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Effect of Recombinant Human Growth Hormone and Rosiglitazone for HIV-Associated Abdominal Fat Accumulation on Adiponectin and other Markers of Inflammation

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Abstract

Background/Objective—In a previous report of HIV-infected patients with fat redistribution, we found that recombinant human growth hormone (rhGH) therapy reduced visceral adipose tissue (VAT) but increased insulin resistance, and that the addition of rosiglitazone reversed the negative effects of rhGH on insulin sensitivity. In this study, we sought to determine the effects of recombinant human growth hormone (rhGH) and rosiglitazone therapy on an array of inflammatory and fibrinolytic markers.

Methods—72 patients with HIV-associated abdominal obesity and insulin resistance were randomized to treatment with rhGH, rosiglitazone, the combination of rhGH and rosiglitazone, or placebo for 12 weeks. Subjects with plasma and serum samples available at weeks 0 (n = 63) and 12 (n = 46-48) were assessed for adiponectin, C-reactive protein (CRP), homocysteine, interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), fibrinogen, plasminogen activator inhibitor-1 (PAI-1) antigen, and tissue plasminogen activator (tPA) antigen.

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Ethics Statement: The study protocol was approved by the institutional review boards of all participating study sites. All subjects provided written informed consent.

Registration: The study was registered at Clinicaltrials.gov (NCT00130286). http://www.clinicaltrials.gov/ct2/show/NCT00130286

Disclosure Statement: MJG served as a consultant to EMD Serono on two occasions, most recently in 2007. His institution (Weill Cornell Medical College) received research support from EMD Serono for a clinical trial of recombinant human growth hormone for which he was the local principal investigator from 2004–2005. DPK and EE received research support from EMD Serono to their institution (St. Luke's-Roosevelt Hospital) for a substudy of the present study (not reported herein). EE served as a consultant to Thera Technologies in 2010, which licensed tesamorelin to EMD Serono.

Results—Treatment with both rosiglitazone alone and the combination of rosiglitazone and rhGH for 12 weeks resulted in significant increases in adiponectin levels from baseline. Adiponectin levels did not change significantly in the rhGH alone arm. There were no significant changes in the other biomarkers amongst the different treatment groups.

Discussion—In this study of HIV-infected patients with altered fat distribution, treatment with rosiglitazone had beneficial effects on adiponectin concentrations, an effect that was also seen with combination rosiglitazone and rhGH. RhGH administration alone, however, did not demonstrate any significant impact on adiponectin levels despite reductions in VAT.

Keywords

Lipodystrophy; adiponectin; rosiglitazone; human growth hormone; HIV-1

Introduction

HIV-associated visceral fat accumulation is associated with an increased risk of metabolic disturbances and cardiovascular disease (CVD) [1]. Various inflammatory and fibrinolytic markers have been identified as potential surrogate predictors of cardiovascular risk in animal models or the general population [2-13] and, to a lesser degree, in HIV-infected patients[14-18]. Several studies have demonstrated elevations in these biomarkers, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and plasminogen activator inhibitor-1 (PAI-1) antigen, in HIV-infected patients with altered fat distribution often in association with insulin resistance [19-21]. The adipokine adiponectin is of particular interest as epidemiological studies have identified hypoadiponectinemia as an independent risk factor for CVD in the general population [2;3]. In the HIV population, adiponectin levels are reduced in patients with fat redistribution and inversely correlated with abdominal visceral fat mass [22]. Several drugs including recombinant human growth hormone (rhGH) have been shown to reduce visceral fat in HIV-infected patients [23-25], but little is known about growth hormone's influence on adiponectin and other cardiovascular biomarkers.

We previously reported the results of a randomized, placebo-controlled study examining the effects of rhGH and rosiglitazone on visceral adipose tissue (VAT) and insulin sensitivity in HIV-infected patients with abdominal fat accumulation [26]. In our primary study, treatment with rhGH for 12 weeks decreased visceral adiposity but increased insulin resistance; the addition of rosiglitazone successfully attenuated the effects on insulin resistance without abrogating the reduction in visceral fat. Herein we report the results of a substudy aimed at exploring the effects of rhGH and rosiglitazone therapy on the secondary outcomes of adiponectin and other inflammatory and fibrinolytic markers selected because of known associations with visceral adiposity and/or CVD risk.

