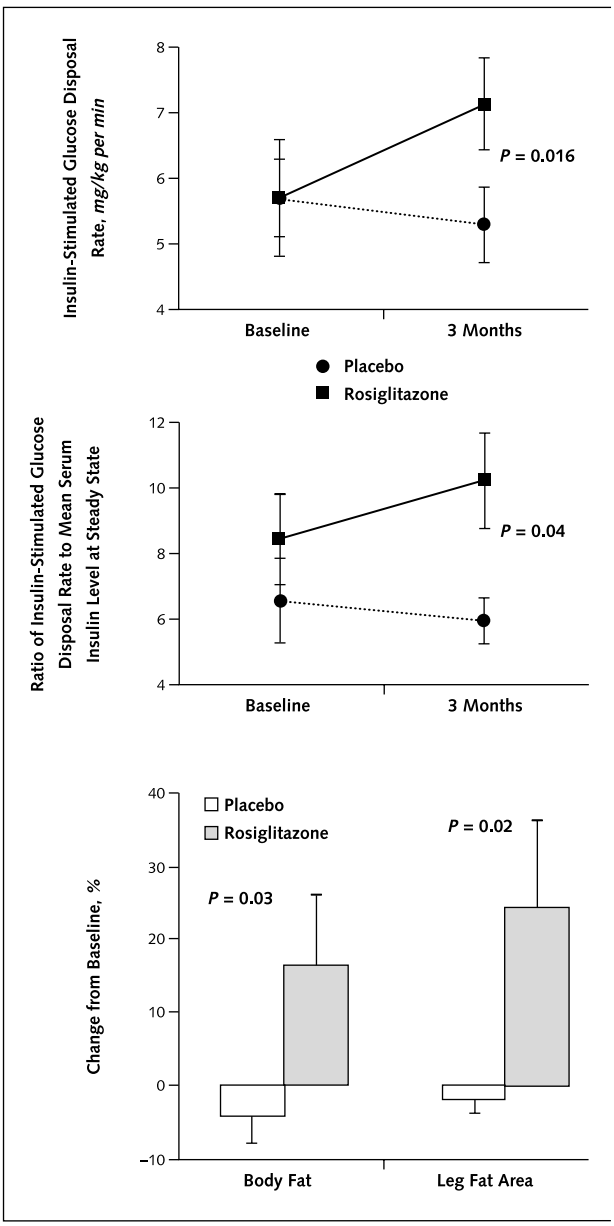
Rosiglitazone treatment resulted in statistically significant improvements in insulin sensitivity measured by glu-

Table 2. **Metabolic Variables at Baseline and the Change after 3 Months of Treatment***

Variable	Baseline		Mean Change after 3 Months		*P* Value†
	Placebo Group (*n* = 12)	Rosiglitazone Group (*n* = 16)	Placebo Group (*n* = 12)	Rosiglitazone Group (*n* = 16)	
Metabolic characteristics					
Glucose disposal rate, *mg/kg per min*	5.7 ± 2.9	5.7 ± 2.3	−0.4 ± 1.6	1.5 ± 2.1	0.02
Ratio of glucose disposal rate to mean serum insulin level at steady state	6.6 ± 4.3	8.5 ± 5.4	−0.7 ± 3.2	1.8 ± 5.3	0.04
Fasting glucose level, *mmol/L (mg/dL)*	5.3 ± 0.7 (95 ± 13)	5.4 ± 1.0 (98 ± 18)	−0.14 ± 0.9 (−2.5 ± 16.5)	−0.41 ± 0.6 (−7.3 ± 11.2)	>0.2
2-h glucose level, *mmol/L (mg/dL)*	9.3 ± 4.1 (168 ± 74)	7.8 ± 2.6 (140 ± 46)	0.1 ± 3.1 (2.3 ± 56.6)	−0.3 ± 1.1 (−5.7 ± 19.5)	0.06
Fasting insulin level, *pmol/L*	163.9 ± 110.4	120.1 ± 69.5	−36.1 ± 88.9	−8.3 ± 95.1	>0.2
Insulin AUC level, *pmol/L* $\times 10^4$ *(120 min)*	7.8 ± 5.0	8.7 ± 4.6	1.8 ± 3.3	−2.3 ± 3.0	0.003
Total cholesterol level, *mmol/L (mg/dL)*	5.7 ± 1.3 (220 ± 52)	5.2 ± 1.3 (202 ± 49)	−0.4 ± 0.6 (−15 ± 25)	0.6 ± 1.0 (25 ± 37)	0.007
LDL cholesterol level, *mmol/L (mg/dL)*	3.2 ± 1.2 (122 ± 47)	2.9 ± 0.8 (112 ± 32)	−0.4 ± 0.5 (−14 ± 21)	0.4 ± 0.8 (15 ± 32)	0.01
HDL cholesterol level, *mmol/L (mg/dL)*	0.9 ± 0.2 (33 ± 7)	1.0 ± 0.3 (37 ± 11)	−0.05 ± 0.10 (−2 ± 4)	−0.08 ± 0.23 (−3 ± 9)	>0.2
Triglyceride level, *mmol/L (mg/dL)*	4.7 ± 3.0 (417 ± 266)	4.4 ± 4.6 (389 ± 409)	0.7 ± 1.7 (62 ± 154)	0.2 ± 1.7 (21 ± 150)	>0.2
Adiponectin level, *μg/mL*	3.0 ± 2.0	3.0 ± 2.0	0.1 ± 1.1	2.2 ± 2.2	0.006
Free fatty acid level, *mmol/L*	0.53 ± 0.2	0.47 ± 0.2	0.01 ± 0.1	−0.09 ± 0.1	0.02
Safety variables					
Hemoglobin level, *g/L*	142 ± 11	143 ± 16	−2.8 ± 7.7	−5.1 ± 7.6	>0.2
ALT level, *U/L*	58 ± 23	51 ± 20	7.2 ± 35	6.3 ± 30	>0.2
Log HIV RNA level, *copies/mL*	2.3 ± 0.9	2.0 ± 0.7	0.3 ± 0.8	0.2 ± 0.8	>0.2
$CD4^+$ cell count, $\times 10^9$ *cells/L*	0.448 ± 0.285	0.484 ± 0.252	0.012 ± 0.101	0.018 ± 0.110	>0.2

