Preferential loss of omental-mesenteric fat during growth hormone therapy of HIV-associated lipodystrophy

Qing He, Ellen S. Engelson, Jeanine B. Albu, Steven B. Heymsfield, and Donald P. Kotler

dystrophy with increased intra-abdominal fat in human immunodeficiency virus (HIV) infection is common in the era of highly active antiretroviral therapy. It contributes to the metabolic derangements, as does in non-HIV-related conditions. Growth hormone administration reduces intra-abdominal fat content. This study compared the relative changes in omental-mesenteric (OMAT) and retroperitoneal adipose tissues (RPAT) during therapy with recombinant human growth hormone (rhGH) in HIV-associated lipodystrophy. Of 30 subjects who began rhGH therapy (6 mg/day), 25 completed 12 wk and 19 completed 24 wk. Fourteen subjects were followed for an additional 12 wk. Volumes of OMAT and RPAT were calculated from total body MRI scans and compared by paired t-tests. Both OMAT and RPAT significantly decreased after 12 and 24 wk of rhGH treatment (P < 0.001), but the reduction was more pronounced in OMAT than in RPAT (P < 0.001). Both OMAT and RPAT increased significantly (P < 0.001) after therapy was discontinued, but OMAT increased significantly more than did RPAT (122 vs. 37%, P < 0.001). There is preferential loss and regain of OMAT, compared with RPAT, in subjects with HIV-associated lipodystrophy undergoing growth hormone treatment. 

intra-abdominal adipose tissue; retroperitoneal adipose tissue; visceral adipose tissue; fat redistribution; body composition; human immunodeficiency virus 

INCREASED INTRA-ABDOMINAL ADIPOSE TISSUE (IAAT) has been linked to metabolic perturbations, especially hyperlipidemia and insulin resistance (21, 29), and reduction of intra-abdominal fat has been shown to improve insulin sensitivity in both animals (2) and humans (17, 26). A substantial proportion of human immunodeficiency virus (HIV)-infected individuals on highly active antiretroviral therapy (HAART) develop fat redistribution, or HIV lipodystrophy, which is characterized by increased IAAT and/or depletion of subcutaneous adipose tissue (3–5). It is believed that fat redistribution affects long-term health outcomes by exacerbating the associated metabolic alterations (9, 12), which is a rationale for its treatment. Studies have shown that growth hormone secretion is suppressed in HIV-positive or HIV-negative subjects with increased IAAT (24, 25), and therapy with recombinant human growth hormone (rhGH) reduces IAAT contents (6, 16, 28). However, the effect of rhGH on relative changes of IAAT subcompartments has not been investigated.

The IAAT compartment is complex and includes the retroperitoneal adipose tissue (RPAT) compartment, which is located posterior to the parietal peritoneal membrane, and the omental and mesenteric adipose tissue (OMAT) compartment, which includes the omentum, the serosal layer of the luminal gastrointestinal tract, and the mesentery. The anatomic differences between OMAT and RPAT are quite straightforward. In addition to their different locations, the venous drainage of OMAT is to the portal system, whereas RPAT drains directly into the systemic circulation. The physiological role of OMAT is not fully appreciated, although it is believed to be an energy reserve depot, whereas RPAT also serves as a cushion and support structure for retroperitoneal organs including the kidneys, pancreas, and large vessels such as the aorta and inferior vena cava. RPAT has a more homogenous signal intensity than OMAT on MRI images, suggesting less vasculature and possible inertness in metabolism. The relative rates of OMAT and RPAT accretion and depletion are unknown. We have observed that, in some wasted HIV-infected subjects, RPAT can be easily identified whereas OMAT has completely depleted, suggesting that the two depots are differentially responsive to stimuli in wasting condition. Therefore, we propose a hypothesis that the two components are different in their associations with metabolic disarray and response to metabolic stimulus is more sensitive in OMAT. The hypothesis was tested at cross section with a lipodystrophy model, which is characterized by increased IAAT and was further tested by investigating the lipolysis rate on administration of growth hormone.

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The rationale to approach the hypothesis is that the supraphysiological dose of growth hormone was shown previously to successfully treat HIV-associated wasting while also having a demonstrable lipolytic effect (19). In this trial it was used to elicit lipolytic effect on IAAT in HIV-infected subjects with excess IAAT. The purpose of this report was to evaluate the relative changes in OMAT and RPAT. This is a subsidiary report of a trial of rhGH (6 mg/day) treatment of HIV-associated lipodystrophy (6).