Methods

Study Design

The current substudy is from a randomized, double-blind, placebo-controlled, multicenter trial using a 2 × 2 factorial design. Eligible subjects were randomized in a 1:1:1:1 ratio to receive recombinant human growth hormone (rhGH) 3mg daily, rosiglitazone 4mg twice

daily, combination rhGH + rosiglitazone, or double placebo treatment for 12 weeks. The primary endpoint of the main study was change in insulin sensitivity index (SI) assessed by frequently sampled intravenous glucose tolerance test (FSIVGTT). Key secondary endpoints included changes in visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) volumes by magnetic resonance imaging (MRI) from baseline to week 12. as previously published [26]. In this sub-study, stored blood samples of study participants were assayed for changes from baseline to week 12 in the inflammatory and fibrinolytic markers of interest.

Participants

Eligible subjects were 18 to 65 years old with documented HIV-1 infection and on stable antiretroviral medications. Subjects were referred by their clinicians or recruited via flyers and print ads. The study was conducted at the General Clinic Research Centers (GCRCs) of Weill Cornell Medical College, Columbia University School of Medicine, and St. Luke's-Roosevelt Hospital Center, all in New York City. A subsite of St. Luke's-Roosevelt Hospital Center, AIDS Community Research Initiative of America, recruited and enrolled participants and conducted outpatient assessments. Subjects had to meet established anthropometric criteria for excess abdominal fat consisting of both waist circumference >88.2 cm for men and 75.3 for women and waist:hip ratio of ≥0.95 for men and ≥0.90 for women [27;28]. They also had to have evidence of insulin resistance based on a quantitative insulin sensitivity check index [29] ≤ 0.33. In the primary study, 77 subjects were enrolled and randomized, of whom 72 initiated study drugs. The 63 subjects included in this secondary analysis were those with available frozen serum and plasma at study entry for performance of the biomarker assays.

Ethics

The study protocol was approved by the institutional review boards of all participating study sites. All subjects provided written informed consent.

Laboratory Methods

Fibrinogen assay was performed at the Biomarkers Core Laboratory of the Irving Institute for Clinical and Translational Research of Columbia University Medical Center. Fibrinogen was measured in an automated clot-rate assay based upon the original method of Clauss using the ST4 instrument (Diagnostica Stago) with an inter-assay coefficient of variation of 2.9%. Serum PAI-1 antigen, tPA antigen, adiponectin, IFN-γ, IL-1, IL-6, CRP and homocysteine assays were performed by the General Core Laboratory of the Weill Cornell Medical College Clinical and Translational Science Center. Serum adiponectin and CRP were determined using a quantitative singleplex immunoassay; serum concentrations of IL-1β, IL-6, IFN-γ, and TNF-α with a quantitative 4-plex multiarray immunoassay (Meso Scale Discovery, Gaithersburg, MD); serum homocysteine with a quantitative enzyme immunoassay kit (Bio-Rad, Hercules, CA); tPA and PAI-1 with quantitative enzyme immunoassay kits (Diagnostica Stago, Parsippany, NJ). Manufacturer average intra-assay and inter-assay coefficients of variation were <10% for adiponectin, CRP, homocysteine, tPA and PAI-1.

Statistical Methods

Baseline data were summarized on all subjects with baseline data on at least one biomarker. Absolute changes from baseline to week 12 (i.e., change = week 12 minus baseline) was defined as the primary endpoint of interest, and absolute change was then compared between the treatment groups. Only patients who had complete data at both time points were included in the analyses of changes in biomarkers, and missing data were not imputed. Normality of error terms from one-way ANOVA was initially tested through the Kolmogorov-Smirnov test. Since the normality of error terms failed, the nonparametric Kruskal-Wallis test was used to compare absolute change between the treatment groups for each outcome of interest. The Dunnett-Hsu multiple comparison adjustment was used for all post-hoc pairwise comparisons to the double placebo arm (via pairwise Wilcoxon rank-sum tests), whenever the overall treatment group effect existed. Two-way ANOVA was explored to evaluate the interaction of rosiglitazone and rhGH. Median and interquartile range (IQR) of original scale data were reported for all analyses. All p-values were two-sided, and $p<0.05$ was considered as statistical significance. Analyses were conducted with SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

Results

Table 1 summarizes the characteristics of the patient population at study entry. Age, body composition and metabolic parameters were similar between study groups.

