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Rosiglitazone Improves Lipoatrophy in Patients Receiving Thymidine-Sparing Regimens

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Abstract

Objective—Thymidine reverse transcriptase inhibitors (tNRTI) are strong inhibitors of PPAR- γ and clearly implicated as a cause of lipoatrophy. Thiazolidenediones (TZD), potent PPAR- γ agonists, would be expected to be beneficial in HIV lipoatrophy, but prior studies have been conflicting. None specifically excluded the use of tNRTIs. We report the first study in individuals treated with tNRTI-sparing regimens using a TZD for treatment of HIV lipoatrophy.

Design: This double-blind, placebo-controlled study evaluated limb fat in HIV-infected subjects with lipoatrophy who discontinued tNRTI at least 24 weeks prior to enrollment.

Methods—Subjects were randomized to rosiglitazone vs. placebo for 48 weeks. Dual energy X-ray absorptiometry (DEXA)-scans and fasting metabolic assessments were serially performed.

Results—We enrolled 71 subjects: 17% were female and 51% white. Baseline characteristics were similar between groups except for higher total cholesterol in the placebo group ($p=0.04$). At 48 weeks, limb fat (grams) increased significantly ($p=0.02$) more in the rosiglitazone than in the placebo group: median (IQR) 448 (138, 1670) vs. 153 (–100, 682), respectively. Of lipids parameters, only total cholesterol increased significantly more in rosiglitazone group ($p=0.008$). Prevalence of metabolic syndrome and total bone mineral density did not change between or within groups.

Conclusion—In the absence of tNRTIs, rosiglitazone significantly improves lipoatrophy without deleterious effect on bone mineral density. Total cholesterol, but not triglycerides, significantly increased in the rosiglitazone arm. The glitazones may be a promising addition for accelerating fat recovery in subjects who had switched off tNRTI and remain with significant lipoatrophy.

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Keywords

Lipoatrophy; Thiazolidenediones; antiretroviral therapy

Background

Although the introduction of antiretroviral therapy (ART) has markedly decreased the morbidity and mortality of HIV infection [1], the benefits of ART have often come at the price of significant metabolic adverse effects. Lipoatrophy, subcutaneous fat wasting of the face and/or extremities, has been described in HIV-infected individuals receiving ART with or without associated central fat accumulation and insulin resistance. Lipoatrophy can be stigmatizing to patients and is associated with depression and decreased quality of life [2].

Thymidine nucleoside reverse transcriptase inhibitors (tNRTIs), stavudine (d4T) and zidovudine (ZDV), have clearly been implicated as a cause of lipoatrophy [3–5]. The tNRTI's down-regulate the nuclear transcription factor peroxisome proliferator-activated receptor- γ (PPAR γ) and thus may inhibit adipogenesis [6,7]. Switching from tNRTIs to other nucleoside analogs, particularly abacavir or tenofovir, has modestly but significantly increased limb fat [3,5,8–10]. However, as these increases are often slow and incomplete, most individuals remain with significant lipoatrophy after antiretroviral switches. Thus, additional treatment options are needed for HIV lipoatrophy.

The insulin-sensitizers thiazolidenediones (TZD) are potent selective agonists of PPAR- γ , which influence the transcription of genes that regulate adipogenesis, glucose, and lipid metabolism [11]. Thiazolidenediones are approved by the US Food and Drug Administration for the treatment of type II diabetes, and have been reported to increase subcutaneous fat in individuals with inherited disorders of mitochondrial function and/or diabetic lipoatrophy [12]. Therefore, they should theoretically be useful in the treatment of HIV lipoatrophy. However, to date, studies of glitazones for HIV lipoatrophy have yielded conflicting results [13–19], possibly due to the fact that none of these studies specifically excluded ongoing use of tNRTIs. This exclusion is of paramount importance as the concomitant use of tNRTI's has been shown to blunt the activity of rosiglitazone on PPAR- γ [6]. Thus, we hypothesize that the TZD rosiglitazone increases limb fat in HIV-infected subjects with established clinical lipoatrophy who are receiving thymidine-sparing regimens.

