Interventions for Visceral Adiposity Associated with Human Immunodeficiency Virus: Application of a Method for Assessing Efficacy

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In addition to lipoatrophy of the subcutaneous fat compartment and lipohypertrophy of the breasts and dorsocervical fat pad, excess visceral fat is considered to be part of human immunodeficiency virus (HIV)-associated lipodystrophy. Because of associations between visceral adiposity and atherosclerotic risk and undesirable clinical and psychological effects, therapies for this morphological alteration are under investigation. The non-HIV literature on the visceral fat effects of various weight-reduction methods provides some insight into the difficulty that lies ahead. We demonstrate the application of a method published by Smith and Zachwieja to 3 studies of HIV that resulted in a significant loss of body fat. The method is meant to control for differences in the initial amount of visceral fat per subcutaneous fat and for absolute weight change. The results show that the body composition differences in HIV may require the development and application of a new method that permits wider variation in fat distribution.

The abnormal fat distribution seen in “HIV-associated lipodystrophy” includes anatomical areas of lipoatrophy and others of lipohypertrophy. The lipohypertrophy is predominantly in the visceral adipose tissue (VAT), which is clinically significant because of its association with an increased risk of diabetes, stroke, and cardiovascular disease in people without HIV infection.

A number of interventions have been investigated for their effects on visceral fat and fat distribution. In a 1999, review of 23 studies in obese HIV-uninfected groups that included MRI or CT imaging before and after a weight-loss intervention, Smith and Zachwieja [1] reported nearly consistent author claims of preferential VAT loss, compared with subcutaneous adipose tissue (SAT) loss. These claims are understood on viewing figure 1 [1], a graph of the percentage change in total body fat versus the percentage of VAT, on which the results of nearly all of the studies reviewed are below the line of identity—that is, there was a preferential loss of VAT that was positively associated with total fat loss. The type of intervention—calorie restriction, exercise, or a pharmacological intervention, specifically diet pills—did not affect these results.

Smith and Zachwieja [1] identified factors other than the particular weight-loss intervention that appeared to influence the degree of VAT loss but were not considered in the original reports of these studies. They argued that the total amount of body fat or weight lost affects how much is lost from the individual adipose tissue compartments, so that the greater the total loss, the greater the decrease in both VAT and SAT. They also maintained that the greater the amount of VAT per quantity of SAT (V/S ratio) prior to weight loss, the greater the proportion of fat loss from the visceral compartment will be. In their review, Smith and Zachwieja...
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Figure 1. In response to a weight-loss intervention, the proportion of adipose tissue loss that is visceral adipose tissue (VAT) is affected by the proportion of total weight loss that is from body fat. Reprinted with permission from [1].

Figure 2. Ratio of visceral adipose tissue (VAT) to subcutaneous adipose tissue prior to a weight-loss intervention vs. VAT sensitivity index (% ΔVAT/% Δ total body fat) after a weight-loss intervention. Reprinted with permission from [1].

[1] provided a method for interpreting and comparing the results of weight-loss trials that factored in both the total amount of fat or body weight lost and the baseline V/S ratio. The authors proposed normalizing for total body fat change with a VAT selectivity index (SI), which is computed as the percentage of VAT divided by the percentage of total body fat. (Total body fat rather than total adipose tissue was chosen because the availability of whole-body measures of SAT is limited and cannot be assumed on the basis of a single-slice MRI or CT scan, as VAT can. The body fat measurement can be obtained by anthopometrics, hydrodensitometry, dual energy x-ray absorptiometry, or multislice MRI.) An intervention that selectively reduces VAT would have a high SI, and one that promotes only SAT loss would have a low SI. Nearly every study reviewed had an SI >1, although exercise trials appeared to have a higher SI than calorie restriction alone. Finally, their graph of SI versus baseline VAT:SAT ratios confirmed that SI is positively influenced by initial body fat distribution (figure 2). To assess the applicability of these recommendations to interventions for VAT reduction in HIV-associated lipodystrophy, I here apply the suggestions of Smith and Zachwieja [1] to 3 trials previously conducted at our institution.

MATERIALS AND METHODS

Growth hormone (GH) trial. Thirty HIV-positive subjects with protuberant abdomens, which were assumed to reflect a high amount of visceral fat, began a 60-week open-label trial that examined 2 different doses of recombinant human GH [2]. For 24 weeks, they received 6 mg/day; they then had a 12-week washout period followed by a 2 mg/day average dose (4 mg every other day) for another 24 weeks. Body composition was measured at 6 time points. Only the results from the 22 subjects who completed 12 weeks of high-dose GH treatment are included in the present analysis.