Table 2 shows the change in inflammatory markers in the four study groups from baseline to 12 weeks. Change in adiponectin levels was significantly different between the four study groups ($p<0.0001$), driven by greater increases in the rosiglitazone and dual therapy arms, each relative to the double placebo arm. Figure 1a illustrates boxplots of the absolute changes in adiponectin by study arm, highlighting the increases in the rosiglitazone-containing arms in contrast to the relatively stable rhGH alone and double placebo arms. Changes in other inflammatory and fibrinolytic markers did not differ significantly between the groups. By two-way ANOVA, there was no statistically significant interaction between rhGH and rosiglitazone with regard to any of the biomarkers. Specifically, the interaction between rhGH and rosiglitazone for adiponectin had a P-value of 0.99, indicating that concurrent use of rhGH did not affect the changes in adiponectin mediated by rosiglitazone. The change in adiponectin did not correlate with change in insulin sensitivity index ($r = 0.08$; $p = 0.58$). As depicted in Figure 1b, CRP declined significantly within all four treatment arms from study entry to week 12 but did not differ across treatment arms.

Discussion

In this study of HIV-infected patients with visceral adiposity, we found that adiponectin levels increased significantly with rosiglitazone and combination rosiglitazone and rhGH treatment, whereas rhGH had no effect on adiponectin concentrations despite reductions in VAT. We did not find significant changes in CRP, fibrinogen, homocysteine, IFNγ, IL-1, IL-6, PAI-1, TNFα, or tPA levels between the study arms, though CRP declined within all four arms.

Adiponectin is an adipose tissue-derived regulatory protein that in the general population is inversely correlated with metabolic disturbances such as obesity, insulin resistance, type 2 diabetes and CVD. In the HIV population, adiponectin has been found to correlate inversely with visceral adiposity, lipoatrophy, insulin resistance and triglyceride levels [22]. It also appears to correlate with subclinical cardiac disease as assessed by coronary reserve flow in HIV-infected subjects [30]. More recently, a larger study found that HIV-infected men had lower levels of adiponectin compared to HIV-uninfected men, and that these levels were inversely associated with increased coronary stenosis on CT angiography [31]. These observations have led to the hypothesis that adiponectin could serve as a novel predictor of cardiovascular risk as well as a potential target for pharmacologic intervention.

Although rhGH therapy elicited significant reductions in VAT, the improvement in adiponectin concentrations in our study was attributable to rosiglitazone action alone and not to rhGH-related effects. Our findings are consistent with another study in HIV-infected subjects with abdominal fat accumulation in which rhGH therapy did not result in any change in adiponectin levels compared to placebo, though a lower physiologic dose of rhGH was employed in that study.[32]

Rosiglitazone is an insulin sensitizer that is known to raise adiponectin levels at the cellular level [33] and in several studies of HIV-negative individuals with type 2 diabetes [34], prediabetes, [35,36] and polycystic ovary syndrome.[37] In the HIV-infected population, our findings are consistent with another study that reported improvement in metabolic indices, including adiponectin, in HIV patients with lipoatrophy and hyperinsulinemia treated with rosiglitazone.[38] The improvement in adiponectin in the rosiglitazone-exposed groups could have been mediated by the drug's effects on insulin resistance, though these exact mechanisms have yet to be elucidated. Surprisingly, we were not able to demonstrate a significant association between the change in adiponectin and change in VAT (data not shown).

Notably, we found that CRP trended down longitudinally in all four study arms from baseline to week 12. A possible explanation for this could be improved compliance with lipid-lowering agents, taken by about half of study subjects, in the setting of being active participants in a study, though we have no data in this regard. Of note, CRP was an independent predictor of five year mortality in the Study of Fat Redistribution and Metabolic Change in HIV infection (FRAM)[39] as well as in an older study of HIV-infected women [40]. Elevated CRP levels were also predictive of acute myocardial infarction in HIV-infected patients in a large database analysis from academic health centers in Boston [16], though results from case-control studies have been conflicting.[14;41] Furthermore, CRP levels were predictive of progression of carotid intima-media thickness over 96 weeks in antiretroviral-naïve patients with HIV infection in a small, single center cohort.[15] The utility of CRP measurement in HIV-infected patients in a clinical setting, however, is uncertain.

We did not observe significant changes in fibrinogen, homocysteine, IFNγ, IL-1, IL-6, PAI-1, TNFα, or tPA level over the study period despite our a priori hypotheses that rhGH-induced reductions in VAT and rosiglitazone-induced improvements in insulin sensitivity would yield favorable changes in each biomarker. Our negative findings may have been due

to limited statistical power in light of our small sample size. It is also possible that our specific pharmacologic interventions were not robust enough or of sustained duration to overcome all the complex metabolic derangements in HIV lipohypertrophy.