METHODS

Study design. The studies were approved by the Institutional Review Board at St. Luke’s-Roosevelt Hospital Center. This was a prospective, open-label trial of rhGH (Serostim, Serono Laboratories, Norwell, MA). Subjects received 6 mg of growth hormone daily for 24 wk followed by 12 wk of washout.

Subjects. A convenience sample of 30 subjects was recruited and followed in New York City. Self-reported truncal enlargement was confirmed on physical examination by two physicians. Subjects were required to be clinically stable and on stable antiretroviral therapy for at least 4 wk before study and throughout the study period. Informed consent was obtained from each subject. Twenty-five subjects completed 12 wk of study, 19 completed 24 wk, and 14 completed 36 wk and had follow-up studies performed. During the whole study period, all subjects were followed by questionnaires of physical activity. Dieting was not recommended.

Body composition measurements. Before and every 12 wk after initiation of rhGH, subjects underwent anthropometric measurements, including body weight, height, waist circumference, and hip circumference, according to the Anthropometric Standardization Reference Manual (15) by an experienced technician. Body mass index (BMI) and waist-to-hip ratio were subsequently calculated.

Metabolic measurements. Several metabolic parameters, including fasting lipid profiles and 2-h oral glucose tolerance tests, were measured and reported in the parent study (6). Oral glucose tolerance tests, performed at baseline, 12 wk, and 36 wk, were of interest to this substudy. Blood samples were drawn for glucose and insulin levels before (fasting) and every 30 min after oral loading with 75 g of dextrose. Plasma glucose was measured with a Beckman glucose analyzer (Fullerton, CA). Plasma insulin was measured by radioimmunoassay (Linco Research, St. Charles, MO) in the Core Laboratories of the Obesity Research Center at St. Luke’s-Roosevelt Hospital Center. A 12-point index of whole body insulin sensitivity (SI) was calculated as described by Matsuda and DeFronzo (18). The normal index at our institution is >3.5.

MRI scanning. Subjects had total body MRI scans (1.5 T, LX Signa, General Electric, Milwaukee, WI) at each measurement time. The programmed protocol obtained T1-weighted images (echo time = 15 ms, repetition time = 200 ms) as described in previous publications (5). Because the retroperitoneal membrane is not always identifiable on these images, subdivision of the IAAT compartment into OMAT and RPAT was achieved by drawing a line concatenating the nadirs of intraperitoneal organs and zeniths of retroperitoneal tissue such as anterior wall of the aorta, the psoas major muscle, or the kidneys and the posterior walls of the ascending and descending colon (Fig. 1). We measured a cylindrical cone of tissue bounded superiority by the dome of the liver and inferiorly by a level 5 cm below the L4–L5 intervertebrate space, which reflects the entire intra-abdominal cavity except for the true pelvis. It should be noted that the adipose tissue volumes presented here are lower than those reflected in the primary study, because pelvic and thoracic adipose tissue are excluded in this analysis. MRI analysis was performed by the same analyst (Q. He) using image analysis software (slice-Omatic, Version 4.0, Tomovision, Montreal, Canada) on a Gateway PC (Gateway, North Sioux City, SD). Data are expressed as volume (in liters) of adipose tissue.

Statistical analysis. Because of the inconsistent sample size due to dropouts, paired t-tests were performed to maximally utilize each data point. The tests compared the changes in OMAT and RPAT as well as the RPAT-to-OMAT ratio (RPAT/OMAT) in 25 subjects from baseline to week 12. Similar comparisons were made in 19 subjects from baseline to week 24. Paired t-tests also compared the two compartments and RPAT/OMAT after the completion of therapy and washout in 14 subjects. A simple linear regression model was used to test for potential relationships between metabolic parameters and anthropometric measurements at baseline. Stepwise multiple linear regression models were used to test the possible associations between metabolic parameters and the two IAAT compartments (OMAT and RPAT). All tests were set on P < 0.05 significance levels. Statistical analyses were performed with the statistical software package SAS (Version 8, SAS Institute, Cary, NC).