Methods

Subjects

This double-blind, placebo-controlled study evaluated limb fat in HIV-infected subjects with lipoatrophy who discontinued tNRTI at least 24 weeks prior to enrollment. The participants were enrolled at Case Western Reserve University and Cleveland Clinic in Cleveland, Ohio from July 2006 to December 2007. The Institutional Review Board (IRB) Committees of both institutions approved the study. All subjects gave written informed consent.

HIV-infected subjects ≥ 18 years old with clinical lipoatrophy were enrolled. Clinical lipoatrophy was defined as fat loss of at least moderate severity in at least two different areas of the following body areas: face, arms, legs, or buttocks. Self reports were confirmed by a physician. To be considered with moderate lipoatrophy and qualify for this study, patients had to self-report their awareness of visible changes in their limbs or face including awareness of visible decrease in limb or facial fat, awareness that their pants or watch are fitting loosely, and of prominent veins in the extremities. Investigator had to also confirm physical documentation that extremities appear extremely thin with global prominence of veins, and

physical evidence of definite depletion of tissue in the area of the buccal fat pads. Inclusion criteria included a past history of receiving tNRTI (d4T or ZDV) for at least 12 cumulative months, discontinuation of tNRTI therapy and receipt of a stable thymidine NRTI-sparing regimen for at least 24 weeks prior to study entry, HIV-1 RNA ≤ 5000 copies/mL, and no intent on the part of the subject or provider to alter ART over the study period. In addition, women of childbearing potential were required to have a negative pregnancy test at study entry and to use strict contraception during the study. Insulin resistance was not a required inclusion criterion.

Individuals were excluded if they had liver cirrhosis, heart failure of New York Heart Association class 3 or 4, diabetes mellitus, or were receiving metformin or glitazones. Individuals who were pregnant or breastfeeding, or who were receiving any hormonal supplementation with recombinant growth hormone, anabolic steroids, estrogen or testosterone (except at replacement doses) were excluded. Additionally, subjects were excluded if they had serum transaminases greater than 2 times the upper limit of normal (ULN), lipase >2.5 ULN, creatinine >3 ULN, PT/PTT greater than 1.2 ULN, absolute neutrophil $<750/\text{mm}^3$, hemoglobin <9.0 g/dL, platelet count $<75,000/\text{mm}^3$, or glucose <70 mg/dL.

Interventions

The subjects were centrally randomized 1:1 in a double-blinded fashion to receive either rosiglitazone or matching placebo for 48 weeks. In the dose-escalation period, subjects received rosiglitazone 4 mg daily for 4 weeks. The dose was then increased to 4 mg twice daily for the remainder of the study. All ART was continued unchanged, and subjects were strictly informed to maintain their current diet and exercise regimens.

Outcome and Follow-up

Study evaluations included physical examination, fasting metabolic assessments, clinical lipoatrophy questionnaires filled out independently by physicians and subjects, dietary questionnaires, and whole body dual-energy x-ray absorptiometry (DEXA) scanning at study entry, weeks 24 and 48. Additional safety visits occurred at weeks 2, 4, 12, 18, and 36.

Total body DEXA scans were performed at a single site (Case) on all study subjects using a Hologic QDR-4500A (Hologic Inc, Bedford, MA). The DEXA were assessed with a dedicated scanner and technologist who was blinded to treatment allocation. Analysis of overall and body site-specific fat were performed on the basis of the standard protocol for body composition examination.

Clinical lipoatrophy scores were obtained by questionnaires at study entry and at weeks 24 and 48. These questionnaires rated the loss of fat in predefined body areas: arms, legs, buttocks and the face. Assessments within each of these sites were rated “0” for “absent”, “1” for “mild”, “2” for “moderate”, and “3” for “severe”. These scores were summed for a lipoatrophy self-rated score. Thus, the lipoatrophy score could vary between 0–12. The same questionnaire was completed separately and independently by the subject and the physician.

The metabolic assessments were done in a fasting state of at least 8 hours. They included glucose, insulin, and lipoprotein levels. The homeostasis model assessment (HOMA-IR) was calculated from fasting insulin and glucose levels as described by Matthews [20].