We acknowledge that our study is limited by its small sample size and relatively high variability of some of the laboratory assays. In addition, since completion of the study, both drugs have come under limitations. RhGH did not receive FDA approval for the indication of treatment of HIV-related abdominal fat accumulation. Instead, tesamorelin (an analogue of growth-hormone releasing hormone) has emerged as the preferred agent for this indication. Moreover, recent studies with tesamorelin demonstrated improvements in adiponectin that correlated with reduction in VAT[42], supporting the drug's potential for concomitant cardiometabolic benefits. Rosiglitazone is less commonly used in clinical practice due to initial concern about increased cardiovascular events based on a 2007 meta-analysis [43]; however, re-analysis of the longer-term RECORD trial (Rosiglitazone Reevaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes) showing no significant elevated risk of heart attack or death compared to standard of care diabetes medications led to the removal of prior FDA restrictions in 2013.[44]

In conclusion, our data indicates that rosiglitazone therapy is associated with improved adiponectin levels in patient with HIV-related abdominal fat accumulation and insulin resistance. Although rhGH therapy has favorable effects on body composition including VAT reduction, it does not appear to have any corresponding benefit on inflammatory or fibrinolytic markers. Instead, dual therapy with an insulin-sensitizing agent seems to be preferable to rhGH alone for HIV-related fat accumulation by abrogating the insulin resistance observed with rhGH and raising adiponectin levels. More studies are ultimately needed to find the optimal combination of therapies to manage altered fat redistribution and adiponectin dysregulation in HIV-infected individuals.

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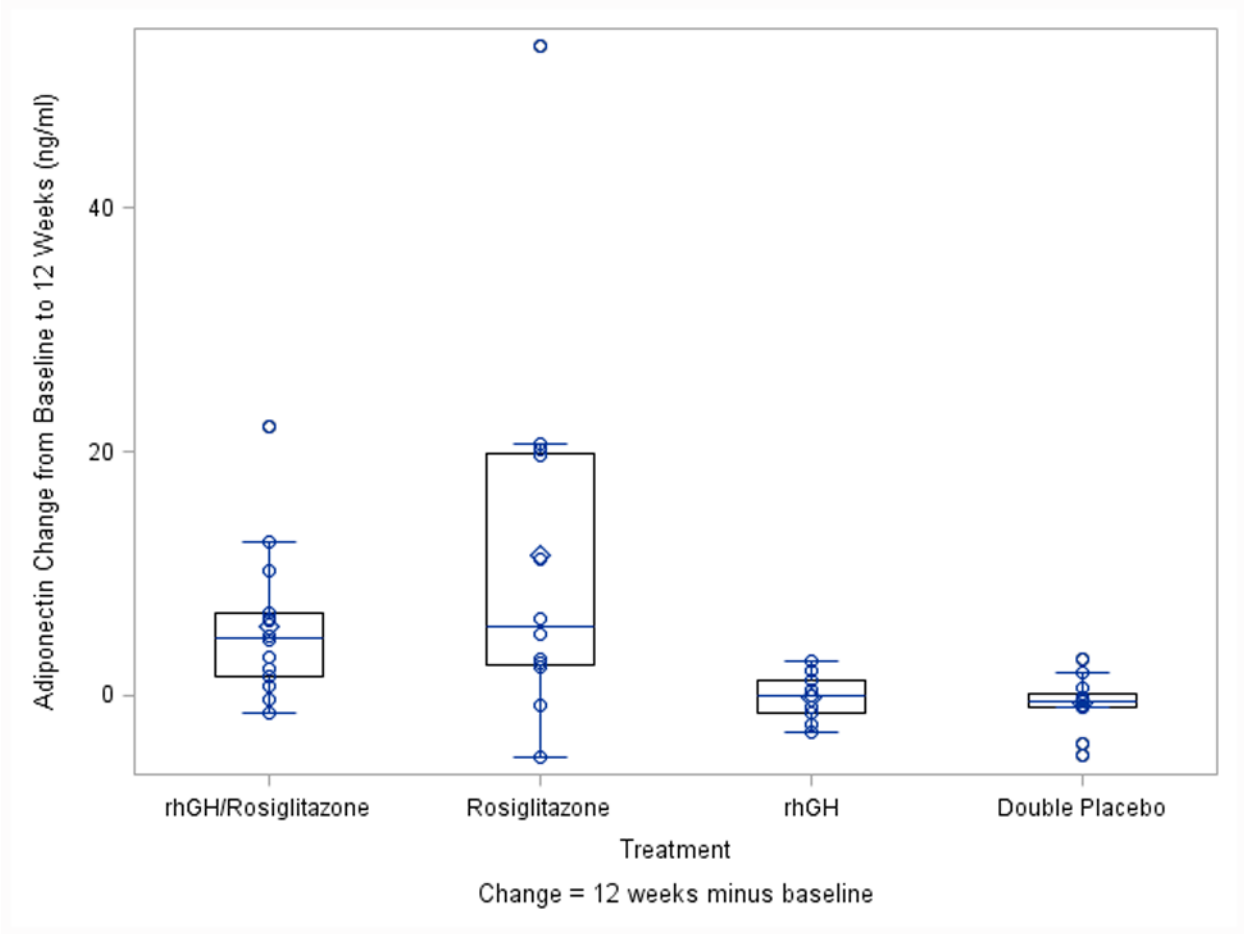