RESULTS

Enrollment was completed between July and December 1998. The enrolled subjects included 26 men and 4 women, 28 white and 2 black. The median year of HIV/AIDS diagnosis was 1988 (range 1982–1993). All subjects had a history of antiretroviral therapy, including protease inhibitors and nucleoside reverse transcriptase inhibitors, and remained on the same regimen throughout the study period. More than 73% had viral loads <400 copies/mm³ (the detection limit). Other baseline characteristics are presented in Table 1. IIAAT averaged 4.2 ± 1.7 liters (mean ± SD, n = 30) at baseline. RPAT and OMAT volumes were 1.4 ± 0.5 and 2.8 ± 1.2 liters, respectively, and their volumes were associated statistically, with an R² of 0.47 (Fig. 2). On average, RPAT accounted for 35.4 ± 7.2% of total intra-abdominal adipose volume (range 21.9–51.7%).
Table 1. *Baseline characteristics*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>42.5 ± 5.8</td>
<td>30–67</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.6 ± 3.2</td>
<td>21–33</td>
</tr>
<tr>
<td>CD4 count, cell/mm³</td>
<td>336 ± 225</td>
<td>0–992</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>96.01 ± 8.6</td>
<td>83.2–113.1</td>
</tr>
<tr>
<td>Hip circumference, cm</td>
<td>94.09 ± 4.6</td>
<td>87.5–101.7</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>1.02 ± 0.07</td>
<td>0.90–1.18</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl*</td>
<td>247.2 ± 82.4</td>
<td>127–443</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl*</td>
<td>31.2 ± 14.6</td>
<td>14–77</td>
</tr>
<tr>
<td>Triglycerides, mg/dl*</td>
<td>483.1 ± 371.3</td>
<td>82–1,699</td>
</tr>
<tr>
<td>Glucose, mg/dl*</td>
<td>87.7 ± 10.6</td>
<td>72–111.5</td>
</tr>
<tr>
<td>Insulin, μU/ml*</td>
<td>20.1 ± 10.2</td>
<td>9.2–54.5</td>
</tr>
</tbody>
</table>

N = 30 subjects. BMI, body mass index; CD4, HDL, high-density lipoprotein. *Fasting concentration.

Twenty-six subjects (86.7%) had low whole body insulin sensitivity indexes (mean 2.1, range 0.8–3.4) before treatment. There were no significant associations between body weight or BMI and various metabolic parameters, including lipid levels and insulin sensitivity indexes, in this group. However, after excluding an outlier who had a congenital pelvic kidney, multiple-regression analysis showed a significantly positive association between OMAT and baseline fasting insulin level (R² = 0.20, P = 0.026) and a negative and strongly significant one between OMAT and ISI (R² = 0.41, P = 0.0006, Fig. 3) but not between RPAT and the same parameters.

After 12 wk of growth hormone treatment, total IAAT, OMAT, and RPAT all were reduced significantly from baseline (all P < 0.001, Table 2). The serial changes on MRI in a typical subject are shown in Fig. 4. The average RPAT/OMAT also rose significantly (P < 0.001). OMAT had a significantly greater percentage change than did RPAT by paired t-test (P < 0.0001). The absolute changes in OMAT from baseline to week 12 were strongly associated with their corresponding baseline volumes (P < 0.0001) (slope: 0.59, 95% confidence interval 0.40–0.79, Fig. 5A). The relationship between baseline volume and absolute change was much weaker for RPAT (P = 0.03; slope 0.28, 95% confidence interval 0.026–0.5; Fig. 5B). At week 12, neither the association between OMAT and fasting insulin level nor the association between OMAT and total body insulin sensitivity index existed.

In the 19 subjects who finished 24 wk of treatment, total IAAT, OMAT, and RPAT were reduced significantly compared with their baseline values (all P < 0.001, Table 3), and RPAT/OMAT remained different from baseline (P < 0.001). Once again, the percent decrease in OMAT was significantly greater than in RPAT by paired t-test (P < 0.001). There were strong relationships between absolute change and baseline volume for both OMAT and RPAT (95% confidence interval of slope is 0.56–0.97 and 0.34–0.9, respectively; Fig. 6). Of note, the slopes and coefficients of determination (R²) of RPAT moved toward those of OMAT by week 24, suggesting that the responsiveness of RPAT to rhGH lagged behind before this time point.

