HHS Public Access

Author manuscript

Antivir Ther. Author manuscript; available in PMC 2017 January 01.

Published in final edited form as:

Antivir Ther. 2016 ; 21(2): 107–116. doi:10.3851/IMP2927.

The effect of recombinant human growth hormone with or without rosiglitazone on hepatic fat content in HIV-1 infected individuals; a randomized clinical trial

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Abstract

Background—Hepatic fat is related to insulin resistance (IR) and visceral adipose tissue (VAT) in HIV+ and uninfected individuals. Growth hormone (GH) reduces VAT but increases IR. We evaluated the effects of recombinant human GH (rhGH) and rosiglitazone (Rosi) on hepatic fat in a substudy of a randomized controlled trial.

Methods—HIV+ subjects with abdominal obesity and IR (QUICKI ≤ 0.33) were randomized to rhGH 3 mg daily, Rosi 4 mg twice daily, the combination, or double placebo. Hepatic fat was measured by magnetic resonance spectroscopy (MRS), visceral fat by MRI, and IR by frequently sampled IV glucose tolerance tests at baseline and week 12.

Results—31 subjects were studied at both time points. Significant correlations between hepatic fat and VAT ($r = 0.41$, $p=0.02$) and QUICKI ($r = 0.39$, $p<0.05$) were seen at baseline. Insulin resistance rose with rhGH but not Rosi. When rhGH treatment groups were combined, hepatic fat expressed as percent change decreased significantly ($p<0.05$) but did not change in Rosi ($p=0.71$). There were no correlations between changes in hepatic fat and VAT ($p=0.4$) or QUICKI ($p=0.6$).

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These data were previously presented in poster form at the 14th International Workshop on Comorbidities and Adverse Drug Reactions in HIV, Washington, DC, July 19–21, 2012. Abstract P10.

Disclosure statement MJG has 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 ESE have received research support from EMD Serono to their institution (St. Luke's-Roosevelt Hospital) for the present substudy and for past studies of HIV-associated wasting and lipodystrophy. There are no further patents, products in development or marketed products to declare.

Author contributions:

DK - conception and design of sub-study; preparation of manuscript

QH - design of sub-study; performance and analysis of measurements of hepatic fat

ESE - performance of statistical analysis, preparation of manuscript

JBA - supervision and interpretation of glucose metabolism measurements

MJG - conception and design of main study, critical reading of manuscript

In a substudy of 21 subjects, a trend was noticed between changes in hepatic fat and serum IGF-1 (p=0.09).

Conclusions—Hepatic fat correlates significantly with both VAT and IR, but changes in hepatic fat do not correlate with changes in VAT and glucose metabolism. Hepatic fat content is reduced by rhGH but Rosi has no effect. These results suggest an independent effect of growth hormone or IGF-1 on hepatic fat. The study was registered at Clinicaltrials.gov (NCT00130286).

Introduction

Intrahepatic fat accumulation, or hepatic steatosis, is common in human immunodeficiency virus (HIV) infection. Non-alcoholic steatohepatitis in obese and non-obese non-HIV individuals has been associated with the development of progressive liver disease [1], as well as dyslipidemia, insulin resistance, and elevated cardiovascular risk [2–4]. Hepatic steatosis was a frequent finding in untreated, HIV-infected patients [5]. It also is found frequently in effectively treated patients, often in association with truncal obesity and other elements of the metabolic syndrome, especially visceral adipose tissue (VAT) accumulation, insulin resistance (IR), and dyslipidemia [6], all of which have been well documented in treated patients [7, 8], and have been referred to as HIV-associated lipodystrophy. The effect of pharmacologically manipulating VAT and IR on hepatic fat content has not been studied in HIV infection.

The body composition and metabolic alterations in HIV-associated lipodystrophy also resemble those of Growth Hormone (GH) deficiency [9]. Hepatic steatosis has been described in adult GH deficiency and with hypopituitarism [10, 11]. Decreased growth hormone secretion has been documented in both men and women with abdominal obesity in the absence of pathologic processes to explain GH deficiency [12]. Partial GH deficiency also has been documented in HIV-associated lipodystrophy [13]. Therapy with growth hormone reduces abdominal obesity, especially visceral fat content [14, 15]. Growth hormone therapy also was shown to reverse hepatic steatosis in GH deficiency [16]. However, while GH therapy lowers VAT in HIV+ patients, it increases insulin resistance [17]. Rosiglitazone has been shown to reduce IR and hepatic fat content in HIV− and HIV+ subjects [18, 19]. The effect of a combination of GH and rosiglitazone has not been studied.

