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Effects of rosiglitazone on abnormal lipid kinetics in HIV-associated dyslipidemic lipodystrophy: a stable isotope study

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Abstract

HIV-associated dyslipemic lipodystrophy (HADL) is a heterogeneous syndrome of fat redistribution, hypertriglyceridemia, and insulin resistance, associated with markedly accelerated rates of lipolysis, intraadipocyte and intrahepatic reesterification, and very low-density lipoprotein–triglyceride synthesis and release. The objective of the study was to determine if rosiglitazone can ameliorate these lipid kinetic defects in patients with HADL. Infusions of [$^{13}C_1$]palmitate and [$^2H_5$]glycerol were used to measure total and net lipolysis, adipocyte and hepatic reesterification, and plasma free fatty acid (FFA) oxidation in 9 men with HADL, before and after 3 months of treatment with rosiglitazone (8 mg/d). Rosiglitazone treatment significantly increased both total lipolysis (R_a FFA_{total} from 3.37 ± 0.40 to 4.57 ± 0.68 mmol FFA per kilogram fat per hour, $P < .05$) and adipocyte reesterification (1.25 ± 0.35 to 2.43 ± 0.65 mmol FFA per kilogram fat per hour, $P < .05$). However, there was no change in net lipolysis (R_a FFA_{net} 2.47 ± 0.43 to 2.42 ± 0.37 mmol FFA per kilogram fat per hour), plasma FFA oxidation (0.30 ± 0.046 to 0.32 ± 0.04 mmol FFA per kilogram lean body mass per hour), or FFA flux available for hepatic reesterification (0.59 ± 0.07 to 0.56 ± 0.10 mmol FFA per kilogram fat per hour). There were significant decreases in fasting plasma insulin concentrations and insulin resistance, but not in fasting plasma lipid or glucose concentrations. There was a significant decrease in waist to hip ratio (0.98 ± 0.02 to 0.95 ± 0.02, $P < .05$) consistent with a significant increase in hip circumference (0.93 ± 0.02 to 0.95 ± 0.02 m, $P < .05$), without change in waist circumference. Rosiglitazone significantly increased adipocyte reesterification and improved insulin sensitivity, but the potential benefit of these changes was compromised by increase in total lipolysis. Combining rosiglitazone with agents designed to blunt lipolysis could expand depleted peripheral adipose depots in patients with HIV lipodystrophy.

1. Introduction

HIV-associated dyslipemic lipodystrophy (HADL) is a heterogeneous condition characterized by fat redistribution (peripheral lipoatrophy and central fat accumulation), profound dyslipidemia (hypertriglyceridemia, low high-density lipoprotein cholesterol [HDL-C] levels), and insulin resistance [1], which are strongly associated with increased risk for cardiovascular disease [2-5]. Suboptimal responses to conventional therapies in correcting the abnormal metabolic profile of these patients stress the urgent need to develop new strategies that target the specific underlying defects. Furthermore, therapeutic options to expand the depleted peripheral fat depots (ie, to reverse peripheral lipoatrophy) in this condition are limited.

Severely dysregulated lipid turnover in the fasted [6] and fed [7] states underlies the metabolic defects—and potentially the anthropomorphic changes—that characterize HIV lipodystrophy. The principal kinetic defect in the fasted state is a markedly accelerated rate of total lipolysis (R_a free fatty acid $[FFA]_t$) [6,8,9], resulting in a significant increase in the release of FFA into the plasma (net lipolysis,

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R_a FFA_n) despite a modest but significant increase in the rate of intraadipocyte reesterification. Plasma fatty oxidation does not increase adequately; hence, there is accelerated flux of FFAs to the liver for reesterification, followed by increased synthesis and export of very low-density lipoprotein (VLDL)–triglycerides. All these defects appear to flow from defective adipocyte function leading to unrestrained lipolysis, and this disturbance is perhaps most marked in peripheral adipose depots and manifested as peripheral lipoatrophy.