In 14 subjects who were followed for 12 wk after discontinuation of growth hormone (week 36), IAAT volume and corresponding subcompartments all rose (all P < 0.001, Table 4). The RPAT/OMAT decreased

Table 2. Comparison of two adipose tissue compartments before and after 12 wk of treatment with recombinant human growth hormone (6 mg/day)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline</th>
<th>Week 12</th>
<th>Percent Change</th>
<th>Range of Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMAT, liters</td>
<td>2.93 ± 1.20</td>
<td>1.56 ± 0.73*</td>
<td>-46 ± 21</td>
<td>-0.27, 3.9</td>
</tr>
<tr>
<td>RPAT, liters</td>
<td>1.52 ± 0.54</td>
<td>1.05 ± 0.51*</td>
<td>-32 ± 21</td>
<td>-0.44, 1.2</td>
</tr>
<tr>
<td>Total IAAT,</td>
<td>4.46 ± 1.60</td>
<td>2.61 ± 1.15*</td>
<td>-41 ± 20</td>
<td>-0.72, 5.08</td>
</tr>
<tr>
<td>RPAT/OMAT</td>
<td>0.56 ± 0.16</td>
<td>0.76 ± 0.32*</td>
<td>-33 ± 36</td>
<td>-1.08, 0.14</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 25 subjects. OMAT, omental mesenteric adipose tissue; RPAT = retroperitoneal adipose tissue; IAAT, intra-abdominal adipose tissue. RPAT/OMAT, ratio of RPAT to OMAT. *Significantly different from baseline by paired t-tests (P < 0.001).

Fig. 2. Correlation between OMAT and RPAT among 30 subjects at baseline.

Fig. 3. Negative association between volume of OMAT and whole body insulin sensitivity index.
significantly from 0.90 to 0.57 ($P < 0.001$). The percent gains for OMAT were significantly greater than RPAT by paired $t$-test ($P = 0.0002$). The association between OMAT and ISI ($R^2 = 0.42$, $P = 0.02$) reappeared at week 36 but still not the association between RPAT and ISI, after exclusion of the same outlier.

**DISCUSSION**

The population presented in this study was typical for HIV-associated lipodystrophy with high visceral adipose tissue. Of note, the waist circumference, hip circumference, and waist-to-hip ratios were elevated, in agreement with reported anthropometric characteristics by other researchers (8) and by our own recent presentation of a different HIV-positive lipodystrophic sample (11).

**Table 3. Comparison of two adipose tissue compartments before and after 24 wk of treatment with recombinant human growth hormone (6 mg/day)**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 24</th>
<th>Percent Change, %</th>
<th>Range of Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMAT, liters</td>
<td>2.95 ± 1.30</td>
<td>1.26 ± 0.60*</td>
<td>−55 ± 21</td>
<td>0.45, 4.16</td>
</tr>
<tr>
<td>RPAT, liters</td>
<td>1.60 ± 0.56</td>
<td>0.93 ± 0.37*</td>
<td>−40 ± 19</td>
<td>−0.19, 1.76</td>
</tr>
<tr>
<td>Total IAAT,</td>
<td>4.55 ± 1.73</td>
<td>2.19 ± 0.89*</td>
<td>−50 ± 19</td>
<td>0.26, 5.4</td>
</tr>
<tr>
<td>RPAT/OMAT, %</td>
<td>0.58 ± 0.16</td>
<td>0.86 ± 0.38*</td>
<td>−88 ± 38</td>
<td>−151, −30</td>
</tr>
</tbody>
</table>

Values are means ± SD; $n = 19$. *Significantly different from baseline by paired $t$-tests ($P < 0.001$).
We and others have shown that rhGH decreases IAAT in HIV-infected and uninfected subjects (6, 10, 16). The present study extends those findings (6) by comparing the relative changes in anatomically distinct subcompartments of IAAT, specifically OMAT and RPAT. This subdivision of IAAT on MRI images has been reported previously by other investigators (1) and has a sound basis in anatomy. OMAT is drained by the portal venous system, whereas RPAT drains into the systemic circulation. There also are functional differences, with OMAT fat being an energy source, whereas RPAT also serves a structural role. Garg and colleagues (7) previously noted that “mechanical” fat is distinct from “metabolically-active” adipose tissue and may persist despite otherwise complete lipatrophy in congenital lipodystrophy syndromes.

The RPAT accounted for an average of 35% of total IAAT volume in this study, which is close to the 34% reported for a moderate overweight, HIV-negative sample with a similar mean ± SD in BMI of 25.6 ± 2.7 (1).

As in non-HIV obesity, truncal enlargement in HIV-related lipodystrophy involves increases in both OMAT and RPAT compartments.

The results of this study indicate that both OMAT and RPAT shrank significantly from baseline during rhGH treatment. However, the loss was not uniform; OMAT was preferentially lost over RPAT. The percent changes in OMAT were greater than those in RPAT both during and after treatment. RPAT/OMAT significantly increased during therapy and fell after therapy, also indicating the greater relative change in OMAT.

