Total Energy Expenditure and Carbohydrate Oxidation Are Increased in the Human Immunodeficiency Virus Lipodystrophy Syndrome

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To determine whether total energy expenditure (TEE) is increased in the human immunodeficiency virus (HIV) lipodystrophy syndrome, we compared energy expenditure (EE) and substrate oxidation rates in 12 HIV-infected men with lipodystrophy, 7 HIV-infected men without lipodystrophy, and 14 healthy controls. TEE and nutrient oxidation rates were assessed by whole-room indirect calorimetry. Resting energy expenditure (REE) was measured by indirect calorimetry using the open-circuit technique. Body composition was assessed by dual-energy x-ray absorptiometry (DEXA). Insulin sensitivity was measured using the insulin-modified frequently sampled intravenous glucose tolerance test. TEE adjusted for lean body mass (LBM) was significantly higher in the HIV-infected group with lipodystrophy compared to HIV-infected patients without lipodystrophy (2,873.3 ± 69 *v* 2,573.9 ± 92 kcal/d, $P = .02$) and compared to healthy controls (2,873.3 ± 69 *v* 2,404.0 ± 64 kcal/d, $P < .001$). REE and sleeping metabolic rate (SMR) adjusted for LBM were also significantly higher in the HIV-infected group with lipodystrophy compared to both HIV-infected and healthy controls. Carbohydrate oxidation rates adjusted for LBM were higher in men with HIV lipodystrophy as compared to healthy controls (362.5 ± 23 *v* 250.0 ± 22 g/d, $P = < .01$) and tended to be higher as compared to HIV-infected controls (362.5 ± 23.6 *v* 297.3 ± 31 g/d, $P = .1$). In conclusion, TEE and carbohydrate oxidation are increased in the HIV lipodystrophy syndrome. The increase in TEE appears to be due to increases in REE. The pathogenesis of elevated EE in HIV lipodystrophy and other forms of lipodystrophy remains to be determined.
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CHANGES IN BODY FAT distribution and metabolic disturbances including insulin resistance and dyslipidemia are common in human immunodeficiency virus (HIV)-infected patients receiving potent antiretroviral therapy.[1] Together, these problems comprise the HIV lipodystrophy syndrome. Most cases of lipodystrophy are encountered in patients treated with protease inhibitor (PI)-based antiretroviral therapy.[1,2] In a previous study, we found that PI-treated patients with lipodystrophy had significantly greater resting energy expenditure expressed (REE) per kilogram of lean body mass (LBM) compared to PI-treated and PI-naive patients without lipodystrophy,[3] suggesting that hypermetabolism may be another feature of the HIV lipodystrophy syndrome.

Several studies report increased REE in HIV-infected men and women with and without weight loss both before[4,5] and after[6,7] the introduction of highly active antiretroviral therapy (HAART). In contrast, total energy expenditure (TEE) is generally thought to be normal in asymptomatic HIV infection. In 2 studies 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.[8,9] TEE was appropriately reduced in patients with HIV infection during periods of weight loss, although REE remained high.[8] This reduction in TEE was due primarily to a reduction in physical activity. To our knowledge, there have been no studies of TEE in HIV infection reported in the era of potent antiretroviral therapy.

In a previous study, REE was similar in PI-treated and PI-naive subjects without lipodystrophy but increased in PI-treated patients with lipodystrophy.[3] However, HIV-negative controls were not included in that study. The present study extends results of that first study and reports TEE 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 body mass index (BMI) who were studied in the same calorimeter under the same dietary and physical activity protocols.

MATERIALS AND METHODS

HIV-infected subjects were recruited from local HIV primary care practices. Subjects gave written informed consent under a protocol approved by the Institutional Review Board at the University of Colorado Health Sciences Center (UCHSC). 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 greater than 0.95. This ratio was chosen because it is a validated predictor of central adiposity in the general population. 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 less than 0.95. Subjects were excluded if they had received high-dose glucocorticoid therapy in the past year or had an active opportunistic infection or malignancy. Healthy control subjects were drawn from an existing database 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. These healthy controls had not been tested for HIV infection. All

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subjects were studied during inpatient admissions to the General Clinical Research Center (GCRC) at UCHSC.

Blood samples for analysis of CD4 counts and viral load measurements were collected after a 12-hour overnight fast. Glucose was measured by a glucose hexokinase assay and insulin by competitive radioimmunoassay (Pharmacia, Peapack, NJ).

