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Total energy expenditure and carbohydrate oxidation are increased in the HIV lipodystrophy syndrome

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## INTRODUCTION

Changes in body fat distribution and metabolic disturbances are common in HIV-infected patients receiving potent antiretroviral therapy. Together, these problems comprise the HIV lipodystrophy syndrome. In a previous study, we found that PI-treated patients with lipodystrophy had significantly greater resting energy expenditure per kilogram of lean body mass compared to PI-treated and PI-naïve patients without lipodystrophy, suggesting that hypermetabolism may be another feature of the HIV lipodystrophy syndrome.

Several studies report increased *resting* energy expenditure in HIV-infected men and women with and without weight loss both before and after the introduction of highly active antiretroviral therapy (HAART). In contrast, *total* energy expenditure is generally thought to be normal in asymptomatic HIV infection. In a study conducted prior to the introduction of potent antiretroviral therapy, TEE in HIV-infected men with stable weight was similar to reference values obtained in healthy men of similar age. To our knowledge, there have been no studies of total energy expenditure in HIV infection reported in the era of potent antiretroviral therapy.

In a previous study, REE was similar in PI-treated and PI-naïve subjects without lipodystrophy but increased in PI-treated patients with lipodystrophy. However, HIV-negative controls were not included in that study. The present study extends results of that first study and reports total energy expenditure and nutrient oxidation rates in a subset of the subjects who underwent a 24-hour stay in a whole-room calorimeter. Results from these subjects were compared to existing data from healthy controls matched for age, gender and BMI who were studied in the same calorimeter under the same dietary and physical activity protocols.

## METHODS

HIV-infected men were included in the group with lipodystrophy (HIV-LD) if the subject, the subject's primary care provider and the primary investigator noted accumulation of central fat in addition to loss of fat from at least one depot, and the waist-hip ratio (WHR) was  $> 0.95$ . HIV-infected men were included in the group without lipodystrophy (HIV-infected controls) if the subject, the subject's primary care provider

and the primary investigator agreed that the patient showed no signs of lipohypertrophy or lipoatrophy and WHR ratio was  $< 0.95$ . Healthy control subjects were drawn from an existing data base of subjects who had been studied in the same whole-room calorimeter under similar conditions and were matched to the HIV-infected subjects based on age, gender and BMI. All subjects were studied during inpatient admissions to the General Clinical Research Center at UCHSC.

The insulin-modified frequently sampled IV glucose tolerance test was used to assess insulin sensitivity ( $S_i$ ) in the HIV-infected subjects. Total fat and lean body mass were determined by DEXA. Computed tomography was used to estimate visceral adipose tissue area.

Resting energy expenditure (REE) was determined by indirect calorimetry using the open circuit technique after a 10-12 hour overnight fast. Metabolic rate was calculated using the Weir equation. Total daily energy expenditure and substrate oxidation rates were measured in a whole-room indirect calorimeter, located on the GCRC. While in the whole-room calorimeter, subjects consumed a diet that provided 55% of energy as carbohydrate, 30% as fat and 15% as protein. To approximate activities of daily living, subjects underwent a modest exercise regimen in the chamber.

## **STATISTICAL ANALYSES**

Statistical analyses were performed using SAS Version 8 (SAS Institute, Cary, NC). The energy expenditure outcomes were analyzed separately. One-way analysis of variance followed by independent sample t-tests were used to compare EE among the three groups. Since LBM is known to be the major determinant of energy expenditure, simple linear regression was used to estimate the relationship between EE and LBM separately in each group. The slope of the regression represents the increase in EE per kg LBM and provides an estimate of metabolic activity of lean tissues. This slope is preferred over the ratio of EE to LBM because it does not assume a zero-intercept. Analysis of covariance was used to test equality of slopes among the three groups. When slopes were not found to be significantly different, a common slope was estimated, otherwise the separate slopes are reported. To account for differences in LBM, EE was adjusted to the mean value of LBM in the combined sample (60 kg). When the slopes did not differ, the lines relating

EE to LBM are parallel and differences among the groups do not depend on the value of LBM to which adjustment is made. When the slopes do differ, group differences depend on the adjustment value. Therefore, group differences at several values of LBM were examined. Analyses of EE outcomes were repeated after adjusting for LBM and fat mass simultaneously. As this adjustment did not substantially alter the results, the simpler results adjusting only for LBM are presented.

Table 1. Patient characteristics

	<b>HIV-LD</b>	<b>HIV-infected controls</b>	<b>Healthy controls</b>
<b>N</b>	12	6	16
<b>Age</b>	41.4 ± 5.3	37.6 ± 3.4	35.2 ± 8.6
<b>BMI (kg/m<sup>2</sup>)</b>	24.3 ± 3.8	25.2 ± 1.9	23.8 ± 1.9
<b>WHR</b>	1.01 ± 0.05	0.89 ± 0.03*	0.88 ± 0.05
<b>HIV RNA levels</b>	< 200 (<200, 1467)	< 200 (<200, 847)	Not done
<b>CD4 count (x10<sup>6</sup>/l)</b>	456.5 ± 236.0	710.6 ± 311.6	Not done
<b>S<sub>I(22)</sub> x 10<sup>-4</sup>(min<sup>-1</sup>/vU/ml)</b>	0.66 (0.58, 1.2)	2.0 (1.9,2.03)*	Not done

Data are means ± SD except S<sub>I(22)</sub> and HIV RNA levels which are reported as median values with 25<sup>th</sup> and 75<sup>th</sup> percentiles in parentheses. HIV-infected patients with lipodystrophy versus HIV-infected controls: \* P < 0.01.