In the context of this complex set of kinetic and metabolic disturbances stemming from dysfunctional peripheral adipose depots, the thiazolidinediones present an attractive therapeutic modality. Thiazolidinediones greatly reduce whole-body insulin resistance in patients with type 2 diabetes mellitus, in large part by activating peroxisome proliferator-activated receptor γ (PPARγ)–mediated signaling in adipocytes. The specific mechanisms whereby insulin sensitivity is enhanced is complex, but is linked to the requirement of normal PPARγ-mediated gene transcriptional networks involved in the regulation of lipogenesis and adipogenesis [10,11]. Studies in a variety of animal models show that PPARγ agonists such as the thiazolidinediones promote expansion of fat depots preferentially in regions analogous to subcutaneous adipose tissues in humans relative to regions analogous to visceral adipose tissue [12]. The thiazolidinedione rosiglitazone has been used in clinical trials to ameliorate insulin resistance, peripheral lipoatrophy, and dyslipidemia in HADL patients. The results have been mixed, with a general trend toward improvement in insulin sensitivity [13-17] but no change or worsening of hypertriglyceridemia [13,18,19]. With regard to body fat distribution, the results of the clinical studies are controversial. Some studies found no effect on lipoatrophy with maximal doses of rosiglitazone for a prolonged duration [18,19], whereas others have noted increase in the size of subcutaneous fat depots [20,14].

In the present study, we attempted to understand the reasons for these complex and sometimes conflicting clinical outcomes of treatment with rosiglitazone by measuring its effects on the underlying lipid kinetic abnormalities. We used stable isotope infusions and mass spectrometry measurements to study lipid turnover comprehensively in the fasted state in 9 men with HADL, together with measurement of body composition, glycemic indices, and plasma lipid profiles, before and after treatment with rosiglitazone.

2. Materials and methods

2.1. Subjects

The study was approved by the Institutional Review Board for Human Studies at Baylor College of Medicine. Nine men with HADL, aged 45 to 50 years, were recruited by written informed consent. *HIV-associated dyslipemic lipodystrophy* was defined by (1) fat loss in the extremities and increased abdominal girth, as observed by the patient and confirmed by the primary physician, and (2) fasting plasma triglyceride concentration greater than 200 mg/dL (2.26 mmol/L). All HADL subjects had the "mixed" phenotype of HIV lipodystrophy (peripheral fat atrophy and central adiposity) as described by Saint-Marc et al [21]. They were free of diabetes mellitus, thyroid disorders, hypercortisolemia, liver or renal impairment, and hypogonadism and had had no other opportunistic infections or illnesses for 5 years. All had sedentary lifestyles, and none consumed unusual diets or dietary supplements. The complete HIV lipodystrophy case definition score [22] could not be obtained because standardized computed tomographic measurements of abdominal and peripheral fat were not performed.

Lipid-lowering medications were discontinued at least 6 weeks before the baseline stable isotope infusion protocol used to measure lipid kinetics. All subjects had been on a continuous, stable regimen of highly active antiretroviral drugs for at least 6 months before the stud;, and these drugs were continued throughout the study.

Serum insulin and glucose concentrations were measured, and insulin resistance was assessed by the homeostasis model assessment (HOMA-IR) [23]. All subjects had normal glucose tolerance (as defined by American Diabetes Association criteria) before initiating rosiglitazone treatment. Rosiglitazone was given at a dose of 8 mg/d for a duration of 3 months, with stable isotope studies performed before and after therapy.

2.2. Metabolic study protocol

The protocol consisted of intravenous infusions of stable isotopes to measure lipid kinetics and indirect calorimetry to measure substrate oxidation in the fasted state. For 2 days preceding each metabolic study protocol, subjects consumed a standard, balanced eucaloric diet consisting of 22.5 kcal and 1 g protein per kilogram body weight per day to prevent negative energy balance. They were fasted for 10 hours before the start of the stable isotope infusions.