The insulin-modified frequently sampled intravenous glucose tolerance test was used to assess insulin sensitivity in the HIV-infected subjects.[10] After a 10- to 12-hour overnight fast, intravenous cannulas were placed in antecubital veins of both arms. A bolus of a 50% glucose solution (0.3 g/kg) was injected at time 0 and a bolus of regular human insulin (0.03 U/kg) was given after 20 minutes. Blood samples were collected at −15, −10, −5, −1, 2, 3, 4, 5, 6, 8, 10, 14, 19, 22, 25, 30, 40, 50, 70, 100, 140, and 180 minutes for determination of plasma glucose and insulin concentrations. The insulin sensitivity index (S_I) was calculated from the insulin-modified version of the MINMOD program. The fractional SD (the error in estimating the parameters) for all S_I values was less than 50%.

Body weight was measured on a calibrated scale with the subjects wearing hospital gowns only. In the HIV-infected subjects, waist circumference was measured at the level of the umbilicus while the subject was standing and after a normal expiration. Hip circumference was measured at the level of the greatest gluteal protruberence. All waist and hip measurements of the HIV-infected subjects were done by the same investigator. A slightly different technique had been used to measure the WHR of the healthy controls. Waist circumference was measured at half the distance between the xiphoid rocess and the navel at mid-exhalation, while hip circumference was measured at the level of the greater trochanter.

Total fat and LBM were determined by dual-energy x-ray absorptiometry (DEXA) using a model DPX-1Q whole body scanner (Lunar Radiation Corp, Madison, WI). Estimates were made of the amount of fat in the trunk and the extremities as previously described.[3]

Computed tomography (CT) measurement of abdominal fat in HIV-infected subjects was performed on a GE9800 scanner (General Electric, Waukesha, WI). A scout image was used to approximate a single 10-mm thick axial image through lumbar vertebrae L4-L5. The image was taken during suspended respiration after a normal expiration. Total abdominal adipose tissue area (TAT) was calculated by delineating the surface with a light pen and then computing the adipose tissue surfaces with an attenuation range of −190 to −30 Hounsfield units. Visceral adipose tissue area (VAT) was measured by drawing a line within the muscle wall surrounding the abdominal cavity. Subcutaneous adipose tissue area (SAT) was calculated by subtracting the visceral adipose tissue area from the total abdominal adipose tissue area. All CT fat measurements were made by a radiologist who was unaware of the subject's clinical characteristics.

REE was determined by indirect calorimetry using the open circuit technique with the subject in the supine position after a 10- to 12-hour overnight fast. The criterion for a valid metabolic rate was a minimum of 15 minutes of steady-state, defined as less than 10% fluctuation in minute ventilation and oxygen consumption and less than 5% fluctuation in respiratory quotient. Metabolic rate was calculated using the Weir equation.[11]

Daily TEE and substrate oxidation rates were measured in a whole-room indirect calorimeter, located on the GCRC, as previously described.[12] For the 3 days prior to their chamber stay and measurement of insulin sensitivity, the HIV-infected subjects consumed a eucaloric diet (based on REE measurements) that provided 55% of energy as carbohydrate, 30% as fat, and 15% as protein. All food was prepared by the GCRC kitchen, and all subjects were asked to abstain from planned physical activity for 48 hours prior to entering the calorimeter. Subjects entered the chamber at 8 AM and left the following day at 7 AM. Results were extrapolated to 24 hours. Oxygen consumption and carbon dioxide production were determined from the flow rate and differences in gas concentrations between entering and exiting air. Values were corrected for temperature, barometric pressure, and humidity. Energy expenditure (EE) was calculated from oxygen consumption and respiratory quotient. The operation of the chamber was controlled by a personal computer using a software program written in TURBO C. The program was based on the calculations described by Jequier et al.[13] Values for all indexes were averaged over 2-minute intervals and recorded in a data file. An activity button was linked to the computer and was used to mark events (sleep, meals, exercise). This button was pressed before commencing and upon completing an event. Subjects collected all of their urine while in the calorimeter. Aliquots were analyzed for total nitrogen content.