All visits included assessment for clinical adverse events, use of concomitant medications, targeted physical examination, complete blood count, biochemistry (including electrolytes, liver transaminase levels, and creatinine concentration). Adherence to study medication was determined by pill count of dispensed versus returned pills at each study visit. Permanent cessation of the drug was mandatory for grade 4 adverse events or pregnancy.

Statistical Analysis

The primary outcome measure was the change in limb fat at 48 weeks between the rosiglitazone and placebo group. A sample size of 70 subjects (35 in each arm) was required to detect a difference of 0.5 kg change in limb fat between the treatment groups with 80% power, assuming a standard deviation of 0.7 kg and allowing for a dropout rate of 10%. Secondary outcome measures included changes in metabolic parameters. The change from baseline to week 48 was compared within- and between-groups.

Variables were assessed for normality before tests of significance were carried out. Additionally, in the normally distributed variables, tests of equality of variances were also done. For two-sample tests, Student's *t* tests were used when the variables were normally distributed (with the appropriate formulation when variances were unequal) and Wilcoxon rank sum tests were used when the distribution was not normal. For one-sample tests (or change-from baseline variables), paired *t* tests or Wilcoxon signed rank tests were used. A *p* value of 0.05 was considered statistically significant. All analyses were carried out using SAS, v.8.2 (The SAS Institute, Carey, NC).

Results

Baseline Characteristics

We enrolled 71 subjects for this study, 34 of whom were randomized to receive rosiglitazone. Table 1 shows the baseline characteristics of the study groups. Demographics, clinical and HIV disease parameters were similar between groups. There were no statistically significant differences in body mass index (BMI), limb fat, total bone mineral density (BMD) or insulin resistance parameters at study entry. At study entry the placebo group had significantly (*p*=0.04) higher total cholesterol. At baseline, the median (IQR) limb fat (grams) was similar between the rosiglitazone and placebo arms: 4696 (3644, 7758) and 5967 (3514, 8435); *p*=0.70. At entry, 26 (37%) had insulin resistance defined as insulin levels > 15μU/mL or 26 (37%) had HOMA-IR > 3.6. Both the durations of past tNRTI therapy and duration subsequently off tNRTIs were similar between the two groups.

Adverse events

None of our subjects modified their entry NRTIs during the study period. In the rosiglitazone group, one subject changed ART from nevirapine to efavirenz. In the placebo group, one subject switched from lopinavir/ ritonavir (LPV/r) to atazanavir/ ritonavir (ATV/r) and another switched from ATV/r to LPV/r.

Nine subjects (four in the rosiglitazone arm) were lost to follow-up. Of these, only one subject (in the rosiglitazone arm) discontinued the study secondary to a possible adverse event. This subject had exacerbation of a chronic documented coronary artery disease manifested by increasing chest pain; he was receiving atazanavir/ ritonavir and coformulated emtricitabine/ tenofovir. Four subjects, only one of whom on rosiglitazone, had grade 2 elevations of their transaminases (ALT/AST) that were not believed to be study related (history of prior elevations of transaminases and underlying chronic hepatitis C).

Changes in the Primary Endpoint: Limb Fat

The primary endpoint, change in DEXA-measured limb fat, is depicted in Figure 1 and Table 2. Limb fat increased significantly (*p*<0.03) from baseline to 48 weeks within both groups as would be expected after discontinuation of tNRTI. Additionally there was a significant (*p*=0.02) difference in the change in limb fat between the rosiglitazone and placebo groups. The median (IQR) increase in limb fat (grams) in the rosiglitazone group was 448 (138, 1670) compared to 153 (−100, 682) in the placebo group. The mean ± SD increase in limb fat (grams)

was 911 ± 1215 vs. 254 ± 1039 in the rosiglitazone vs. placebo group, respectively. At 24 weeks, the difference in limb fat between the groups did not reach but did approach statistical significance ($p=0.07$). Within the rosiglitazone group, limb fat significantly ($p<0.001$) increased from baseline by 24 weeks. As with the absolute values, percent change in limb fat significantly differed within and between-groups (Table 2). Trunk fat increased significantly ($p=0.002$) from baseline to 48 weeks in the rosiglitazone group. The changes were not significant within the placebo group or between the two groups.