The primary outcome variables were the rate of appearance (R_a) of glycerol, an index of the rate of total lipolysis; R_a palmitate, an index of net lipolysis; palmitate oxidation, an index of plasma fatty acid oxidation; and R_a FFA and FFA oxidation. In addition, rates of reesterification of fatty acids within the adipocyte and hepatic reesterification were calculated.

At 7:00 AM, after baseline blood and breath samples were collected, an intravenous 2-hour primed infusion of [1-^{13}C] sodium acetate (prime, 5 μmol kg^{-1}; infusion, 5 μmol kg^{-1} h^{-1}) was started. At the third hour, a prime of 5 μmol kg^{-1} of $NaH^{13}CO_3$ was given followed by primed-constant infusions of [1^{-13}C]potassium palmitate (prime, 2.4 μmol/kg; infusion 4.8, μmol kg^{-1} h^{-1}) and [$^2H_5$]glycerol (prime, 4.5 μmol/kg; infusion, 9.0 μmol kg^{-1} h^{-1}) started and maintained for 3 hours. Blood samples were collected hourly during the study and every 15 minutes during the third and final hours. Indirect calorimetry (Deltatrac; Sensormedics, Fullerton, CA) was performed for 30 minutes during the second hour.

2.3. Sample analyses

Plasma glucose concentrations were measured by the glucose oxidase method (YSI, Yellow Springs, OH), and plasma insulin by highly specific radioimmunoassay (Linco Research, St Charles, MO). Plasma FFA concentrations were measured by a spectrophotometric assay (Wako, Neusse, Germany).

Plasma palmitate concentrations were determined by in vitro isotope dilution [24] with the use of [2,2-$^2H_2$]palmitate (98% ^{2}H; Cambridge Isotope Laboratories, Andover, MA) as internal standard. The tracer to tracee ratios of plasma free palmitate were determined by negative chemical ionization gas chromatography–mass spectrometry (GC/MS) using a Hewlett-Packard 5989B GC/MS system (Hewlett Packard, Fullerton, CA) [25]. The pentafluorobenzyl derivative was prepared and analyzed by selectively monitoring ions from mass to charge ratios (m/z) 255 to 256. The plasma glycerol tracer to tracee ratio was measured by negative chemical ionization GC/MS on its heptafluorobutyric acid derivative, with selective monitoring of ions from m/z 680 to 685 [24]. Breath $^{13}CO_2$ content was determined by gas isotope ratio mass spectrometry on a Europa Tracermass Stable Isotope Analyzer (Europa Scientific, Crewe, United Kingdom).

2.4. Calculations

R_a palmitate and R_a glycerol were calculated from the following:

$$R_a = \left(\mathrm{Tr} / \mathrm{Tr}_{\mathrm{Inf}} / \mathrm{Tr} / \mathrm{Tr}_p - 1\right) \times i,$$

where $\mathrm{Tr}/\mathrm{Tr}_{\mathrm{Inf}}$ is the tracer to tracee ratio (mole %) in the infusate, $\mathrm{Tr}/\mathrm{Tr}_p$ is the ratio in plasma at tracer to tracee steady state (plateau), and i is the tracer infusion rate.

$$\text{Plasma palmitate oxidation rate(millimoles per kilogram LBM per hour)} = \left[\left(\dot{V}CO_2 / \mathrm{ARF}\right) \times \mathrm{IE}_{CO2}\right] / \left(\mathrm{Tr} / \mathrm{Tr}_{\mathrm{palmitate}}\right),$$

where $\dot{V}CO_2$ is the excretion rate of CO_2 in breath; ARF is the acetate recovery factor, a constant to adjust for the fraction of labeled breath CO_2 recovered after an infusion of [$^{13}C_1$]acetate in the fasted state [26]; IE_{CO2} is the isotopic enrichment of CO_2 (atom % excess); and $\mathrm{Tr}/\mathrm{Tr}_{\mathrm{palmitate}}$ is the steady-state tracer to tracee ratio of plasma palmitate (mole % excess).