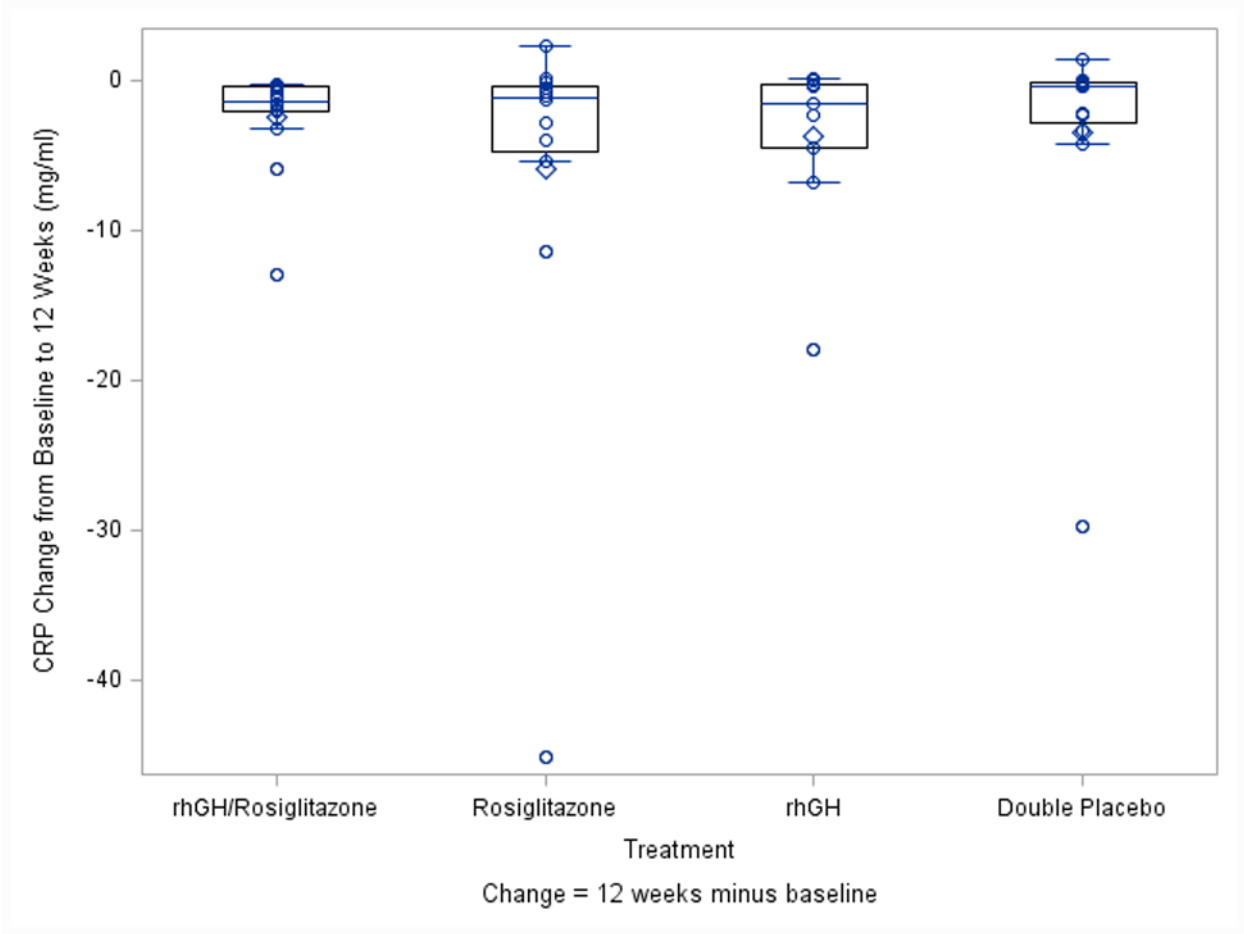

Figure 1.