To assess if all patients would similarly benefit from rosiglitazone treatment regardless of how much baseline lipoatrophy was present, we compared the 48-week change in limb fat of the subjects with lower baseline limb fat (below median value) vs. subjects with higher baseline limb fat (above median value). We evaluated subjects in the rosiglitazone treatment group to assess if subsequent limb fat change was similar regardless of the degree of lipoatrophy present at baseline. The median limb fat was 4600 grams at baseline in the subjects in the rosiglitazone treatment group ($n=34$). For the 17 subjects with baseline limb fat less than the median, the increase in limb fat (grams) was median (IQR) 358 (98, 448) vs. 1446 (178, 2268) ($p=0.052$) in the group with baseline limb fat greater than the median. In the rosiglitazone group, no significant ($R=0.29$; $p=0.13$) correlation was seen between limb fat at baseline and the subsequent limb fat change over 48 weeks. Limb fat increased to a similar degree regardless of the extent of baseline lipoatrophy. These findings suggest that subjects benefited from rosiglitazone treatment similarly regardless of how much limb fat was present at baseline.

In both the rosiglitazone and placebo groups, BMI increased significantly ($p<0.03$) from baseline to 48 weeks, but did not significantly differ between groups at 48 weeks. Absolute as well as percent change in limb fat over 48 weeks in the rosiglitazone group was not found to significantly (all $p>0.13$) correlate with baseline values of: BMI, insulin levels, HOMA-IR, or duration off tNRTIs. Also the limb fat change in the rosiglitazone group did not significantly correlate (all $p > 0.69$) with changes in insulin levels or HOMA-IR.

Changes in secondary endpoints

Subjective assessment of fat changes—To evaluate subjective assessments of fat changes by both physicians and subjects, we evaluated the changes in clinical lipoatrophy scores. There were no significant differences between rosiglitazone and placebo groups in either the subjects' or physicians' scores at study entry. At 48 weeks, there was a significant ($p<0.03$) difference in change in physician lipoatrophy scores between the rosiglitazone and placebo groups (Table 2). This difference was not significant by 24 weeks ($p=0.74$). In subject lipoatrophy scores, no significant differences were seen between the rosiglitazone and placebo groups at 24 or 48 weeks. Within the rosiglitazone group, physicians and subjects lipoatrophy scores changed significantly ($p < 0.007$) from baseline to 24 and 48 weeks. In evaluating facial atrophy scores, there was no difference between the groups in either subject or physician scores at 24 or 48 weeks. Within only the rosiglitazone group, the facial lipoatrophy scores changed significantly ($p<0.001$) from baseline to 48 weeks for subject and physician lipoatrophy scores.

Fasting Lipid Profile—Table 2 describes the changes in lipid profile from baseline to week 48. Six subjects (three in each group) were censored from the lipid analysis because they started lipid-lowering agents during the study period. In each group, one started a fibrate and two started statins. Total cholesterol was the only lipid parameter with significant differences between the two groups at 24 ($p=0.004$) and 48 weeks ($p=0.008$). Non-HDL cholesterol (mg/dL) levels were statistically significantly higher in the rosiglitazone group at 24 weeks ($p=0.04$), but these differences between the groups did not reach statistical significance ($p=0.05$) at 48 weeks. Also, no between or within-group differences were seen in triglycerides and HDL-cholesterol levels at either 24 or 48 weeks.

Insulin Resistance Parameters—Table 2 shows the median changes from baseline in insulin levels and HOMA-IR in both groups. At 48 weeks, there were significant ($p<0.03$) differences between the rosiglitazone and placebo groups for both markers. These differences were not significant at 24 weeks. Only the rosiglitazone group had a significant ($p=0.01$) improvement in these insulin resistance parameters. Changes over 48 weeks in limb fat, as well as in insulin and HOMA-IR, did not differ ($p>0.12$), between those who had insulin resistance at baseline and those who did not.