R_a FFA(millimoles per kilogram fat per hour) = R_a palmitate/plasma (palmitate/FFA) ratio.
Plasma−derived FFA oxidation rate (millimoles per kilogram LBM per hour) = palmitate oxidation/plasma (palmitate/FFA) ratio.
Intraadipocyte FFA reesterification rate (millimoles per kilogram fat per hour) = (R_a glycerol × 3) − R_a FFA.
Intrahepatic FFA reesterification rate (millimoles per kilogram fat per hour) = R_a FFA − FFA oxidation.

Using the homeostatic model assessment of Matthews et al [23], HOMA-IR was calculated.

2.5. Body composition assessment

Total body and regional fat mass (FM) and total fat-free mass (FFM) were measured by dual-energy x-ray absorptiometry in all subjects at baseline and after 3 months of rosiglitazone treatment at the Body Composition Laboratory of the Children's Nutrition Research Center. Subjects were scanned in a supine position using a fan-beam Hologic QDR-Delphi-A instrument (Hologic, Bedford, MA) with software version 11.2.2. As part of the body composition analysis, the data for the whole-body scan are divided into 6 regions: left and right arm, left and right leg, trunk (including pelvis), and head. Precision for whole-body FM and FFM measurements is ±1.5% to 2.5%, whereas the precision for the regional measurements is typically ±5% to 8%. Waist and hip circumferences were measured according to a standard protocol.

All the above measurements were performed in each subject before and immediately after treatment with rosiglitazone at a dose of 8 mg/d for 3 months.

2.6. Statistical analysis

Pre- and posttreatment data were compared by paired t test. Differences were considered significant at $P < .05$. Data are expressed as mean ± SE.

Table 1
Baseline HIV characteristics of study subjects

Subject	CD4 count (mm^3)	Viral load (copies/mL)	Duration of HIV (y)	HAART	Duration of HAART (y)
1	484	842	16	ILS	10
2	460	524	12	LSNNeR	4
3	573	399	3	LSNe	3
4	313	399	8	AbDK	2
5	443	399	7	CNRSq	14
6	708	50	13	CK	7
7	611	1477	6	DIS	8
8	1598	399	8	AEK	8
9	408	399	7	LKS	8

HAART indicates highly active antiretroviral therapy; A, amprenavir; Ab, abacavir; I, indinavir; C, Combivir (Z/L); D, didanosine; E, efavirenz; K, Kaletra (Lo/R); L, lamivudine; N, nevirapine; Ne, nelfinavir; R, ritonavir; S, stavudine; Sq, saquinavir.

3. Results

3.1. HIV parameters

All subjects had been receiving a stable regimen of highly active antiretroviral therapy for at least 6 months (Table 1) at the start of the study and continued taking the same medications throughout the study. The RNA viral load was less than 1600 copies per milliliter in all subjects. At baseline, all had normal plasma concentrations of thyroid-stimulating hormone, free thyroxine, testosterone, hemoglobin, and indices of renal and liver function.

3.2. Lipid and glycemic profiles

All subjects had normal glucose tolerance at baseline. After rosiglitazone therapy, there was a significant decrease in insulin resistance as measured by the HOMA model (3.6 ± 0.4 to 2.4 ± 0.3, $P < .05$) and in fasting plasma insulin concentrations (14.5 ± 1.6 to 9.9 ± 1.5 μIU/mL, $P < .05$) without a change in fasting glucose concentrations (5.5 ± 0.2 to 5.2 ± 0.2 mmol/L, P = not significant [NS]) or glycosylated hemoglobin levels (5.1% ± 0.2% to 5.2% ± 0.1%).

There were nonsignificant changes in the fasting plasma concentrations of total cholesterol (4.7 ± 0.4 to 5.0 ± 0.6 mmol/L, P = NS), triglycerides (3.2 ± 0.5 to 4.4 ± 1.0 mmol/L, P = NS), low-density lipoprotein cholesterol (3.1 ± 0.3 to 3.4 ± 0.4 mmol/L, P = NS), and HDL-C (0.9 ± 0.1 to 0.8 ± 0.1 mmol/L, P = NS) (Table 2).