The primary aim of this study was to determine the individual and interacting effects of recombinant human growth hormone (rhGH) (EMD Serono, Rockland, MA) and rosiglitazone (Rosi) (Glaxo Smith Kline, Philadelphia, PA) on hepatic lipid content in HIV-infected subjects with VAT accumulation and insulin resistance. We predicted that supraphysiologic doses of rhGH in patients with HIV-associated lipodystrophy would lead to a reduction in hepatic fat content. We also predicted that rhGH and Rosi would have a synergistic effect on hepatic fat content. The secondary aim was to examine the relationships among hepatic lipid content, glucose metabolism, and IR at baseline and with changes in response to study drugs. This study was a sub-study of an investigator-initiated clinical trial “Randomized, Double-Blind, Placebo-Controlled Trial of Recombinant Human Growth Hormone and Rosiglitazone for HIV-Associated Abdominal Obesity with Insulin Resistance” [NIH R01-DK065515].

Methods

This was a prospective, randomized, double-blind, placebo-controlled trial at 4 clinical sites in New York City. Eligible subjects were randomized in a 1:1:1:1 ratio to receive rhGH, 3 mg daily, Rosi, 4 mg bid, rhGH + Rosi, or double placebo treatment for 12 weeks. The parent study included a 12-week open-label extension phase during which they received rhGH, 2 mg qod + Rosi, 4 mg bid, for an additional 12 weeks, but the present results are limited to the double-blind phase of the study. Randomization was stratified by study site and presence or absence of impaired glucose tolerance. The specific methods used for randomization and the rules for on-treatment dose modifications are detailed in the manuscript describing the parent study [20].

The primary endpoint for this sub-study was the change in hepatic fat content after 12 weeks of therapy. The primary endpoint of the parent study was the change in insulin sensitivity index (Si) over 12 weeks, as measured by the frequently sampled intravenous glucose tolerance test, while key secondary endpoints included changes in VAT and subcutaneous adipose tissue (SAT) volumes by magnetic resonance imaging (MRI), and total and regional fat mass and lean mass by dual energy X-ray absorptiometry (DEXA). The study protocol was approved by the institutional review boards at all participating study sites, and all subjects gave informed consent. The study was registered at Clinicaltrials.gov (NCT00130286).

Study subjects

Eligible subjects were HIV-infected, clinically stable, aged 18 to 65 years, and on stable antiretroviral medications. Key anthropometric inclusion criteria included waist circumference > 88.2 cm for men and >75.3 cm for women plus waist-to-hip ratio ≥ 0.95 for men and ≥ 0.90 for women. Study subjects also were insulin resistant, based on a quantitative insulin sensitivity check index [21] (QUICKI) ≤ 0.33, but not diabetic, based on oral glucose tolerance testing at screening. Other inclusions included weight > 36 kg, liver transaminase values ≤ 2.5 times the upper limit of normal and fasting triglycerides ≤ 750 mg/dL. Major exclusion criteria included active malignancy or systemic infection, prior diagnosis of pancreatitis, carpal tunnel syndrome, diabetes mellitus, coronary artery disease, any disorder associated with moderate to severe edema, and untreated or uncontrolled hypertension, or contraindication to MRI. Other exclusions included progestational agents, unless used for oral contraception, systemic glucocorticoids, appetite stimulants or other therapy for AIDS-associated wasting, systemic chemotherapy, interferon or radiation therapy, and other investigational agents. Subjects were permitted to continue lipid lowering agents and physiologic replacement testosterone therapy for hypogonadism (but no other androgenic/ anabolic agents) if started ≥ 12 weeks and ≥ 30 days prior to study entry, respectively.

This sub-study was conceived after the initial protocol was initiated, required a separate informed consent, and was not mandatory. The parent study protocol was approved by the institutional review boards of all participating study sites (Weill Cornell Medical College Institutional Review Board, Columbia University Medical Center Institutional Review Board, St. Luke's-Roosevelt Institutional Review Board, and the Western Institutional

Review Board for the AIDS Clinical Research Initiative of America), while the St. Luke's-Roosevelt Institutional Review Board approved the substudy. Of the 72 subjects who initiated therapy in the parent study, 39 agreed to the sub-study and 31 completed testing for hepatic fat content both at baseline and after 12 weeks. The results of baseline body composition, hepatic fat content, and insulin sensitivity are based on 39 subjects, while the effects of the interventions on body composition, hepatic fat content, and insulin resistance are based on the 31 subjects that were studied at both time points. A previous publication included the results of baseline studies of hepatic fat content, MRI, and insulin resistance in thirteen subjects from this study [22].