Safety measures—Table 2 details the safety parameters. No significant change in total BMD was detected within or between study arms from baseline to week 48. The change seen in the rosiglitazone arm represents an approximately 1% increase in BMD with no change in the placebo arm. No significant differences were seen in waist-hip ratio, or blood pressure, or prevalence of metabolic syndrome between study arms throughout the study period. HIV-1 RNA and CD4+ cell counts remained stable throughout the study period in both arms. At week 48, 98% of the study subjects had an HIV-1 RNA < 400 copies/mL.

Discussion

Lipoatrophy continues to affect a significant proportion of people living with HIV. ART “switches” have been the only therapy to date proven to reverse lipoatrophy [3,5,8–10]. However, the improvements in limb fat seen with these “switches” have been very slow and for the most part incomplete. Thus, more options are needed for the many individuals who remain with significant lipoatrophy.

This present study demonstrates that rosiglitazone significantly improves limb fat in subjects receiving thymidine-sparing regimens. These findings support that rosiglitazone adds to the available treatment options for ART-associated lipoatrophy. Our finding of increased limb fat from baseline in the placebo arm, in addition to in the rosiglitazone arm, is consistent with the slow improvement of lipoatrophy after discontinuation of tNRTI described in prior “switch studies.” In addition to these observed changes in both arms, significantly greater increase in limb fat was seen in the rosiglitazone arm compared with the placebo arm in our study. This finding supports an effect the study drug beyond that of the tNRTI switch. Additionally, our observation of approximately 900 grams mean increase in limb fat surpasses the mean increase of 350–450 grams of limb fat seen at 24–48 weeks in successful switch studies [3,5,10]. The greater magnitude of these observed fat changes further supports an effect of rosiglitazone on the improvement of lipoatrophy.

Although prior studies of glitazones for the treatment of lipoatrophy have been conflicting, [13–19,21,22] none of them specifically excluded the active use of tNRTI. Indeed, this is of paramount importance since Mallon et al have shown that concomitant use of tNRTIs blunt the activity of rosiglitazone on PPAR γ [6]. Also supporting the importance of tNRTI cessation in lipoatrophy, a clinical study showed that limb fat increases in the subset of subjects without d4T in the backbone were significantly ($p=0.0013$) greater than limb fat changes in the subjects with d4T [17]. The amount of fat change seen in the glitazone group after 48 weeks, a mean 380 and 450 grams overall and in subjects without d4T backbone, respectively, was less overall than in our study. We were not powered to assess subset analysis of the response to rosiglitazone vs. placebo based on prior exposure d4T vs. AZT. Despite improvement in DEXA-measured limb fat, subjective changes were not seen, a similar finding to other studies that were considered successful [3,23]. This is likely due to the degree of improvement of limb fat, which although significant, is not large enough during the 48-week of the study to lead to obvious clinically visible body fat change. Additionally, trunk fat increased significantly in the rosiglitazone group but not between the two groups. This may have also affected the perceptions of change in limb fat.

We acknowledge that our patients had relatively high baseline limb fat compared to prior studies. However prior studies have included patients actively on thymidine NRTIs and thus with more severe lipoatrophy. In our study, patients had already stopped tNRTIs for a median duration 3.75 years, and thus it is very likely that their lipoatrophy had already improved by the time they entered our study. Nonetheless, the finding that rosiglitazone may speed up the recovery of limb fat after discontinuation of tNRTIs is important and clinically relevant to the many patients who currently remain with lipoatrophy. Also, despite the fact that a normal limb fat is considered to be about 7–9 kg, some obese patients have a pre-lipoatrophy limb fat of up to 28 kg (McComsey, personal observation), and thus they could lose more than 50% of their limb fat and still be considered above the “normal” range..

In most of the prior studies in which rosiglitazone was shown to increase limb fat [15,16], subjects had been chosen based on their insulin resistance status. Although the differing findings in these prior studies may have been related in part to tNRTIs, the role of insulin resistance in determining the response to TZD agents is not clear. In our present study, subjects were evaluated regardless of their insulin-resistance status. Over the 48 weeks of the study, insulin resistance parameters significantly improved from baseline in the rosiglitazone group and were significantly different between the groups as detailed in Table 2. Also, we did not find a correlation between baseline insulin resistance indices and subsequent changes in limb fat over 48 weeks nor that subsequent improvement in limb fat at 48 weeks differed between those with and without baseline insulin resistance.