* All values are means ± SD. ALT = alanine aminotransferase; AUC = area under the curve; HDL = high-density lipoprotein; LDL = low-density lipoprotein.
† *P* values for mean change from baseline represent between-group effect from analysis of covariance with baseline value as covariate.

Figure. **Insulin sensitivity and body fat response to rosiglitazone.**



Top and **Middle.** Insulin-stimulated glucose disposal rate determined by hyperinsulinemic euglycemic clamp testing and the ratio of insulin-stimulated glucose disposal rate to mean serum insulin level at steady state are presented. Circles indicate placebo ($n = 11$), and squares indicate rosiglitazone ($n = 15$). Clamp testing data were not available for 2 patients because of limited intravenous access, and the ratio was not available for 1 patient because of a sample processing error. **Bottom.** Mean percentage change from baseline in total body fat and subcutaneous leg fat area in patients treated with placebo ($n = 12$) or rosiglitazone ($n = 16$). Error bars represent SEs, and P values represent treatment effect between groups by analysis of covariance, controlling for baseline values.

cose disposal and the ratio of glucose disposal to insulin compared with placebo (**Figure**). Similarly, rosiglitazone-treated patients experienced statistically significant reductions in insulin response to glucose challenge (insulin area under the curve) (**Table 2**) compared with placebo. Adiponectin levels increased statistically significantly and free fatty acids levels decreased with rosiglitazone. Total cholesterol and low-density lipoprotein cholesterol levels increased statistically significantly with rosiglitazone therapy compared with placebo (**Table 2**).

Although body mass index did not statistically significantly change, total percentage of body fat statistically significantly increased with rosiglitazone compared with placebo (**Table 3**). Furthermore, peripheral fat statistically significantly increased, as determined by subcutaneous leg fat area measured by cross-sectional computed tomography. This represented a 24% increase in fat area from baseline with rosiglitazone compared with a 2% decrease in the placebo group ($P = 0.02$) (**Table 3** and **Figure**). No statistically significant effect of rosiglitazone was detected by computed tomography of abdominal subcutaneous or visceral fat compared with placebo. However, self-reported severity of lipoatrophy statistically significantly improved with rosiglitazone compared with placebo ($P = 0.02$) by analysis of covariance, controlling for differences in baseline values (**Table 3**). Total energy intake and resting energy expenditure during the 3-month trial did not statistically significantly change (data not shown).

No patient withdrew from the study because of side effects. Edema was not clinically evident in study participants, and no patient developed congestive heart failure during the study. Rosiglitazone did not statistically significantly affect blood pressure (data not shown). One patient in the rosiglitazone group developed anemia (defined as hemoglobin level < 110 g/L), a known potential side effect of rosiglitazone. Changes in $CD4^+$ cell count and HIV viral load were not statistically significant between groups. Mean adherence to study medication, assessed by pill count, was 99% at the 3-month visit.