A. Change in Adiponectin by Study Arm; P = 0.0004 across treatment arms by Kruskal-Wallis test. Within arm changes: rhGH/rosiglitazone P = 0.0010; rosiglitazone P = 0.0073; rhGH P = 0.82; double placebo P = 0.27. Boxplots display the median (line inside box), first and third quartiles (lower and upper edges of box), mean (diamond), and whiskers (maximum and minimum observations aside from outliers). Open circles depict the individual data points. B. Change in C-reactive Protein by Study Arm; P = 0.74 across treatment arms by Kruskal-Wallis test. Within arm changes: rhGH/rosiglitazone P = 0.0001; rosiglitazone P = 0.012; rhGH P = 0.0078; double placebo P = 0.014.

Table 1

Baseline Characteristics of Study Participants with Data on At Least One Biomarker (Total N=63)

Category	Variable	Variable Subcategory	rhGH/Rosiglitazone (n = 20)	Rosiglitazone (n = 15)	rhGH (n = 13)	Double Placebo (n = 15)
Demographic	Age, years		46.0 (41.5,52.0)	47.0 (45.0,52.0)	49.0 (47.0,51.0)	48.0 (42.0,55.0)
	Sex	Male	17 (85.0%)	13 (86.7%)	10 (76.9%)	11 (73.3%)
	Race	White	14 (70.0%)	11 (73.3%)	8 (61.5%)	10 (66.7%)
		Black	5 (25.0%)	4 (26.7%)	5 (38.5%)	6 (33.3%)
		> 1 race	1 (5.0%)	0	0	0
	Ethnicity	Hispanic	7 (35.0%)	8 (53.3%)	2 (15.4%)	7 (46.7%)
		Non-Hispanic	13 (65.0%)	7 (46.7%)	11 (84.6%)	8 (53.3%)
HIV	Antiretro-viral regimen	≥2 NRTIs + NNRTI	6 (30.0%)	6 (40.0%)	6 (46.1%)	7 (46.7%)
		≥ 2 NRTIs + PI	10 (50.0%)	7 (46.7%)	5 (38.5%)	7 (46.7%)
		≥ 3 NRTIs	2 (10.0%)	0	1 (7.7%)	0
		Other	2 (10.0%)	2 (13.3%)	1 (7.7%)	1 (6.7%)
		Stavudine or zidovudine use	5 (25.5%)	5 (33.3%)	4 (30.8%)	5 (33.3%)
Concomitant Medications	Fibrate		3 (15.0%)	2 (13.3%)	2 (15.4%)	3 (20.0%)
	Statin		7 (35.0%)	7 (46.7%)	4 (30.8%)	3 (20.0%)
	Fish oil		0	1 (6.7%)	0	1 (6.7%)
	Antihypertensive		6 (30.0%)	5 (33.3%)	4 (30.1%)	5 (33.3%)
Anthropometric	Height, cm		171.5 (166.5,176.5)	173.2 (167.0,177.4)	173.8 (167.7,179.6)	172.1 (165.9,175.4)
	Weight, kg		85.1 (75.3,94.1)	76.7 (71.4,83.0)	88.5 (82.1,99.2)	79.4 (71.3,98.8)
	Body mass index, kg/m^2		29.4 (25.3,31.5)	26.2 (25.0,28.5)	29.6 (28.9,32.0)	28.1 (25.5,33.9)
	Waist circumference, cm		101.4 (97.0,108.0)	98.2 (95.2,102.7)	106.2 (103.3,108.8)	99.8 (94.2,113.4)
	Hip circumference, cm		97.8 (95.8,100.0)	95.0 (92.9,97.2)	101.5 (99.2,106.9)	96.7 (92.3,109.3)
	Waist:hip ratio		1.0 (1.0,1.1)	1.0 (1.0,1.1)	1.0 (1.0,1.1)	1.0 (1.0,1.1)
Laboratory Values	Fasting insulin, miU/mL		18.1 (15.2,23.4)	18.9 (12.2,25.0)	17.1 (12.2,23.8)	16.0 (11.9,17.6)
	Fasting glucose, mg/dL		90.5 (83.5,96.5)	89.0 (81.0,92.0)	94.0 (90.0,104.0)	95.0 (89.0,98.0)
	QUICKI		0.31 (0.30,0.32)	0.31 (0.30,0.33)	0.31 (0.29,0.33)	0.32 (0.30,0.33)
	CD4 count*, cells × 10^6/L		556.0 (378.0,755.0)	737.0 (458.0,792.0)	495.0 (312.0,682.0)	604.0 (282.0,718.0)