We found that rosiglitazone had a negative, but modest impact on lipid profile. Total cholesterol did increase significantly in the rosiglitazone group as compared to placebo over 48 weeks. Although as baseline placebo values were significantly higher, this increase may represent a regression to the mean. Non-HDL cholesterol changes over 48 weeks approached statistical significance. Unlike other studies [13], triglycerides were not significantly affected. The prevalence of metabolic syndrome was also not significantly affected.

In conclusion, in the absence of tNRTI, rosiglitazone significantly improved peripheral lipoatrophy even in subjects without insulin resistance. Rosiglitazone was safe in our study population. Although total cholesterol increased significantly in the rosiglitazone group, other lipid parameters and the prevalence of metabolic syndrome was not adversely affected. HIV immunological and virological control was not affected, and there was no negative impact on total bone mineral density. This is the first trial to our knowledge to examine the efficacy of rosiglitazone in subjects exclusively receiving thymidine-sparing regimens. The glitazones may be a promising addition for speeding the recovery of limb fat in HIV infected subjects who have already switched off tNRTIs and remain with significant lipoatrophy.

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Rosiglitazone group:

Placebo group:

Figure 1.
Median limb fat by treatment group

Table 1

Baseline Characteristics

Median (IQR)	Rosiglitazone (n=34)	Placebo (n=37)
Age in years	47 (44, 52)	52 (44, 54)
Men, N (%)	29 (85)	30 (81)
White, N (%)	19 (56)	17 (45)
CD4+ cell count, cells/mm ³	596 (437, 706)	691 (423, 861)
Nadir CD4+ cell count, cells/mm ³	205 (98, 271)	123 (64, 247)
HIV-1 RNA <50 copies/mL, N(%)	28 (82)	29 (78)
Duration HIV diagnosis (months)	146 (122, 194)	170 (122, 231)
Duration on ART (months)	114 (96, 127)	105 (74, 123)
Duration on tNRTI (months)	65 (48, 94)	69 (24, 83)
Duration off tNRTI (months)	47 (14, 59)	42 (11, 64)
NNRTI at study entry, N (%)	15 (44)	14 (37)
PI at study entry, N (%)	19 (56)	23 (62)
TDF at study entry, N (%)	25 (74)	27 (73)
ABC at study entry, N (%)	16 (47)	15 (45)
AZT history, N (%)	29 (85)	26 (70)
D4T history, N (%)	25 (74)	25 (68)
Limb fat, grams	4696 (3644, 7758)	5967 (3514, 8435)
Total fat mass, grams	13553 (10821, 21702)	17508 (11911, 20994)
Trunk fat mass, grams	9237 (6194, 14081)	10057 (6873, 12226)
Trunk-limb fat mass ratio	1.9 (1.5, 2.1)	1.7 (1.3, 2.1)
Leg fat/ BMI	117 (88, 198)	141 (97, 210)
Lipoatrophy score, subject	8 (6, 10)	7 (5, 8)
Lipoatrophy score, physician	8 (5, 10)	7 (6, 9)
Facial lipoatrophy score subject	2 (1, 2)	2 (1, 2)
Facial lipoatrophy score physician	2 (1, 3)	2 (1, 2)
Systolic Blood Pressure, mmHg	120 (110, 130)	120 (112, 130)
Diastolic Blood Pressure, mmHg	80 (72, 88)	80 (74, 85)
Total cholesterol, mg/dL	174 (140, 215)	187 (172, 235) [#]
HDL, mg/dL	35 (31, 44)	38(35, 42)
Non-HDL cholesterol, mg/dL	142 (109, 181)	149 (133, 181)
TG, mg/dL	160 (93, 331)	201 (111, 301)
Insulin, IU/mL	14 (9, 19)	12 (9, 21)
Insulin >15 IU/mL at entry, N (%)	14 (41)	12 (32)
HOMA-IR	3.2 (1.9, 4.3)	2.4 (1.7, 4.8)
HOMA-IR >3.6 at entry, N (%)	14 (41)	12 (32)
BMD, g/cm ²	1.08 (1.01, 1.16)	1.11 (1.04, 1.17)
BMI, kg/m ²	25.3 (22.5, 30.8)	25.8 (22.8, 27.9)