Measurements

Proton magnetic resonance spectroscopy (MRS)—MRS was performed on the same 1.5T MRI system used for the body composition studies (see below). Hepatic lipid content was measured in a single voxel ($2 \times 2 \times 1.9$ cm^3) within the right lobe of the liver using a validated methodology [23]. Subjects lay prone on the MRI table and were asked to breathe shallowly. A whole body coil was used for radio frequency excitation and a 5-inch round general-purpose surface coil as receiver of the spectroscopic signal. T1-weighted MRI scouts were used for localization of the voxel of interest (VOI), which avoided major ductal and vascular structures, as well as SAT. A single-voxel point resolved spectroscopy (PRESS) technique (GE PROBE program) with 3 second repetition time (TR) = 3 seconds and 35 millisecond echo time (TE) was applied. One hundred twenty-eight acquisitions with 8 number of excitation (NEX) were recorded in order to obtain a sufficient signal-noise ratio over a measuring time of 6 minutes. Automatic shimming of the VOI was performed. The proton signals from water (H_2O at 4.7 ppm) and the methylene group of lipids (-CH2- at 1.3 ppm) were quantified using jMRUI analytic software (http://www.mrui.uab.es/mrui/). Hepatic lipid content was calculated by the ratio of Integration (methylene proton) over Integration (water proton), which represents a proton concentration ratio in the chemical groups in the measurement sample.

Body composition

Whole body Magnetic Resonance Imaging (MRI) scans were performed using a 1.5 T system (Signa LX version 10; GE Medical Systems, Milwaukee) using a previously validated research protocol [24]. Subjects lay supine with arms extended above their heads and were scanned in two segments with a common landmark at the L4–L5 inter-vertebral space. The spin-echo sequence had a 200ms repetition time and a 14ms echo time and acquired approximately 40 axial T1-weighted images with 10-mm thickness at 40-mm intervals. The MRI images were analyzed by one analyst (QH) using research image analysis software (SliceOmatic, version 4.0; Tomovision Inc, Montreal). Whole body adipose tissue was first segmented into visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) compartments. Adipose tissue volumes were calculated according to the following formula: $V=\Sigma(T+I) \times S_i$, where T and I are slice thickness and inter-slice interval respectively, and S_i is the area of the tissue of interest on an individual image slice. Total body fat and lean mass were assessed using DEXA (Lunar DPX, Lunar Radiation Corp., Madison WI) as previously described [25].

Glucose metabolism

The screening measurement of glucose metabolism was calculated quantitative insulin sensitivity check index (QUICKI = [1 / [log fasting insulin (lU/ mL) + log glucose (mg / dL)] (21). Thirty one subjects underwent two, three hour insulin-modified frequently sampled intravenous glucose tolerance tests, at baseline and after 12 weeks of therapy [26]. Samples for glucose and insulin determination were collected at −20, −15, −10, −5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 9, 22, 24, 25, 27, 30, 40, 50, 60, 90, 100, 120, 140, 160, and 180 minutes. At time 0, 300 mg/Kg of glucose (50% dextrose) was administered by intravenous bolus followed by 0.03 U/kg of insulin at the 20-minute time point. Insulin sensitivity index (Si) was calculated using MinMod software (27). Subjects also underwent routine safety laboratory testing at weeks 2, 4, 6, 8, and 12.

Glucose and insulin concentrations were assayed in bulk on stored frozen samples at the New York Obesity Research Center Core Laboratory, St. Luke's-Roosevelt Hospital Center. Insulin was assayed using a commercial ^{125}I labeling radioimmunoassay and glucose was assayed using a Beckman Glucose Analyzer.

Serum IGF-1 measurements—Serum IGF-1 levels were determined in a subgroup of 41 subjects in the parent study, including 22 subjects who also underwent hepatic fat measurements at baseline and 12 after weeks of therapy. Serum IGF-1 concentrations were determined in the General Core Laboratory of the Weill Cornell Clinical and Translational Science Center using a quantitative sandwich enzyme immunoassay kit (R&D Systems, Inc., Minneapolis, MN) following the manufacturer's instructions. The intra-assay coefficient of variation is 3.5%–4.3%, and the inter-assay coefficient of variation is 7.5%–8.3%.

Statistical analysis

The overall randomization sequence in the parent study [20] was generated in SAS (SAS Institute Inc., Cary, NC) by a study statistician and provided to the research pharmacist. Study subjects and all study personnel were blinded to group assignments. Only the research pharmacist and study statistician had access to information about group assignment.