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 produce energy balance on this relatively sedentary day, daily energy intake was estimated for each subject using the subject's measured REE multiplied by an activity factor of 1.3. To approximate activities of daily living, subjects underwent a modest exercise regimen in the chamber. Prescribed stepping and walking exercises were performed by each subject. Stepping was done on a 6-inch high-step platform in 3 separate 10 minute bouts of increasing intensity (2, 3, and 4 laps every 10 seconds for 10 minutes at each speed). Each intensity bout was separated by a 10-minute period of sitting quietly. Immediately following the stepping protocol, walking was performed in 3 different bouts, each separated by a 10-minute period of sitting quietly. A walking lap involved walking across an 8-foot wide area and back to the starting point. The 3 different walking speeds were: 1 lap/10 seconds, 1.5 laps/10 seconds, and 2 laps/10 seconds.

Statistical Analyses

Statistical analyses were performed using SAS Version 8 (SAS Institute, Cary, NC). The EE outcomes were analyzed separately. For each EE outcome, 3 analyses were performed to study differences among the 3 groups and to determine whether these differences related to different rates of metabolic activity of lean tissue (known to be the major determinant of EE) or to some effect independent of LBM: (a) one-way analysis of variance (ANOVA) followed by independent-sample *t* tests was used to compare unadjusted EE among the 3 groups. (b) 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 kilogram 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.[14,15] Analysis of covariance (ANCOVA) was used to test equality of slopes among the 3 groups. (c) Differences in LBM may explain some of the unadjusted differences noted in (a), and remaining differences would be due to other factors. 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, the lines are not parallel and group differences depend on the adjustment value. Therefore, in these cases, 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.

RESULTS

Table 1 shows the characteristics of HIV-infected subjects and healthy controls. All of the subjects were male. Patients with HIV lipodystrophy were significantly older than healthy controls ($P < .01$). BMI was similar among the groups. By design, the mean WHR of the HIV-LD subjects was signifi-

Table 1. Patient Characteristics

	HIV-LD	HIV-Infected Controls	Healthy Controls
No.	12	7	14
Age (yr)	41.4 ± 5.3	37.1 ± 3.4	33.6 ± 7.0*
BMI (kg/m^2)	24.3 ± 3.8	25.0 ± 1.9	23.6 ± 2.0
WHR	1.02 ± 0.04	0.89 ± 0.03*	0.87 ± 0.06
Duration of HIV infection (yr)	11.5 ± 1.5	9.8 ± 3.9	NA
% with h/o opportunistic infection	8.3%	14.3%	NA
HIV RNA levels	<200 (<200, 1,467)	<200 (<200, 2,793)	NA
CD4 cell count ($\times 10^6$/L)	456.5 ± 236.0	756.6 ± 300.7‡	Not done
$S_{I(22)} \times 10^{-4}$ (min^{-1}/μU/mL)	0.66 (0.58, 1.2)	2.0 (1.9, 3.1)†	Not done

NOTE. Data are means ± SD, except $S_{I(22)}$ and HIV RNA levels, which are reported as median values with 25th and 75th percentiles in parentheses.

HIV-infected patients with lipodystrophy *v* healthy controls: *$P < .01$.

HIV-infected patients with lipodystrophy *v* HIV-infected controls: †$P < .01$, ‡$P < .05$.

Abbreviations: NA, not applicable; h/o, history of.

cantly greater as compared to WHR in the HIV-infected control group ($P < .01$). Because a different technique was used to measure WHR in healthy controls, this measurement cannot be compared to WHR from the HIV-infected subjects. Nevertheless, the mean WHR of 0.87 indicates that they did not have significant central adiposity.

Subjects in the HIV-LD group were significantly less insulin sensitive as compared to HIV-infected controls ($P < .01$). For comparison, in healthy adults with normal glucose tolerance, mean S_I is about 2.0×10^{-4} (min^{-1}/μU/mL).[10] Plasma lipid levels did not differ significantly between the HIV-infected groups (data not shown). Median plasma HIV-1 RNA measurements were similar in the HIV-LD group and in HIV-infected controls, but CD4 cell counts were higher in HIV-infected controls as compared to the HIV-LD group ($P < .05$). There was no difference in duration of HIV disease or history of opportunistic infection between the HIV-infected groups. One of 12 (8.3%) patients in the HIV lipodystrophy group had a history of opportunistic infection, while 1 of 7 (14.3%) in the HIV-infected control group had such a history. Ten of 12 HIV-infected subjects who met criteria for central fat accumulation also had lipoatrophy of the extremities as manifested by venous prominence and a pseudomuscular appearance. The 2 patients without lipoatrophy of the extremities had facial lipoatrophy manifested by sunken cheeks. All patients in the HIV-LD group and in the HIV-infected control group were receiving PI-based antiretroviral therapy.