Table 2
Serum biochemistry pre– and post–rosiglitazone therapy

Parameters	Pretreatment	Posttreatment	P
Total cholesterol (mmol/L)	4.7 ± 0.4	5.0 ± 0.6	NS
HDL-C (mmol/L)	0.9 ± 0.1	0.8 ± 0.1	NS
LDL-C (mmol/L)	3.1 ± 0.3	3.4 ± 0.4	NS
Triglycerides (mmol/L)	3.2 ± 0.5	4.4 ± 1.0	NS
Fasting plasma glucose (mmol/L)	5.5 ± 0.2	5.2 ± 0.2	NS
Fasting plasma insulin (μIU/L)	14.5 ± 1.6	9.9 ± 1.5	<.05
HOMA -IR	3.6 ± 0.4	2.4 ± 0.3	<.05
HbA_{1c} (%)	5.1 ± 0.2	5.2 ± 0.1	NS
ALT (U/L)	41.9 ± 5.8	30.0 ± 2.5	NS
AST (U/L)	31.3 ± 3.2	27.4 ± 1.9	NS

LDL-C indicates low-density lipoprotein cholesterol; HbA_{1c}, glycosylated hemoglobin; ALT, alanine transaminase; AST, aspartate transaminase.

3.3. Body composition

Body weight, total FM, and total FFM did not change significantly following rosiglitazone treatment. However, there was a significant increase in hip circumference (0.93 ± 0.02 to 0.95 ± 0.02 m, $P < .05$) and decrease in waist to hip ratio (0.98 ± 0.02 to 0.95 ± 0.02, $P < .02$), without a change in waist circumference (0.91 ± 0.10 to 0.91 ± 0.10, P = NS) (Table 3).

3.4. Lipid kinetics

Basal rates of appearance of glycerol and palmitate, intraadipocyte reesterification, and fat oxidation were similar to values reported by us previously[6,8,9]. After 3 months of rosiglitazone treatment, there was a significant increase in the plasma rate of appearance (R_a) of glycerol and, hence, of FFAs (R_a glycerol: 1.12 ± 0.13 to 1.52 ± 0.23 mmol glycerol per kilogram fat per hour, $P < 0.05$; R_a FFA_{total}: 3.37 ± 0.40 to 4.57 ± 0.68 mmol FFA per kilogram fat per hour, $P < .05$). This was accompanied by a significant increase in intraadipocyte FFA reesterification (1.25 ± 0.35 to 2.43 ± 0.65 mmol FFA per kilogram fat per hour, $P < .05$). The rate of net lipolysis remained unchanged (R_a palmitate: 0.89 ± 0.13 to 0.80 ± 0.08 mmol palmitate per kilogram fat per hour, P = NS; R_a FFA_{net}: 2.47 ± 0.43 to 2.42 ± 0.37 mmol FFA per

Table 3
Body composition parameters pre– and post–rosiglitazone therapy

	Pretreatment	Posttreatment	P
Weight (kg)	76.2 ± 3.4	75.1 ± 2.9	.26
BMI (kg/m^2)	23.8 ± 0.7	23.7 ± 0.8	.76
Waist (m)	0.91 ± 0.10	0.91 ± 0.10	.48
Hip (m)	0.93 ± 0.02	0.95 ± 0.02	.04
Waist to hip ratio	0.98 ± 0.02	0.95 ± 0.02	.01
Total body fat (kg)	13.2 ± 2.0	13.2 ± 1.9	.92
LBM (kg)	60.3 ± 1.7	60.2 ± 1.6	.90
Arm fat content (kg)	1.2 ± 0.2	1.2 ± 0.2	.99
Leg fat content (kg)	2.4 ± 0.4	2.4 ± 0.4	.98
Trunk and pelvic fat (kg)	4.4 ± 1.7	4.7 ± 1.8	.89