Baseline data were summarized on all randomized subjects who had a baseline MRS. Analyses of changes from baseline to week 12 of metabolic or body composition parameters included only subjects with data for individual variables at both time points; missing data were not imputed. Sex and race were compared between groups by Fisher's Exact Test. For continuous variables, means and standard deviations (SD) were calculated at baseline and week 12 by study arm. Within-group comparisons between baseline and week 12 were made by paired t-test. Between-group comparisons of baseline measures were performed by one-way analysis of variance (ANOVA) and for change over 12 weeks by general linear model, adjusting for the corresponding baseline values. Dunnett-Hsu adjustment was used for post-hoc pair-wise comparisons. In addition, two-way ANCOVA was performed to evaluate the interaction of rosiglitazone and rhGH. The effect of rhGH on serum IGF-1 concentration was evaluated by the Student's T test, after combining groups taking or not taking rhGH. Correlations between continuous variables were by Spearman's method. All p-values were

two-sided, and $p<0.05$ was considered as statistical significance. Analyses were conducted with SAS software, version 9.2 (SAS Institute, Cary, NC).

Since no pertinent data were available on hepatic fat content and GH treatment in HIV infection and since this was an exploratory study, sample size calculation was not performed.

The parent study was monitored by an independent Data and Safety Monitoring Board that reviewed accrual, data completeness, and adverse event data by blinded study arm. No efficacy data were reviewed, and no statistical testing was done for the interim safety reviews.

Results

Effect of therapy on body composition—The mean ages of the sub-study groups ranged from 46–49 years, were comprised of 67–89% men, and the majority of study subjects were African-American (56–71%), with 21–33% Caucasian and the rest Latino (Table 1). No significant differences in any body composition measures were found at baseline. Body weight rose modestly in patients taking Rosi and did not change in patients taking rhGH alone. However, patients taking rhGH, with or without Rosi, sustained significant increases in lean mass by DXA ($p=0.016$, $p=0.003$, respectively), though not skeletal muscle mass by MRI, with a between-group trend towards statistical significance ($p=0.07$) (Table 2). In addition, patients taking rhGH, with or without Rosi had statistically significant decreases in body fat, both DXA leg fat ($p<0.01$) and VAT ($p=0.01$) in both within group and between group analyses, but rhGH did not affect SAT in any group (Table 2). In contrast, treatment with Rosi alone led to increases in total adipose tissue by MRI ($p<0.05$).

Effect of therapy on hepatic fat content—Hepatic fat content fell in both rhGH groups, by around 11% from baseline in patients taking rhGH and by around 22% in patients taking both rhGH and Rosi (Figure 1a). In contrast, hepatic fat content rose by 6.5% in the group taking Rosi and by 10.8% in the double placebo group. The overall p value by 2-way ANOVA was 0.18. Since there was no significant rhGH × Rosi interaction for change in hepatic lipid by 2-way ANOVA ($p=0.26$), the groups were pooled. There was a strong trend toward decreased hepatic fat in the subjects taking rhGH ($p=0.056$) when expressed as the absolute fall in hepatic fat content, but no change in the subjects taking Rosi ($p=0.71$) was seen. However, when the change in hepatic fat content was expressed as a percent of baseline, the change in patients receiving rhGH, −22%, was statistically significant ($p<0.05$) (Figure 1b).

Associations among hepatic fat content, VAT, and glucose metabolism—At baseline, there were significant correlations between hepatic lipid content and VAT ($r = 0.41$, $p=0.02$) and QUICKI ($r=-0.39$, $p<0.05$). There was no correlation between change in hepatic fat content and change in VAT ($p=0.4$). There also was no correlation between change in hepatic fat content and change in QUICKI ($p = 0.6$) or FSIVGTT ($p=0.57$).

Effect of therapy on IGF-1

Association between changes in hepatic fat and serum IGF-1 contents—Serum IGF-1 and hepatic fat content were measured in 22 subjects from the four groups, including 13 subjects taking rhGH and 9 subjects not taking rhGH. Serum IGF-1 concentration rose in the subjects taking rhGH from 99±28 ng/ml to 228±90 ng/ ml and did not change in the subgroup not taking rhGH (96±36 vs 96±23; the between group difference was statistically significant ($p<0.001$). Regression analysis between changes in serum IGF-1 concentration and hepatic fat content demonstrated a trend towards significance when liver fat change was expressed as absolute change in percent hepatic fat content ($p=0.09$, Fig2) but not when expressed as percentage change in percent hepatic fat content ($p=0.21$, data not shown). However, the absolute change in hepatic fat content also was related to baseline hepatic fat content, which varied between 4.3% and 45% in the rhGH groups ($r^2 = 0.34$, $p=0.036$, data not shown). For this reason, the relationship between the changes in IGF-1 concentration and changes in hepatic fat content may vary based on the baseline hepatic fat content.