Median (IQR)	Rosiglitazone (n=34)	Placebo (n=37)
Waist-hip ratio	0.98 (0.95, 1.05)	0.98 (0.94, 1.03)
Metabolic syndrome at entry, N (%)	14 (41)	11 (30)

Significant differences between groups at baseline (p=0.04)

Table 2
Change in Limb Fat and Fasting Metabolic Parameters by Treatment Group at Weeks 0 to 48

Median (IQR)	Rosiglitazone (n=29)	P (within group)	Placebo (n=32)	P (within group)	P (between groups)
Limb fat, grams	+ 448 (138, 1670)	<0.001	+ 153 (-100, 682)	0.03	0.02
Total fat mass, grams	+1711 (314, 3788)	<0.001	+659 (-571, 1507)	0.10	0.03
Trunk fat, grams	+ 1206 (-56, 14081)	0.002	+584 (-289, 1088)	0.08	0.07
Trunk-limb fat ratio	0.01 (-0.16, 0.76)	0.29	0.005 (-0.09, 0.092)	0.86	0.63
Leg fat/ BMI	+ 9.7 (0.1, 23.5)	0.003	0.65 (-4.6, 8.0)	0.32	0.04
Limb fat, % change	+ 11.5 (2.8, 24.0)	<0.001	+ 3.6 (-2.8, 9.4)	0.04	0.01
Lipoatrophy score, subject	-2.0 (-4.0, -2.0)	<0.001	-0.5 (-4.0, 1)	0.01	0.15
Lipoatrophy score, physician	-2.0 (-3.0, -1.0)	<0.001	-1.0 (-2.0, 1.0)	0.15	0.03
Facial lipoatrophy score, subject	-1 (-1, 0)	<0.001	0 (-1, 0)	0.06	0.26
Facial lipoatrophy score, physician	0 (-1, 0)	<0.001	0 (-1, 0)	0.12	0.54
Total cholesterol, mg/dL	+ 22 (-8.0, 37.0) (n=27)	0.02	-8 (-23.0, 13.0) (n=29)	0.22	0.008
TG, mg/dL	+19 (-32, -66) (n=27)	0.46	-1 (-61, 24) (n=29)	0.38	0.19
HDL, mg/dL	0 (-2, 8) (n=27)	0.28	0 (-1, 3) (n=29)	0.51	0.68
non HDL mg/dL	+8 (-10, 32) (n=27)	0.10	-2 (-17, 15) (n=29)	0.38	0.05
Insulin,	- 4.0 (-7.0, 2.0)	0.01	-0.5 (-4.0, 5.5)	0.58	0.02
HOMA-IR	- 0.8 (-1.9, 0.4)	0.01	-0.3 (-0.8, 1.4)	0.76	0.03
BMD, g/cm ²	- 0.001 (-0.020, 0.014)	0.60	0 (-0.015, 0.017)	0.71	0.64
BMI, kg/m ²	+ 0.9 (0.08, 1.6)	<0.001	+0.5 (-0.08, 1.3)	0.03	0.24
Waist-hip ratio	- 0.003 (-0.020, 0.029)	0.69	+ 0.008 (-0.024, 0.025)	0.83	0.96
SBP, mmHg	- 8 (- 11, 4)	0.18	- 1 (- 14, 10)	0.30	0.82
DBP, mmHg	- 1 (- 8, 8)	0.50	- 1.5 (- 10, 5)	0.26	0.76

Median (IQR)	Rosiglitazone (n=29)	P (within group)	Placebo (n=32)	P (within group)	P (between groups)
Metabolic syndrome at 48 weeks, N (%)	13 (43) (N=30)		7 (23) (N=31)		0.1
CD4+ cell count, cells/mm ³	- 66 (- 189, 266)	0.88	- 45 (- 213, 270)	0.85	0.99