Table 4
Lipid kinetics pre– and post–rosiglitazone therapy

Parameters	Pretreatment	Posttreatment	*P*
R_a glycerol (mmol FFA kg^{-1} fat h^{-1})	1.12 ± 0.13	1.52 ± 0.23	.020
Total lipolysis (R_a FFA_{total}) (mmol FFA kg^{-1} fat h^{-1})	3.37 ± 0.40	4.57 ± 0.68	.031
R_a palmitate (mmol FFA kg^{-1} fat h^{-1})	0.89 ± 0.13	0.80 ± 0.08	.799
Net lipolysis (R_a FFA_{net}) (mmol FFA kg^{-1} fat h^{-1})	2.47 ± 0.43	2.43 ± 0.38	.319
Intraadipocyte FFA reesterification (mmol FFA kg^{-1} fat h^{-1})	1.25 ± 0.35	2.43 ± 0.65	.031
Plasma FFA oxidation (mmol FFA kg^{-1} LBM h^{-1})	0.30 ± 0.04	0.32 ± 0.04	.601
Intrahepatic reesterification (mmol FFA kg^{-1} fat h^{-1})	0.59 ± 0.07	0.56 ± 0.10	.684

kilogram fat per hour, P = NS). Both oxidation of plasma FFA (0.30 ± 0.04 to 0.32 ± 0.04 mmol FFA per kilogram lean body mass [LBM] per hour, P = NS) and the rate of intrahepatic reesterification (0.59 ± 0.07 to 0.56 ± 0.10 mmol FFA per kilogram fat per hour, P = NS) remained unchanged after rosiglitazone treatment (Table 4).

4. Discussion

The results of the present study demonstrate several striking effects of rosiglitazone on the abnormal lipid kinetics characteristic of HADL that explain some of the conflicting biochemical, metabolic, or body composition outcomes in clinical trials of this PPARγ agonist and circumscribe a specific aspect of lipid metabolism in which it could exert a beneficial effect. Rosiglitazone treatment for 3 months induced a significant increase in the already elevated rate of total lipolysis and of intraadipocyte reesterification, but not in the rates of net lipolysis, plasma FFA oxidation, or intrahepatic reesterification. There were also an increase in hip circumference and a decrease in the waist to hip ratio. These findings suggest a complex but consistent response to rosiglitazone in lipodystrophic adipose depots that has 2 consequences consistent with the apparently paradoxical clinical trial observations.

First, the increased rate of intraadipocyte reesterification —essentially, an increase in immediate recycling of hydrolyzed fatty acids back into triglycerides within the adipocyte—has a salutary effect in retaining triglycerides within subcutaneous adipose depots and thus expanding or a least maintaining the size of these depots. This marked increase in the rate of intraadipocyte reesterification is consistent with the known molecular effects of PPARγ signaling on adipocytes. For example, PPARγ2 activation up-regulates the expression of adipose triglyceride lipase, which catalyzes the first step in adipocyte triglyceride hydrolysis; this would accelerate total lipolysis in adipose tissues [27]. However, a concomitant, classic effect of PPARγ2 activation in adipocytes is to up-regulate expression of phosphoenolpyruvate carboxykinase, which enhances glyceroneogenesis and would thus promote triglyceride resynthesis [28]. Thus, PPARγ agonism in adipose tissues would create a futile cycle of triglyceride hydrolysis and reesterification (manifested as accelerated total lipolysis together with accelerated reesterification), but ultimately permit enhanced lipid retention within viable adipocytes [29] by promoting glyceroneogenesis as well as blunting local glucocorticoid generation [30,31]. Second, the lack of change in the rate of net release of FFAs (a consequence of increased total lipolysis with correspondingly increased intraadipocyte triglyceride recycling) without a further increase in oxidative disposal of these fatty acids explains why the levels of the plasma lipid fractions are unchanged. The implication is that rosiglitazone lacks an effect on hepatic handling of FFAs in the fasted state, hepatic lipogenesis, or VLDL-triglyceride synthesis. This, too, is consistent with what is known regarding the effects of specific PPARγ agonists on these parameters. Beysen et al [32] have shown that pioglitazone, but not rosiglitazone, can blunt hepatic de novo lipogenesis and diminish VLDL-TG synthesis and release in humans. Hence, rosiglitazone would not be expected to exert any measurable effect on fasting plasma lipid or lipoprotein levels at any step "distal" to adipocyte FFA release; and an unchanged rate of net lipolysis would give rise to unaltered levels of fasting triglycerides. Thus, the rosiglitazone-induced increase in intraadipoctye reesterification would promote adipocyte triglyceride retention; but this beneficial effect is blunted by its concomitant acceleration of triglyceride hydrolysis within adipocytes. These findings also add strength to the previous studies by ourselves and others [6,8,9] that a fundamental defect in HADL is an increased total lipolysis within adipose tissues and with inability of adipocytes to retain fat stores.