Discussion

The primary finding of this sub-study is that the administration of rhGH led to a fall in hepatic fat content in this group of HIV+ patients with VAT accumulation, IR and elevated baseline hepatic lipid contents. Several previous studies, including one which included some of these study subjects, have shown significant correlations among hepatic fat content, VAT content, and IR [22, 28] as seen at baseline in this study. A study by Stanley et al, in HIV-infected subjects with similar mean age and BMI as in our groups, though with less insulin resistance and liver fat, demonstrated a fall in hepatic fat content after 6 months of therapy with tesamorelin, a growth hormone releasing factor (29). The decrease in hepatic fat content was quantitatively greater in patients also taking Rosi, though that group had higher hepatic fat content at baseline. The relative fall in hepatic fat content was not statistically different in the rhGH and rhGH + Rosi groups in this study, 11 and 22%, respectively. However, changes in hepatic fat content were not associated statistically with changes in VAT or glucose metabolism/IR. It is possible that the results would be different if a larger group were studies, i.e., that the current study was underpowered to detect the change sought.

Serum IGF-1 concentrations were analyzed in 22 subjects also undergoing measurements of hepatic fat content. Mean serum IGF-1 concentrations rose from 99 to 228 ng/ml during therapy and did not change in the groups not receiving rhGH (mean IGF-1 96 ng/ml at both time points). As the range of normal values using this research kit, according to the manufacturer, is 40–258 ng/ml, 4 of 12 subjects treated with rhGH had elevated IGF-1 concentrations at the end of the study (data not shown), indicating that the effects seen are pharmacologic, as opposed to replacement.

There was a trend towards significance in the absolute change in hepatic fat content and the change in serum IGF-1 concentration between baseline and week 12 (Figure 2). Though this study may have been underpowered to detect the relationship, there also was a significant relationship between the change in hepatic fat content and baseline values. Since the latter measure varied widely in this study, 4.3%–45%, it is likely that the strength of the

relationship also will vary based on baseline status. In any event, it appears as though the effect of a change in IGF-1 on hepatic fat content is stronger than is the effect of a change in VAT.

The mechanism underlying the fall in hepatic lipid content in the rhGH groups is uncertain and a review of the literature provides conflicting data. While rhGH treatment decreased VAT, which should promote fat loss from the liver, it increased IR, which should increase hepatic fat content. This effect of growth hormone is the likely explanation for the lack of association between changes in visceral fat content and IR noted previously [17]. However, the results of several studies suggest that growth hormone therapy might decrease hepatic fat content in patients with HIV-lipodystrophy. Takahashi et al presented the results of a well-studied case of growth hormone therapy in an adult with coexisting adult growth hormone deficiency, who was shown to have non-alcoholic steatohepatitis on liver biopsy [16]. They treated the patient with increasing doses of rhGH for 6 months until serum IGF-1 levels reached the normal range and documented decreases in hepatic fat content in a repeat liver biopsy, from 33.5% to 7.2%, by histologic quantitation. They also demonstrated decreases in markers of inflammation and oxidative stress. Many human and animal studies have shown that inflammatory stimuli affect lipid metabolism, including *de novo* triglyceride and cholesterol synthesis [30]. Runchey et al demonstrated an inverse relationship between hepatic fat content, estimated by ultrasound and circulating insulin–like growth factor-1 in an analysis of NHANES data, though the relationship became non-significant after adjustment for covariates [31].

Schwarz et al, using the same rhGH dose as in this study, studied HIV-infected subjects anthropometrically similar to those in this study [32]. Using stable isotope techniques they documented an increase in hepatic gluconeogenesis and a decrease in *de novo* lipogenesis. They noted that *de novo* lipogenesis is a biochemical bridge between carbohydrate and lipid metabolism and that a GH-induced increase in lipolysis and free fatty acid delivery to the liver could be the stimulus to decrease *de novo* lipogenesis and divert lactate, glycerol, and amino acids to gluconeogenesis and away from glucose oxidation. In this way, the fall in hepatic lipid content and increase in hepatic insulin resistance as a result of pharmacologic rhGH therapy are linked. However, studies by Hadigan et al demonstrated elevated rates of basal lipolysis in HIV-infected subjects receiving combination antiretroviral therapy, and the benefit of further increasing lipolysis is unclear [33].

D'Amico et al gave physiologic replacement doses for 6 months to relatively growth hormone deficient HIV+ men with a mean BMI of around 29 and elevated waist-to-hip ratio and demonstrated a fall in total body lipolysis, free fatty acid flux, and hepatic lipid re-esterification despite normal apoB-100 synthetic rates [34, 35]. A decrease in FFA supply to the liver could explain lower rates of re-esterification and result in decreased hepatic fat content. However, hepatic fat content was not measured in this study.