**Table 2. Body composition**

	<b>HIV-LD</b>	<b>HIV-infected controls</b>	<b>Healthy controls</b>
<b>% body fat</b>	18.3 ± 5.6	17.8 ± 2.3	17.2 ± 6.2
<b>Total body fat (kg)</b>	14.1 ± 5.9	14.3 ± 2.4	13.8 ± 4.9
<b>Lean body mass (kg)</b>	57.9 ± 6.3	62.7 ± 6.7	59.9 ± 6.1
<b>% of total body fat in the trunk</b>	71.5 ± 6.9	66.2 ± 4.2*	52.8 ± 6.9 <sup>†</sup>
<b>% of total body fat in the extremities</b>	23.3 ± 7.1	27.5 ± 4.4*	42.2 ± 5.1 <sup>†</sup>
<b>VAT (cm<sup>2</sup>)</b>	198.8 ± 73.4	138.8 ± 45.1	Not done

Data are means ± SD. HIV-infected patients with lipodystrophy versus healthy controls:

<sup>†</sup>P < 0.001. HIV-infected controls versus healthy controls: \*P < 0.001

**Table 3: Energy expenditure (estimate + SE) for total day (TEE), resting (REE) and sleeping (SMR) periods. For each measurement, p-values are given in parentheses for the comparison with the HIV-LD group.**

	<u>HIV-LD</u>	<u>HIV-infected controls</u>	<u>Healthy controls</u>
<b><u>Total Energy Expenditure (TEE)</u></b>			
<b>Unadjusted (kcal/d)</b>	2820.3 ± 104.4	2696.5 ± 135.7 (0.506)	2459.5 ± 96.1 (0.015)
<b>Adjusted for LBM (kcal/d)</b>	<b>2897.5 ± 73.4</b>	<b>2565.2 ± 104.4</b> (0.016)	<b>2450.8 ± 62.6</b> (<0.001)
<b>Slope (kcal/kg LBM/d)</b>	51.9 ± 11.8	20.9 ± 16.6 (0.139)	46.3 ± 10.6 (0.723)
<b><u>Resting Energy Expenditure (REE)</u></b>			
<b>Unadjusted (kcal/d)</b>	2157.4 ± 98.1	1947.2 ± 60.7 (0.102)	1744.3 ± 48.1 (<0.001)
<b>Adjusted for LBM (kcal/d)</b>	<b>2246.9 ± 50.3</b>	<b>1925.7 ± 74.2</b> (0.001)	<b>1737.1 ± 42.8</b> (<0.001)
<b>Slope (kcal/kg LBM/d)</b>	<b>44.5 ± 7.9</b>	<b>7.8 ± 11.0</b> (0.012)	<b>21.5 ± 7.3</b> (0.041)

**Table 4. Energy balance and nutrient oxidation rates**

	<b>HIV-LD</b>	<b>HIV-infected controls</b>	<b>Healthy controls</b>
<b>Energy balance (kcal/d)</b>	292.7 ± 89.7	63.8 ± 124.5	- 44.6 ± 62.1*
<b>Carbohydrate balance(gm/d)</b>	59.6 ± 19.6	53.6 ± 9.7	49.8 ± 22.4
<b>Fat balance (gm/d)</b>	13.3 ± 11.7	-1.1 ± 11.1	-6.4 ± 9.4
<b>Protein balance (gm/d)</b>	18.8 ± 6.1	1.3 ± 6.9	-17.0 ± 6.9*
<b>Carb oxidation (gm/d)</b>	355.5 ± 26.5	314.6 ± 37.4	265.7 ± 23.7*
<b>Carb oxidation adjusted for LBM (gm/d)</b>	<b>367.4 ± 24.1</b>	<b>294.0 ± 34.3<sup>†</sup></b>	<b>264.4 ± 21.2*</b>
<b>Fat oxidation (gm/d)</b>	91.7 ± 9.8	94.7 ± 13.9	88.6 ± 8.8
<b>Fat oxidation adjusted for LBM (gm/d)</b>	93.6 ± 9.9	91.5 ± 14.1	88.3 ± 8.8

Data are means ± SE. HIV-infected patients with lipodystrophy versus healthy controls:

\*P ≤ 0.01. HIV-infected patients with lipodystrophy versus HIV-infected controls: <sup>†</sup>P = 0.09

## **SUMMARY OF RESULTS**

1. TEE adjusted for lean body mass was significantly greater in HIV-LD subjects as compared to both healthy controls and HIV-infected controls.
2. REE adjusted to mean lean body mass for the entire sample (60 kg) was significantly greater in the HIV-LD subjects as compared to both HIV-infected and healthy controls. REE adjusted for LBM was significantly greater in the HIV-LD group as compared to HIV-infected controls when LBM was > 49 kg, and as compared with the healthy controls when LBM was > 54 kg.
3. The slope of the regression equation for REE and LBM was significantly greater for HIV-LD patients as compared to HIV-infected and healthy controls.
4. Carbohydrate oxidation adjusted for lean body mass was significantly greater in the HIV-LD group as compared to healthy controls and tended to be higher than in HIV-infected controls ( $p = 0.09$ ).

## **CONCLUSIONS**

1. **Total energy expenditure is increased in HIV-infected patients with lipodystrophy as compared to HIV-infected and healthy controls.**
2. **Increases in TEE appear to be explained by an increase in basal metabolism.**
3. **The slope of the regression equation for REE and LBM was significantly greater for HIV-infected subjects with lipodystrophy as compared to HIV-infected and healthy controls. This suggests that the hypermetabolism associated with HIV lipodystrophy originates in some component of the LBM.**
4. **In HIV-infected subjects with lipodystrophy, carbohydrate oxidation adjusted for lean body mass is increased as compared to HIV-infected and healthy controls.**



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