In this study, rosiglitazone treatment resulted in a small but significant increase in hip circumference without a change in waist circumference, resulting in a decrease in the waist to hip ratio. This observation suggests, but does not confirm, that the overall fat retention may be occurring preferentially in the peripheral adipocytes of the femorogluteal region, a prominent site of lipoatrophy in HADL patients. These findings are similar to the changes in waist and hip circumferences and the waist to hip ratio reported in the Diabetes Reduction Assessment with Ramipiril and Rosiglitazone (DREAM) study, which measured responses to rosiglitazone for a median of 3 years in non-HIV prediabetic patients [33]. However, regional dual-energy x-ray absorptiometry scan data did not show increased FM in the limbs following rosiglitazone treatment. Hence, there may be variations among different "peripheral" adipose compartments with respect to responses to rosiglitazone, so that the femorogluteal area might be more sensitive to this PPARγ agonist with regard to the ability to retain fat retention inpatients with HADL. Further studies are needed to examine differential fat turnover in regional adipocyte stores and correlate them with this kinetic model of HADL.

The effect of rosiglitazone on insulin sensitivity, lipids, and body morphology in patients with the HIV lipodystrophy has been evaluated in several previous clinical trials [13-15,18-20,34]. Despite a consistent improvement in insulin sensitivity in most studies [13-17], plasma triglyceride concentrations have tended to worsen [13,18,19]. Our study is consistent with the published literature supporting a significant improvement in insulin sensitivity, but without any increase in plasma triglyceride concentrations, and demonstrates mechanisms that could underlie this apparently paradoxical outcome.

Previous studies examining the effect of rosiglitazone on improving peripheral lipoatrophy show conflicting results. Hadigan et al [14] and other groups [14,16,19,20] reported a significant improvement in subcutaneous fat, whereas other investigators did not find any improvement [18,35], after prolonged therapy with rosiglitazone at maximal doses. We found a potential improvement in femorogluteal FM (as reflected by an increase in the hip circumference) and propose that this result may be explained by the salutary effect of rosiglitazone on intraadipocyte reesterification in lipoatrophic tissues. Consistent with our finding, a recent study reported significant improvement in lipoatrophy when patients infected with HIV were treated with rosiglitazone [36].

In conclusion, rosiglitazone therapy has several metabolic effects in patients with HADL. There is a direct effect on promoting intraadipocyte reesterification. However, this potentially beneficial effect is offset by increased total lipolysis that translates to limited fat retention and increasing futile cycling. Limitations of this study include the small sample size, open-label nature of the intervention, and the different anti-retroviral regimens of the subjects. Nevertheless, these data provide a plausible mechanistic explanation for the apparently contradictory reports of the effects of rosiglitazone on peripheral lipoatrophy in the medical literature. Future studies evaluating a combination of PPARγ agonists with potent inhibitors of hormone-sensitive lipase and adipocyte triglyceride lipase could offer specificity to the therapeutic approach by improving both the altered lipid kinetics and metabolic phenotype of HADL.

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