Mayerson studied the effects of Rosi in type 2 diabetics without HIV infection and demonstrated significant decreases in fasting glucose and insulin concentrations plus a decrease in plasma FFA concentrations, the latter likely due to increased insulin-mediated suppression of adipocyte lipolysis [36]. No changes in body composition were found,

though regional fat content was not measured. Hepatic fat content fell by 39%, from 9.3% to 5.7%. Sutinen and colleagues demonstrated around a 15% decrease in hepatic fat content after treatment with rosiglitazone, 8 mg daily for 6 months, in HIV-infected subjects selected for lipoatrophy [37]. The mean BMI in that study was 23, compared to 29 in the current study, and mean VAT and fasting insulin values also were lower. Hepatic fat content also was much lower in Sutinen's patients (8%) than in the current study (23%).

In the parent study and in this sub-study, rhGH led to a fall in VAT while Rosi did not independently affect VAT or SAT [20]. Growth hormone therapy has been shown to increase lean body mass and lower body fat content in malnourished HIV-infected and non-infected individuals [38, 39], as well as in HIV+ patients with visceral fat accumulation [40–42], and that effect was seen in this study. The loss of body fat may include both VAT and SAT, though a much greater proportion of VAT is lost. For example, while VAT accounted for only 15% of VAT+SAT (4.4+29.7 L) in the rhGH group, VAT accounted for 75% of the change in VAT+SAT (0.9+0.3 L) during therapy. In contrast, therapy with thiazolidinediones in non-HIV infected subjects leads to increased body fat content, predominantly SAT, and no change in lean mass or VAT, plus improvement in insulin sensitivity [43–45]. The effect of Rosi in HIV-infected patients is controversial in that some studies demonstrated an increase in SAT content while others showed no effect of therapy [46–50]. Therapy with Rosi led to a significant increase in limb fat in the parent study but not in this sub-study [20]. The variable response to Rosi in HIV-infected subjects in the literature could be related to concurrent or prior treatment with thymidine analogue nucleoside reverse transcriptase inhibitors and mitochondrial dysfunction in adipose tissue. In the parent study, 29% of the patients were taking thymidine analogue reverse transcriptase inhibitors at the time of enrollment and 66% had undetectable HIV viral loads (20). Information about previous thymidine analogue treatment was not collected. It is possible that thymidine analogue-associated mitochondrial damage affected the results of this study.

The effect of Rosi in this study in HIV-infected subjects differ from studies of rosiglitazone and pioglitazone in non-HIV infected patients where a consistent effect in reducing hepatic fat content has been reported (reviewed in 51). As above, the difference between HIV-infected subjects in this study and HIV-uninfected subjects may be related to prior or ongoing treatment with nucleoside reverse transcriptase inhibitors.

Macallan and colleagues gave rhGH, 2 mg/day and/or Rosi 4 mg bid to HIV-infected patients with lipodystrophy [52]. Their patients had more severe lipoatrophy than in the current study, had a mean BMI of 23 compared to 29 in this study, and only 20% had fasting hyperinsulinemia at baseline, while insulin resistance was a key inclusion criterion in this study. However, rhGH decreased VAT, increased lean mass, and increased insulin resistance, while Rosi increased limb fat content, decreased IR and abrogated the adverse effects of rhGH on IR as seen in the parent study. Hepatic fat content was not measured in that study.

The major strengths of this study are its randomized, controlled design, a diverse study group, and the use of sophisticated measures of body composition and hepatic fat content. The major limitations of this study are the small group sizes and the limited availability of the specific drugs chosen for this study. The FDA denied approval for rhGH for the

indication of HIV-associated visceral fat accumulation based on safety concerns, despite evidence of benefit in lowering VAT content in phase 3 studies [40, 41]. However, a growth hormone releasing agent did receive FDA approval for this indication [53, 54] and an effect of this therapy on hepatic fat content has been demonstrated {29}. The use of Rosiglitazone also is limited because of concerns about cardiovascular risk [55, 56], though pioglitazone is available for use and has very similar pharmacologic activity.

In conclusion, this study demonstrates that therapy with growth hormone decreases hepatic fat content in HIV-infected patients with hepatic steatosis, VAT accumulation, and IR. Rosi does not modulate the effect of rhGH on hepatic fat content nor have an independent effect.

Acknowledgement statement

The authors thank Norma Muurahainen, MD, PhD for helpful discussions. The authors also gratefully acknowledge the efforts of the Data and Safety Monitoring Board (Judith Currier [chair], Ann Danoff, and Morris Schambelan), the assistance of Pavan Mankal, and we thank the dedicated study participants.