Table 2 shows the results of body composition measurements. There were no significant differences among the the 3 groups in percent body fat, total body fat, or LBM as determined by DEXA. Compared to healthy controls, the HIV-LD group had a significantly greater percent of total body fat present in the trunk ($P < .001$) and a significantly lower percent of total body fat present in the extremities ($P < .001$). Compared to HIV-infected controls, patients with lipodystrophy tended to have a greater percent of total body fat in the trunk ($P = .06$) and a lower percent of body fat in the extremities ($P = .1$). Visceral adipose tissue area also tended to be greater in the HIV-LD group as compared to the HIV-infected controls ($P = .07$).

TEE was significantly higher in HIV-LD subjects as compared to healthy controls ($P < 0.01$) but was not significantly different as compared to TEE in HIV-infected controls (Table 3). TEE adjusted for LBM was significantly greater in HIV-LD subjects as compared to both healthy controls ($P < 0.001$) and HIV-infected controls ($P < .05$). Unadjusted TEE and TEE adjusted for LBM did not differ significantly between the HIV-infected and healthy control groups. Among the HIV-infected subjects with lipodystrophy and the healthy controls, TEE was highly correlated with LBM ($r = 0.91$, $P < .0001$ and $r = 0.77$, $P = < .01$, respectively). Due probably to the small sample size of the HIV-infected control group, TEE and LBM were positively but not significantly correlated. Slopes of the TEE versus LBM relationship did not differ among groups.

REE was significantly higher in the HIV-LD group as compared to both HIV-infected ($P < .05$) and healthy controls ($P < .001$). REE adjusted to mean LBM for the entire sample (60 kg) was significantly greater in the HIV-LD subjects as compared to

Table 2. Body Composition

	HIV-LD	HIV-Infected Controls	Healthy Controls
% body fat	18.3 ± 5.6	18.7 ± 3.3	17.3 ± 6.6
Total body fat (kg)	14.1 ± 5.9	14.6 ± 2.4	13.8 ± 5.3
LBM (kg)	57.9 ± 6.3	61.2 ± 7.3	59.2 ± 5.9
% of total body fat in the trunk	71.5 ± 6.9	64.6 ± 5.8	53.1 ± 5.7*,†
% of total body fat in the extremities	23.3 ± 7.1	29.3 ± 6.3	41.9 ± 5.4*,†
VAT (cm^2)	198.8 ± 73.4	136.8 ± 40.6	Not done

NOTE. Data are means ± SD.

HIV-infected patients with lipodystrophy *v* healthy controls: *$P < .001$.

HIV-infected controls *v* healthy controls: †$P < .01$.

Table 3. Energy Expenditure (Estimate + SE) for Total Day (TEE), Resting (REE), and Sleeping (SMR) Periods.

	HIV-LD	HIV-Infected Controls	Healthy Controls
TEE			
Unadjusted (kcal/d)	2,820.3 ± 104	2,659.4 ± 137 (.358)	2,406.7 ± 97 (.007)
Adjusted for LBM (kcal/d)	2,873.3 ± 69	2,573.9 ± 92 (.016)	2,404.0 ± 64 (<.001)
Slope (kcal/kg LBM/d)	51.9 ± 11	21.8 ± 13 (.089)	49.2 ± 11 (.863)
REE			
Unadjusted (kcal/d)	2,157.4 ± 73	1,902.4 ± 95 (.042)	1,712.1 ± 70 (<.001)
Adjusted for LBM* (kcal/d)	2,246.9 ± 51	1,885.1 ± 65 (.002)	1,718.5 ± 47 (<.001)
Slope (kcal/kg LBM/d)	44.5 ± 8	14.3 ± 9 (.021)	19.4 ± 8 (.036)
SMR			
Unadjusted (kcal/d)	1,964.4 ± 72	1,744.0 ± 94 (0.074)	1,519.5 ± 67 (<.001)
Adjusted for LBM (kcal/d)	2,000.5 ± 49	1,685.9 ± 65 (.001)	1,517.7 ± 45 (<.001)
Slope (kcal/kg LBM/d)	31.1 ± 8	25.1 ± 10 (.642)	30.3 ± 8 (.943)

NOTE. Slopes are from a model allowing different LBM slopes for each group. When the slopes were not significantly different between groups, mean expenditures adjusted for LBM were estimated assuming a common slope.