Ours is the first longitudinal in vivo study to show differential responses of OMAT and RPAT to rhGH in HIV-infected subjects, although the notion that different adipose tissue compartments can be distinguished metabolically is well accepted among investigators. However, the specific interrelationships are not entirely clear. Most authors ascribe the increased cardiovascular risk in upper body obesity to visceral fat (14, 21). In this study, insulin sensitivity indexes related to OMAT, but not RPAT, before therapy and after 12-wk washout. Thus our observation pointed out more precisely that OMAT related to metabolic disarray, thus suggesting the functional distinction between two depots.

The exact cellular and molecular mechanisms underlying a difference in responsiveness among adipose tissue subcompartments is not entirely clear. A rat model showed fewer GH binding sites per adipocyte in retroperitoneal adipose tissue than in intra-abdominal fat such as epidydimal fat (13). Conceptually, it suggests that RPAT is relatively inert to GH stimulation. In short, data suggest that a distinction exists between OMAT and RPAT. OMAT is more metabolically active, whereas RPAT has mechanical function and is less metabolically active.

Our finding that OMAT preferentially responds to growth hormone administration or withdrawal supports Garg et al.’s (7) distinction between OMAT and RPAT and has clinical implications. The association exists between OMAT, rather than RPAT, and fasting insulin and ISI at baseline. The present data support the hypothesis that the two depots have different quantitative effects on glucose metabolism. Even though such associations were not noted at week 12, the loss of relationship at this specific therapy time point is at

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### Table 4. Change in two adipose tissue compartments 12 wk after withdrawal of recombinant human growth hormone therapy

<table>
<thead>
<tr>
<th></th>
<th>Week 24</th>
<th>Week 36</th>
<th>Percent Change, %</th>
<th>Range of Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMAT, liters</td>
<td>1.13 ± 0.55</td>
<td>2.27 ± 1.24*</td>
<td>122 ± 88</td>
<td>-0.26, 3.46</td>
</tr>
<tr>
<td>RPAT, liters</td>
<td>0.85 ± 0.33</td>
<td>1.14 ± 0.41*</td>
<td>37 ± 29</td>
<td>-0.16, 0.68</td>
</tr>
<tr>
<td>Total IAAT, liters</td>
<td>1.99 ± 0.77</td>
<td>3.41 ± 1.49*</td>
<td>80 ± 53</td>
<td>-0.43, 4.14</td>
</tr>
<tr>
<td>RPAT/OMAT, %</td>
<td>0.90 ± 0.41</td>
<td>0.58 ± 0.22*</td>
<td>-33 ± 16</td>
<td>-0.93, -0.01</td>
</tr>
</tbody>
</table>

Values are means ± SD; n = 14 subjects. *Significantly different from week 24 by paired t-tests (p < 0.001).
tributable to the large dose of growth hormone whose counterinsulin effect is well known. In fact, recent reports show that exacerbated abnormal lipid profiles with rhGH (3 mg/day) improved over a 6-mo treatment course (6, 27), suggesting improvement of insulin sensitivity. Our parent data also showed that fasting glucose decreased from 12 to 24 wk of therapy despite continuation of rhGH treatment (6), pointing out less insulin resistance. Whereas rhGH acutely increased insulin resistance, prolonged therapy, with decreased IAAT, subsequently led to a fall in insulin resistance in other studies as well (10, 16). Supraphysiological doses might not be required chronically, because most of the treatment effect occurred during the first 12 wk of therapy. The “normalization” of metabolic parameters over the treatment course also implies that OMAT might contribute to metabolic disarray in HIV-associated lipodystrophy. On the other hand, the preferential regain of OMAT after withdrawal of rhGH among HIV-infected individuals suggests that the factors underlying fat redistribution persist despite rhGH treatment, and maintenance therapy may be required to suppress OMAT rebound. It is of clinical benefit to find a balancing dose, which might maintain its suppression of visceral adipose tissue accumulation at the same time minimizing its anti-insulin effects.

In conclusion, rhGH reduces IAAT with a preferential loss of OMAT, compared with RPAT, and a preferential rebound in OMAT on discontinuation of rhGH among HIV-infected lipodystrophy subjects. There is a significant association between OMAT, but not RPAT, and insulin resistance in HIV-associated lipodystrophy. A limitation is that our observation was based on a supraphysiological dose of rhGH and needs to be confirmed with a similar study on a more physiological dose. Further studies to sort out the causal relationship between specific adipose tissue subcompartments and metabolic abnormalities are also warranted and are important in designing interventions for lipodystrophy and other alterations in body fat content.

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