Funding This work was supported by the National Institutes of Health, and the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health, through Grant Numbers R01 DK065515, K24 AI078884, UL1 RR024996, UL1 RR024156 and P30 DK026687. The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Funding for this substudy as well as recombinant human growth hormone and placebo were generously provided by EMD Serono while rosiglitazone and matching placebo were provided by GlaxoSmithKline. Neither pharmaceutical sponsor had a role in the design, conduct, or analysis of the study.

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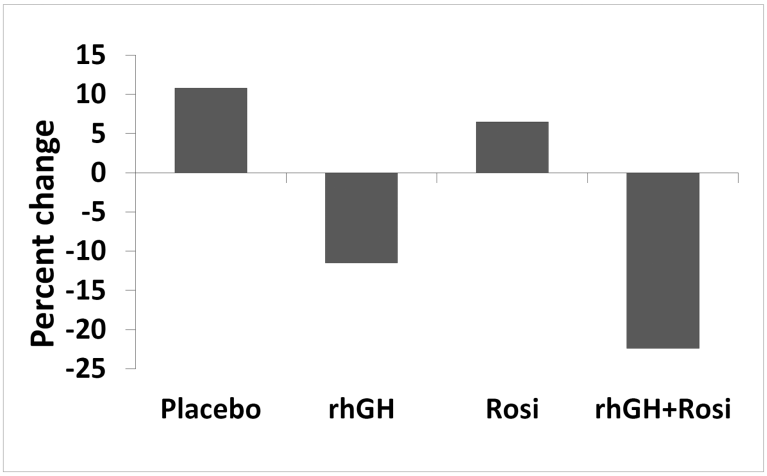

Figure 1a.

Relative change in liver fat (as percent of liver fat + water) after 12 weeks of treatment (p=0.32 by general linear model (controlled for baseline)

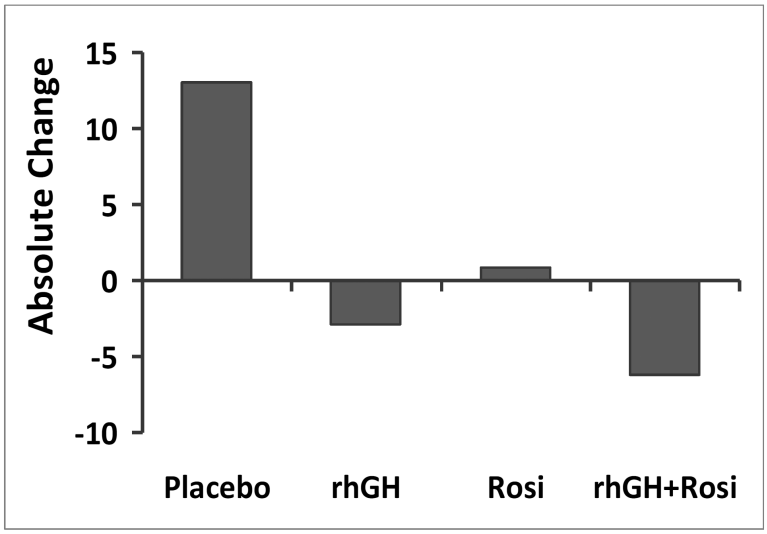

Figure 1b.

Absolute change in liver fat as percent of baseline, after 12 weeks of treatment (p=0.26 by general linear model (controlled for baseline)

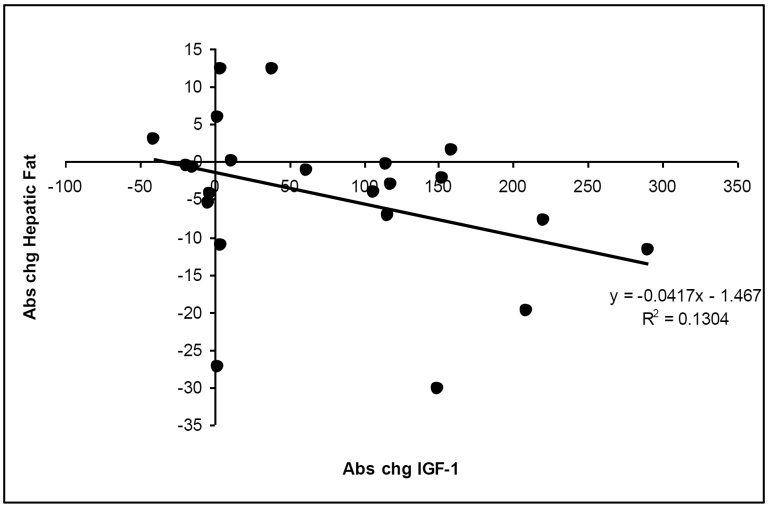

Figure 2.
Relationship between the changes in serum IGF-1 concentration and hepatic fat content