*When slopes were significantly different, EEs were adjusted at the mean LBM for all groups. For each measurement, *P* values are given in parentheses for the comparsion with the HIV-LD group.

both HIV-infected ($P < .01$) and healthy controls ($P < .001$). REE adjusted for LBM was significantly greater in the HIV-LD group as compared to HIV-infected controls when LBM was greater than 49 kg, and as compared with the healthy controls when LBM was greater than 54 kg. REE was significantly correlated with LBM for the HIV-LD subjects ($r = 0.83$, $P < .001$) and for healthy controls ($r = 0.66$, $P = .01$) and positively but not significantly correlated for HIV-infected controls. The slope of the regression equation for REE and LBM was significantly greater for HIV-LD patients as compared to both HIV-infected and healthy controls ($P < .05$).

REE and TEE adjusted for LBM were significantly and negatively associated with insulin sensitivity ($r = -0.65$, $P < .01$ and $r = -0.49$, $P < .05$, respectively). There was no significant correlation between CD4 cell count, HIV RNA levels, or measures of regional adiposity and any measure of EE.

Sleeping metabolic rate (SMR) was also significantly higher in the HIV-LD group as compared to healthy controls ($P < .001$). SMR adjusted for LBM was significantly greater in HIV-LD subjects as compared to both the HIV-infected ($P = .001$) and healthy controls ($P < .001$). Slopes of the SMR versus LBM relationship did not differ among the groups. Twenty-four–hour respiratory quotient (RQ) did not differ significantly between groups, but sleep RQ was significantly greater in the HIV-LD group as compared to the healthy controls ($P < .05$, data not shown).

Importantly, when simple ratios of EE per kilogram LBM were used to quantify energy expended per unit of metabolically active tissue, TEE/kg LBM, REE/kg LBM, and SMR/kg LBM were all significantly greater in the HIV-LD patients as compared to both the HIV-infected and healthy controls (data not shown).

Results of 24-hour energy and substrate balance and expenditure are shown in Table 4. The HIV-LD group was in positive energy balance during the calorimeter stay, but energy balance was not significantly greater as compared to the control groups. Protein balance was significantly greater in the HIV-LD groups as compared to healthy controls ($P < .01$). Fat and carbohydrate balance did not differ significantly between groups, but carbohydrate oxidation adjusted for LBM was significantly greater in the HIV-LD group as compared to healthy controls ($P < .01$) and tended to be higher than in HIV-infected controls ($P = .1$). Fat oxidation rates did not differ significantly among the groups. Protein oxidation rates also did not differ among the groups (data not shown).

DISCUSSION

We studied non-obese PI-treated patients with lipodystrophy that was manifested by an increase in abdominal girth and loss of fat from at least one depot and compared them to HIV-infected subjects without lipodystrophy and healthy controls.

TEE was increased in HIV-infected patients with lipodystrophy as compared to HIV-infected and healthy controls. This

Table 4. Energy Balance and Nutrient Oxidation Rates

	HIV-LD	HIV-Infected Controls	Healthy Controls
Energy balance (kcal/d)	292.7 ± 89	13.8 ± 116	17.6 ± 50
Carbohydrate balance (g/d)	59.6 ± 19	47.3 ± 10	66.3 ± 22
Fat balance (g/d)	13.3 ± 11	−4.9 ± 10	−5.9 ± 10
Protein balance (g/d)	18.8 ± 6	3.0 ± 6	−18.7 ± 7*
Carbohydrate oxidation (g/d)	355.5 ± 31	309.2 ± 17	250.1 ± 23*
Carbohydrate oxidation (g/d adjusted for LBM)	362.5 ± 23	297.3 ± 31	250.0 ± 22*
Fat oxidation (g/d)	91.7 ± 9	95.5 ± 7	88.8 ± 11
Fat oxidation adjusted for LBM (kcal/d)	93.1 ± 9	93.2 ± 13	88.9 ± 9

NOTE. Data are means ± SE.

HIV-infected patients with lipodystrophy *v* healthy controls: *$P \leq .01$.

increase appeared to be explained by an increase in REE in these patients. 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. Finally, in HIV-infected subjects with lipodystrophy, carbohydrate oxidation adjusted for LBM was increased as compared to HIV-infected and healthy controls.