Category	Variable	Variable Subcategory	rhGH/Rosiglitazone (n = 20)	Rosiglitazone (n = 15)	rhGH (n = 13)	Double Placebo (n = 15)
	HIV RNA < 400 ** copies/ml		15 (75.0%)	11 (78.6%)	9 (69.2%)	6 (46.2%)
	VAT, L		4.4 (2.7,7.3)	4.8 (4.2,5.6)	4.4 (3.6,6.4)	4.9 (3.8,7.4)
	SAT, L		21.9 (14.2,32.1)	18.3 (15.9,21.7)	24.7 (16.5,33.5)	21.0 (17.1,33.9)
	SI, μU * 10^{-4} * min^{-1} * ml^{-1}		1.7 (1.1,2.4)	1.9 (1.4,2.7)	1.7 (1.1,2.9)	1.6 (1.5,2.9)
	Insulin AUC, pmol/L *2h		405.0 (314.0,749.0)	324.4 (200.4,651.2)	609.1 (225.4,708.7)	327.9 (239.8,872.2)
	Glucose AUC, mmol/L *2h		517.0 (476.8,590.3)	525.3 (389.4,674.1)	518.0 (486.5,664.4)	527.1 (493.3,556.3)

Continuous variables are expressed as median (IQR)

Abbreviations: AUC, area under the curve from 2-hour oral glucose tolerance test; NNRTI, non- nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; QUICKI, quantitative insulin sensitivity check index SAT, subcutaneous adipose tolerance tissue volume; SI, insulin sensitivity by frequently sampled intravenous glucose tolerance test; VAT, visceral adipose tissue volume

* CD4 count available on n = 18, 13, 11, and 11 in rhGH/rosiglitazone, rosiglitazone, rhGH and double placebo arms respectively

** HIV RNA data available on n= 20, 14, 13, and 13 in rhGH/rosiglitazone, rosiglitazone, rhGH and double placebo arms respectively