Exercise trial. The second trial was in HIV-positive women with malnutrition, defined as a body cell mass/height <90% of sex- and race-based laboratory bioimpedance analysis norms. However, the mean body mass indexes (BMIs) were within the normal range. The women were given a protein supplement, progressive resistance exercise training, or both for 14 weeks [3]. Only the 10 women who did exercise alone are included in the present analysis, because they were also the only group that lost a significant amount of total body fat. Eight of 10 women had self-reported increased abdominal girth prior to the trial.

Diet and exercise. The third study is ongoing and is presented here with preliminary results [4]. It is a prospective longitudinal 12-week trial of diet and exercise to determine the effects of weight loss in obese (BMI, 30–38) HIV-infected women. The diet consisted of 1200 kcal daily, with weekly group education, and the women underwent aerobic and resistance exercise training 3 times per week. Results are from the first 8 subjects who completed the trial.

Body composition and data analysis. Body composition was measured similarly in all 3 studies. Whole-body MRIs were done and analyzed for VAT and SAT area, and volume was calculated as described elsewhere [2, 5]. Adipose tissue volume
Table 1. Body composition results from 3 intervention trials conducted in HIV-infected patients.

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Growth hormone (n = 24)</th>
<th>Exercise (n = 10)</th>
<th>Diet and exercise (n = 8)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔV/S</td>
<td>1.9 ± 1.5</td>
<td>0.4 ± 0.1</td>
<td>0.3 ± 0.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ΔBW (%)</td>
<td>0.7 ± 3.7</td>
<td>−0.1 ± 3.6</td>
<td>−6.8 ± 3.8</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>ΔVAT (%)</td>
<td>−41 ± 19</td>
<td>5 ± 26</td>
<td>−20 ± 10</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>ΔSAT (%)</td>
<td>−11.3 ± 15.5</td>
<td>−3.1 ± 15.3</td>
<td>−15.7 ± 9.0</td>
<td>.55</td>
</tr>
<tr>
<td>Δ total body fat (%)</td>
<td>−21 ± 14</td>
<td>−7 ± 14</td>
<td>−16 ± 9</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>SI</td>
<td>1.95 ± 4.3</td>
<td>−0.7 ± 3.5</td>
<td>1.25 ± 2.3</td>
<td>.998</td>
</tr>
</tbody>
</table>

NOTE. Δ, change from baseline; BW, body weight; fat, whole-body visceral adipose tissue (VAT) + whole-body subcutaneous adipose tissue; SI, selectivity index (% ΔVAT/%Δfat); V/S, ratio of baseline visceral to subcutaneous adipose tissue at L4–L5.

was converted to mass by multiplying liters of adipose tissue by a factor of 0.93, the density of adipose tissue. The V/S ratio was calculated on the basis of a single MRI slice at the level of the L4–L5 intervertebral space. Because whole-body MRI results were available from these studies, the VAT selectivity index was calculated as the percentage of VAT divided by the percentage of total adipose tissue (i.e., SAT + VAT). Group changes were compared by 1-way analysis of variance. The results of individual studies done at St. Luke’s–Roosevelt Hospital Center (SLRHC) were graphed using Microsoft Excel 97 SR-2. The mean results from each study done at SLRHC were overlaid on scanned versions of the Smith and Zachwieja graphs using Microsoft PowerPoint 97 SR-2.

RESULTS

Body composition results are shown in table 1. The V/S ratio at baseline was highest in the group that received GH. Weight change was greatest in the obese women in the diet and exercise group. GH therapy resulted in a significant decrease in both visceral and subcutaneous fat. Among the 3 trials, VAT and total fat losses were greatest after GH therapy, during which skeletal muscle increased. The malnourished women in the exercise trial gained muscle but also had a significant loss of total adipose tissue and a trend toward a significant loss of SAT. However, VAT nonsignificantly increased. The obese women lost weight that consisted largely of body fat, including VAT, but also included some skeletal muscle. Despite these differences in body composition changes, the SI for VAT loss was similar in all 3 groups.