DISCUSSION

Thiazolidinediones are insulin-sensitizing agents that increase glucose utilization in muscle but also increase adipogenesis through PPAR-γ (40–42). In previous studies, troglitazone increased subcutaneous fat and improved insulin resistance in patients with congenital lipodystrophy (33). We therefore determined the effects of rosiglitazone on body composition, insulin sensitivity, and metabolic indices in a group of HIV-infected patients with lipoatrophy. Patients were chosen for the study on the basis of evidence of fat redistribution and hyperinsulinemia and were receiving a stable antiretroviral regimen.

Our data demonstrated that rosiglitazone (4 mg/d) improved insulin sensitivity and lipoatrophy over 3 months in this sample. Indices of hyperinsulinemia, adiponectin level, and free fatty acid level were also statistically significantly improved. Of importance, the benefits of rosiglitazone were seen despite the ongoing use of antiretroviral therapy, including a protease inhibitor in many of the patients, which has been shown to reduce insulin sensitivity (11).

Table 3. **Body Composition Assessment at Baseline and the Change after 3 Months of Treatment***

Variable	Baseline		Mean Change after 3 Months		*P* Value†
	Placebo Group (*n* = 12)	Rosiglitazone Group (*n* = 16)	Placebo Group (*n* = 12)	Rosiglitazone Group (*n* = 16)	
Body mass index, kg/m^2	25.5 ± 5.2	26.0 ± 5.1	0.12 ± 0.68	0.18 ± 0.72	>0.2
Total body fat, %‡	19.3 ± 6.1	21.9 ± 13.2	−0.83 ± 2.76	1.38 ± 3.03	0.03
Leg fat, *kg*§	2.5 ± 1.0	4.1 ± 3.8	−0.08 ± 0.3	0.05 ± 0.5	0.08
Subcutaneous leg fat area, cm^2‖	31.3 ± 14.4	45.4 ± 48.2	−0.9 ± 1.9	2.3 ± 8.4	0.02
Abdominal subcutaneous adipose tissue area, cm^2‖	129 ± 65	179 ± 177	1.2 ± 23.3	15.8 ± 20.1	0.15
Abdominal visceral adipose tissue area, cm^2‖	167 ± 118	136 ± 47	−3.7 ± 19.8	11.1 ± 27.7	>0.2
Lipoatrophy score¶	9 ± 3	6 ± 3	−0.1 ± 3.0	−1.5 ± 1.9	0.02

* All values are means ± SD.
† *P* values for mean change from baseline represent between-group effect from analysis of covariance with baseline as covariate.
‡ As measured by bioelectrical impedance analysis.
§ As measured by dual-energy x-ray absorptiometry.
‖ As measured by computed tomography.
¶ Lipoatrophy score differed at baseline between treatment groups ($P = 0.02$).

We assessed insulin sensitivity directly by using euglycemic clamp testing, as well as the oral glucose tolerance test, and observed a robust effect of low-dose rosiglitazone over 3 months.

Several potential mechanisms may account for the effects of rosiglitazone in this study. In addition to direct effects on glucose transport and utilization, rosiglitazone may improve insulin sensitivity through beneficial effects on adiponectin level, free fatty acid level, or fat distribution. Adiponectin or adipocyte complement–related protein-30 is secreted from adipocytes and is thought to improve insulin sensitivity by decreasing hepatic glucose production and increasing fatty acid oxidation in muscles (43–46). We and others have previously shown that adiponectin levels are reduced in patients with HIV lipodystrophy in association with reduced extremity fat (26–31). Addy and colleagues (28) found that insulin resistance was related to adiponectin but possibly mediated by exposure to nucleoside reverse transcriptase inhibitors in HIV-infected patients. However, whether the effect of such exposure on adiponectin is direct or indirect through effects on body fat is unclear. In this randomized, placebo-controlled study, we demonstrated that rosiglitazone statistically significantly increased adiponectin levels in patients with HIV lipodystrophy, as suggested by Gelato and colleagues in an open-label pilot study (34). Further studies are needed to determine whether increased adiponectin levels resulting from thiazolidinedione treatment in insulin-resistant, lipoatrophic patients with HIV infection improve cardiovascular disease risk.

Free fatty acid concentrations decreased in response to rosiglitazone. Increased lipolysis has been observed in HIV-infected patients receiving combination antiretroviral therapy (15, 16), and increased free fatty acids levels impair insulin receptor substrate-1–associated phosphatidylinositol-3 kinase phosphorylation (47). Decreasing free fatty acids levels may contribute to improved insulin sensitivity in this population (32). Visnegarwala and colleagues (48) recently showed a reduction in lipolytic rates in 4 patients with HIV lipodystrophy receiving rosiglitazone. The statistically significant improvement in fatty acid concentrations in our larger, randomized study further suggests that thiazolidinediones may decrease lipolysis and improve adipogenesis in this population, even in the setting of ongoing antiretroviral therapy.