Table 1

Baseline data for all subjects with a baseline MRS scan of the liver prior to treatment with growth hormone and/or rosiglitazone or double placebo.

	rhGH	Rosi	rhGH + Rosi	Double Placebo	p
n	9	9	12	9	
Age (mean ± SD)	49±6	47±8	49±12	46±7	0.89
Sex (M/F) (%)	67/33	89/11	75/25	67/33	0.77
Race (Caucasian/AfricanAmerican/ Hispanic) (%)	33/66/0	33/56/11	25/75/0	33/66/0	0.94
QUICKI	0.31±.03	0.32±.03	0.30±.01	0.30±.02	0.22
VAT, liters (mean ± SD)	4.7±2.0	4.6±2.1	5.9±2.5	5.6±2.1	0.64
Hepatic Lipid (%) (mean ± SD)	14.7±9.6	23.3±17.3	25.4±21.0	29.0±23.1	0.50

Table 2

Data before and after 12 weeks of treatment with growth hormone and/or rosiglitazone or double placebo for all subjects with MRS scan of the liver.

	rhGH			Rosi			rhGH + Rosi			Double placebo			p*	
	Baseline	Week 12	p‡	Baseline	Week 12	P	Baseline	Week 12	P	Baseline	Week 12	P	Baseline	Week 12
n	7			6			12			6				
%female	33			11			29			33			0.41°	.
Age, yr	48.7±6.8	.	.	46.7±8.6	.	.	48.6±11.7	.	.	47.2±5.9	.	.	0.97	.
Height, cm	171.3±11.8	.	.	171.1±4.5	.		170.8±7.5	.		169.5±53.7	.	.	0.98	.
Weight, kg	90.4±8.7	90.8±9.4	0.72	81.3±8.3	83.0±9.8	0.077	86.8±13.6	87.6±13.8	0.35	82.1±20.6	82.3±18.8	0.93	0.68	0.93
BMI, kg/m^2	31.0±3.7	31.1±3.2	0.86	27.8±3.4	28.4±4.0	0.076	29.7±3.8	30.0±3.7	0.40	28.7±5.5	28.8±5.0	0.90	0.57	0.95
DXA lean, kg	55.9±8.8	59.2±9.8[a]	0.016	57.0±6.8	57.0±6.1[a]	0.98	56.9±11.0	60.5±11.8[a]	0.0030	50.2±14.0	50.5±11.5[b]	0.90	0.89	0.07
DXA fat, kg	31.2±8.5	28.4±7.5[a]	0.0094	21.3±6.7	23.2±7.0[b]	0.13	26.4±8.4	24.0±8.8[a,b]	0.0072	28.6±10.6	28.4±10.9[b]	0.78	0.20	0.006
VAT, L	4.4±2.0	3.5±1.7[a]	0.0038	5.3±2.1	5.5±2.0[b]	0.55	5.9±2.5	4.5±1.4[a,b]	0.013	5.6±2.4	5.7±2.5[b]	0.94	0.58	0.0086
SAT, L	29.7±10.4	29.4±9.4	0.58	19.5±5.1	20.0±6.9	0.63	24.9±9.2	24.8±8.2	0.90	26.0±10.3	26.0±10.9	0.99	0.27	0.99
TAT, L	36.5±7.2	35.8±6.6	0.40	33.5±5.0	34.7±4.5	0.047	32.1±9.1	31.0±7.0	0.47	33.0±9.8	33.2±10.8	0.92	0.73	0.56
SMM, L	28.1±4.1	30.5±6.0	0.18	28.4±4.1	28.7±4.0	0.46	28.5±6.9	30.7±8.2	0.10	27.0±7.7	27.9±7.6	0.24	0.97	0.64
QUICKI	0.31±0.03	0.29±0.02	0.09	0.31±0.02	0.29±0.02	0.06	0.30±0.01	0.29±0.02	0.16	0.30±0.02	0.30±0.03	0.50	0.54	0.29
Hepatic fat, %	15.9±10.3	13.0±8.2	0.46	27.3±17.5	28.2±18.7	0.80	25.4±21.0	19.2±19.2	0.038	39.1±22.1	38.8±20.6	0.96	0.20	0.26

Letters indicate which intervention groups are similar

*ANOVA except where otherwise indicated; controlled for baseline value at Week 12.

‡Paired t-test °Fisher's exact test