These results are illustrated in figures 3–5. Figure 3 graphs the results from each of the 42 HIV-positive subjects who participated in the 3 studies described above. Although the variables plotted are the same as those in figure 2 of Smith and Zachwieja [1], the lengths of the axes are greater because the ranges of the V/S ratio and SI are wider. The V/S ratio on a single L4–L5 slice ranges ∼0.2–0.5 in healthy people, whereas, in the HIV group, the range was 0 to ∼8. SI ranges were 0.75–2 in the original analysis, whereas the range in HIV-positive groups was approximately 17–12. Figures 4 and 5 show the

![Figure 3](image-url)  
Figure 3. Ratio of visceral adipose tissue (VAT) to subcutaneous adipose tissue prior to a weight-loss intervention vs. VAT sensitivity index (% change in VAT/% change in total body fat) in 42 HIV-infected subjects after interventions for malnutrition (squares, n = 10), visceral adiposity (triangles, n = 22), and obesity (diamonds, n = 10).
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Figure 4. Group means from 3 intervention trials in HIV-infected individuals plotted on a graph of results from 23 studies of HIV-uninfected individuals undergoing a weight-loss intervention [1]. 1, HIV-positive lipodystrophic men and women with visceral adiposity treated with recombinant human growth hormone; 2, HIV-positive malnourished women treated with progressive resistance exercise; and 3, HIV-positive obese women who participated in a diet and exercise weight-loss program are shown. VAT, visceral adipose tissue.

DISCUSSION

The present article indicates considerable differences between results from our laboratory and those from the 23 trials reviewed by Smith and Zachwieja [1]. The differences in V/S ratios may reflect differing amounts of either VAT or SAT. The relatively narrow range in the HIV-uninfected patients prior to undergoing a weight-loss intervention is consistent with a general increase in both VAT and SAT as weight increases. In contrast, the relative heterogeneity in the HIV-positive group is consistent with the variable indications for intervention—malnutrition, lipodystrophy, and obesity. The V/S ratio was highest in the GH group. Also, only the GH group included men, and only 3 of the participants in that study were women. Because men tend to have more visceral fat and less subcutaneous fat in general, this could be a partial explanation for the wide range. However, subjects were only eligible if they appeared to have truncal obesity, including large amounts of VAT, and many of the individuals who participated in that study additionally reported lipoatrophy in the subcutaneous compartment. Although there were some cases of abnormal fat distribution in the malnourished and obese groups, it tended to be less severe.

The SI also is on a different scale for HIV-positive and -negative subjects. Because the variation in the baseline V/S ratio may again be a factor, it is interesting to note that the comparison of the 3 HIV-positive groups showed statistically similar mean SI ratios, despite a mean SI of >1 in the GH and obese groups but of slightly <1 in the malnourished group that exercised. Again, the percentage of VAT lost per percentage of fat lost was essentially the same across groups. This similarity is apparent when the means are successfully plotted on the same graph of VAT versus total fat loss as the other studies. However, the final graph of the V/S ratio versus SI (figure 5) shows the individuals with excess VAT who were taking GH and the malnourished women who exercised to be “off the chart.” Again, in contrast with the obese HIV-positive women and HIV-negative subjects, those selected for GH treatment because of lipodystrophic changes, specifically a protuberant abdomen, had an unusually high V/S ratio, and the malnourished women, despite claims of increased abdominal girth, had very little baseline VAT and thus finished with a low SI.

Although the malnourished and lipodystrophic groups were particularly different from the others at baseline, it is of interest to further consider why the results of interventions in the HIV groups differed from those of HIV-uninfected people. Perhaps HIV or the metabolic changes associated with malnutrition, lipodystrophy, and antiretroviral drugs exert independent effects on VAT change. In addition, perhaps the effect of GH is greater than that of diet and exercise or diet pharmaceuticals on VAT.

Despite the limitations of this preliminary application of the Smith and Zachwieja V/S and SI ratios to HIV studies, it is important for HIV researchers to consider the effects of each when making comparisons among interventions to reduce visceral fat. However, additional statistical methods that can distinguish between initial body-composition differences due to the presence or absence of lipoatrophy or obesity would need to be developed and tested.

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Figure 5. Group means from 3 intervention trials in HIV-infected individuals, plotted on a graph of results from 9 studies in HIV-uninfected individuals undergoing a weight-loss intervention [1]. 1, HIV-positive lipodystrophic men and women with visceral adiposity treated with recombinant human growth hormone; 2, HIV-positive malnourished women treated with progressive resistance exercise; and 3, HIV-positive obese women who participated in a diet and exercise weight-loss program are shown. VAT, visceral adipose tissue.

References