Total body fat and peripheral subcutaneous fat were notably reduced at baseline and statistically significantly increased in response to rosiglitazone compared with placebo. In addition, patients reported statistically significant reductions in severity of self-rated lipoatrophy with rosiglitazone compared with placebo during this 3-month randomized, blinded trial, indicating subjective clinical improvement in fat atrophy. The increases in peripheral fat observed in this study are similar in magnitude to the changes observed in studies of switching antiretroviral regimens (13, 49, 50). For example, in a randomized, open-label study in which abacavir was substituted for zidovudine or stavudine, Carr and colleagues (13) found an 11% increase in limb fat by dual-energy x-ray absorptiometry in patients switching to abacavir therapy after 24 weeks. In our study, after 12 weeks of rosiglitazone therapy, patients had a mean increase of 24% from baseline in leg fat area and had clinical improvement in their lipoatrophy.

In our study, increases in body fat were observed despite continued use of nucleoside analogues, and therefore the addition of rosiglitazone may be an alternative for individuals in whom antiretroviral switching is not preferred. Also, total body fat and extremity fat decreased in the placebo-treated patients but increased in the rosiglitazone-treated patients, suggesting that PPAR-γ agonists may mitigate the ongoing effects of antiretroviral agents on adipogenesis. Further studies investigating the role of thiazolidinediones to prevent the loss of subcutaneous fat with antiretroviral initiation will be important.

Recently, interest has centered on the metabolic consequences of subcutaneous fat loss in animal and human models. For example, in a model evaluating metabolism in fatless mice, severe insulin resistance and increased free

fatty acid levels were statistically significantly improved with subcutaneous fat implantation (51). Similarly, PPAR-γ agonists may improve insulin sensitivity by stimulating fat cell differentiation and increasing subcutaneous fat among HIV-infected patients with subcutaneous lipoatrophy. In previous studies, Yki-Järvinen and colleagues (35) did not observe an improvement in subcutaneous fat, whereas Gelato and colleagues (34) found an increase in extremity fat in response to rosiglitazone in an open-label study of patients with HIV lipodystrophy. In addition to body composition, we selected patients on the basis of presence of hyperinsulinemia. This may explain the differences between our study and the study by Yki-Järvinen and colleagues (35). Further studies must investigate the mechanisms of improved insulin sensitivity in response to thiazolidinediones and identify patient groups (that is, metabolic phenotype and antiviral medications) that are most likely to benefit from PPAR-γ–agonist therapy. For example, patients with subcutaneous fat atrophy and insulin resistance may benefit from thiazolidinediones. In contrast, treatment with thiazolidinediones may not be appropriate for HIV-infected patients with more generalized obesity and excess visceral fat, in whom further fat gain may not be advantageous and treatment with metformin may be more suitable (52).

The relatively small sample size and short duration of our study limit our ability to extrapolate about the utility of rosiglitazone in the larger population of HIV-infected patients and its potential long-term benefits with respect to fat distribution and reduction of risk for cardiovascular disease. On the basis of strictly defined prespecified safety variables, one patient assigned to placebo was removed from the study for an increased aminotransferase level. No adverse effects or statistically significant changes in liver function were detected with rosiglitazone. In addition, rosiglitazone did not affect fluid retention. Consistent with observations in non–HIV-infected patients (53), low-density lipoprotein cholesterol level increased in patients treated with rosiglitazone compared with patients treated with placebo. In contrast to the work of Yki-Järvinen and colleagues (35), triglyceride levels did not statistically significantly change in our study.

Cardiovascular disease has become an increasing concern for HIV-infected patients. Although not a consistent finding in all studies (54), increased myocardial infarction rates with increased duration of antiretroviral medications have been observed (21, 55, 56). Thiazolidinediones have been shown to inhibit vascular smooth-muscle growth in vitro (57) and, in human studies, improved endothelial function (58). Thiazolidinediones may therefore improve cardiovascular function because of direct effects on the vessel wall or indirect effects resulting from improvements in insulin sensitivity, free fatty acid levels, and adiponectin levels. Although the net effect of thiazolidinediones on cardiovascular disease risk in the HIV-infected population remains unclear, our data suggest that thiazolidinediones may have a beneficial effect on important metabolic variables in these patients and highlight the need for further study of this class of agents.

In summary, our data demonstrate positive effects of rosiglitazone on lipoatrophy; insulin sensitivity; and metabolic variables, including adiponectin levels, in HIV-infected patients with lipodystrophy. Further studies of the potential clinical utility of PPAR-γ agonists are necessary before thiazolidinedione use can be endorsed for patients with HIV lipodystrophy. However, such agents may address the pathophysiologic effects of antiretroviral therapy on adipogenesis and insulin sensitivity in this population.

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