Table 2

Changes in Biomarkers by Study Arm

	Rosiglitazone + rhGH n = 20			Rosiglitazone n = 15			rhGH n = 13			Double Placebo n = 15			p-value*
Biomarker	**Baseline**	**12-week**	**12-wk change**	**Baseline**	**12-week**	**12-wk change**	**Baseline**	**12-week**	**12-wk change**	**Baseline**	**12-week**	**12-wk change**	
Adiponectin, ng/ml Median(IQR)	n=14	n = 14	n=14	n=12	n=12	n=12	n=9	n=9	n=9	n=12	n=12	n=12	
	5.2 (3.5,6.6)	10.4 (7.7,14.2)	4.7** (1.5,6.7)	8.2 (5.8,11.8)	15.2 (10.0,27.5)	5.7** (2.6,19.9)	7.6 (4.9,8.7)	7.0 (5.7,9.9)	-0.1 (-1.5,1.2)	7.2 (4.9,11.6)	6.5 (4.6,9.9)	-0.5 (-1.0,0.2)	0.0004
hsCRP, mg/ml Median(IQR)	n=14	n=14	n=14	n=12	n=12	n=12	n=9	n=9	n=9	n=12	n=12	n=12	
	2.33 (0.7,4.6)	0.52 (0.2,1.5)	-1.42 (-2.1,-0.5)	3.09 (0.9,8.0)	1.03 (0.5,2.8)	-1.18 (-4.8,-0.4)	1.76 (0.6,7.9)	0.69 (0.2,1.3)	-1.53 (-4.5,-0.2)	3.36 (0.7,7.4)	0.92 (0.4,3.9)	-0.37 (-2.9,-0.1)	0.74
Homocysteine, µmol/ml Median(IQR)	n=14	n=14	n=14	n=12	n=12	n=12	n=9	n=9	n=9	n=12	n=12	n=12	
	10.5 (8.8,11.8)	11.7 (9.7,13.4)	1.3 (-0.4,2.1)	11.5 (9.1,14.3)	10.2 (9.1,12.6)	-0.6 (-3.3,0.2)	11.5 (10.0,13.4)	10.8 (10.1,11.6)	-0.9 (-1.1,0.8)	10.9 (8.1,13.5)	9.8 (8.5,12.8)	-0.2 (-1.6,2.5)	0.15
IL-1-β, pg/ml Median(IQR)	n=14	n=14	n=14	n=12	n=12	n=12	n=9	n=9	n=9	n=12	n=12	n=12	
	0.6 (0.3,1.5)	0.5 (0.3,1.2)	0 (-0.6,0.0)	0.3 (0.3,0.9)	0.3 (0.3,1.0)	0 (-0.4,0.5)	0.8 (0.3,0.9)	0.8 (0.3,1.0)	0 (0.0,0.7)	0.3 (0.3,1.1)	0.3 (0.3,1.0)	0 (-0.2,0.3)	0.54
IL-6, pg/ml Median(IQR)	n=14	n=14	n=14	n=12	n=12	n=12	n=9	n=9	n=9	n=12	n=12	n=12	
	1.1 (0.8,1.7)	0.9 (0.7,1.5)	-0.1 (-0.3,0.4)	1.2 (0.8,2.5)	0.9 (0.7,1.4)	-0.03 (-1.0,0.2)	1.3 (1.0,1.8)	0.9 (0.6,1.7)	-0.3 (-0.4,-0.2)	0.9 (0.8,1.5)	1.0 (0.6,1.3)	-0.1 (-0.2,0.1)	0.43
TnFα, pg/ml Median(IQR)	n=14	n=14	n=14	n=12	n=12	n=12	n=9	n=9	n=9	n=12	n=12	n=12	
	7.4 (6.2,10.1)	8.0 (6.2,9.9)	0.6 (-0.7,1.2)	6.8 (5.3,9.6)	5.6 (5.3,7.0)	-0.7 (-2.6,-0.2)	7.1 (6.7,8.5)	6.5 (4.5,7.1)	-1.2 (-2.0,-0.5)	7.5 (5.9,8.3)	7.7 (4.5,8.5)	-0.5 (-0.8,1.0)	0.26
IFnγ, pg/ml Median(IQR)	n=14	n=14	n=14	n=12	n=12	n=12	n=9	n=9	n=9	n=12	n=12	n=12	
	2.5 (1.6,4.3)	3.5 (3.0,4.2)	0.7 (-0.1,1.4)	3.7 (2.2,7.4)	3.5 (2.0,6.4)	-0.5 (-2.2,0.9)	3.3 (2.5,5.4)	3.1 (2.7,3.7)	0.5 (-2.7,0.6)	3.9 (1.8,5.9)	3.6 (1.8,5.7)	0.1 (-1.5,2.0)	0.62
Fibrinogen, mg/dL Median(IQR)	n=15	n=15	n=15	n=10	n=10	n=10	n=11	n=11	n=11	n=12	n=12	n=12	
	182.0 (146,236)	197.0 (156,222)	-4 (-34,38)	229.0 (168,271)	206.0 (154,226)	-20.5 (-87,-2)	193.0 (184,300)	223.0 (188,268)	-1 (-25,30)	237.0 (176,285)	210.5 (166.5,249.5)	-10.5 (-36.5,3.5)	0.40
PAI-1 antigen, ng/ml Median(IQR)	n=15	n=15	n=15	n=8	n=8	n=8	n=10	n=10	n=10	n=13	n=13	n=13	
	393.2 (72.9, 480.4)	240.4 (76.6, 474.0)	10.2 (-197.2, 433.5)	611.9 (254.7, 890.2)	434.4 (223.8, 943.9)	-134.1 (-460.8, 306.7)	412.6 (373.4, 598.2)	546.2 (301.2, 822.2)	38.5 (-14.1, 249.2)	320.8 (131.4, 582.2)	477.3 (304.8, 581.4)	-4.1 (-53.4, 73.0)	0.56
tPA antigen, ng/ml Median(IQR)	n=15	n=15	n=15	n=8	n=8	n=8	n=10	n=10	n=10	n=13	n=13	n=13	

	Rosiglitazone + rhGH n = 20			Rosiglitazone n = 15			rhGH n = 13			Double Placebo n = 15			p-value*
Biomarker	**Baseline**	**12-week**	**12-wk change**	**Baseline**	**12-week**	**12-wk change**	**Baseline**	**12-week**	**12-wk change**	**Baseline**	**12-week**	**12-wk change**	
	9.0 (6.2,11.7)	5.6 (4.4,8.2)	-3.5 (-5.6,-1.3)	9.0 (7.6,14.3)	7.7 (5.5,13.5)	-1.1 (-3.7,-0.1)	11.4 (9.3,11.8)	10.1 (7.3,11.5)	-2.1 (-2.2,-0.3)	13.2 (10.8,14.0)	11.7 (7.6,14.8)	0.5 (-3.0,1.2)	0.10

*Kruskal-Wallis test

**p=0.0011 for rosiglitazone + rhGH compared to double placebo group, p=0.0005 for rosiglitazone alone compared to double placebo group after Dunnett-Hsu multiple adjustments