The HIV-infected subjects with lipodystrophy had significantly lower CD4 cell counts as compared to the HIV-infected controls; however, we do not believe that this reflects a difference in HIV disease severity at the time of the study. The groups had a similar history or opportunistic infection and duration of HIV infection. In addition, in both groups, median HIV RNA levels were undetectable. Finally, CD4 cell counts do not necessarily reflect current viral activity, especially in the setting of viral suppression. However, it remains possible that our finding of increased EE in patients with HIV lipodystrophy as compared to HIV-infected controls was confounded by differences in HIV disease severity.

In HIV-infected patients with lipodystrophy, TEE adjusted for LBM was approximately 12% and 19% higher than in HIV-infected and healthy controls, respectively. Likewise, REE adjusted for LBM was approximately 19% and 30% higher in the lipodystrophy group as compared to HIV-infected and healthy controls, respectively. About 60% of REE stems from the metabolic activity of the liver, brain, heart, and kidneys, which constitute only 5.5% of body weight.[16] Compared to these organs, skeletal muscle has a relatively low basal metabolic rate. However, skeletal muscle constitutes about 40% of body weight and thus accounts for another 20% of REE. Adipose tissue likewise has low metabolic activity and accounts for only about 4% of whole-body REE in lean subjects. In order to account for the 18% to 27% increase in REE observed in HIV-infected patients with lipodystrophy, adipose tissue would have to increase its EE by about 5-fold. Therefore, it seems likely that the increased EE of HIV lipodystrophy originates in some component of LBM. The steeper slope of the regression line relating LBM to REE in patients with lipodystrophy supports this idea. A 19% to 30% increase in REE could be due to a 2-fold increase in the basal metabolic rate of the liver *or* skeletal muscle. Alternatively, a change in the proportion of body weight as various organs could explain the differences in REE.[17] For example, hepatomegaly in patients with lipodystrophy could result in increased REE even after adjustment for LBM. Despite the reasoning outlined above, the possibility remains that the increased EE of HIV lipodystrophy stems from a diseased adipose tissue organ.

Mitochondrial dysfunction has been put forward as a possible mechanism for the lipoatrophic component of HIV lipodystrophy.[18] It is unclear, however, how such dysfunction could explain both fat atrophy and increased EE by the adipose tissue organ. Recently, in vitro studies have documented mitochondrial abnormalities in the skeletal muscle of patients with HIV lipodystrophy.[19] The reduced respiratory activities described in the mitochondrial preparations seem to be inconsistent with our in vivo findings of increased EE in patients with the HIV lipodystrophy syndrome unless mitochondria in other tissues are spared. Furthermore, it is unclear how mitochondrial dysfunction in skeletal muscle could lead to changes in body fat distribution.

TEE is comprised of 3 components: REE or basal metabolic rate, postprandial thermogenesis, and physical activity. This study suggests that increased TEE in the HIV lipodystrophy syndrome is due to an increase in basal metabolism. However, we did not directly measure postprandial thermogenesis or energy expended in physical activity. As noted above, increased REE has been reported in several studies of HIV-infected patients with and without weight loss even before the advent of potent antiretroviral therapy, but the mechanism of this increase is not known. Increased REE in the pre-HAART era could have been due to high cytokine levels that accompany uncontrolled HIV infection. In the HAART era, increased REE likely has a different cause. In a large cross-sectional study, HAART administration was independently associated with increased REE.[7] However, in another study of HIV-infected and acquired immunodeficiency syndrome (AIDS) patients, REE was increased at baseline compared to healthy uninfected controls and decreased after starting nelfinavir-based HAART.[20] After 24 weeks, there was no difference in REE between HIV-infected patients and uninfected controls. The reduction in REE was preceded by a decrease in plasma HIV-1 RNA titer, suggesting that sustained suppression of viral replication might promote a decrease in REE. This concept is supported by the positive correlation found between viral load and REE in clinically stable patients.[21] In another study, REE was measured before and after indinavir-based HAART in 7 patients with HIV-associated wasting.[22] REE adjusted for fat-free mass did not change after a median of 62 days of therapy. In the current study, PI-treated patients without lipodystrophy did not have higher REE compared to healthy controls. Looking at the evidence to date, it seems unlikely that antiretroviral therapy has significant and independent effects on REE.

Elevated REE has also been described in patients with congenital and other acquired forms of lipodystrophy[23-25] and elevated TEE has been described in a mother and daughter with a variant of partial lipodystrophy.[26] Perhaps HIV lipodystrophy shares a common mechanism of increased EE with these other lipodystrophy syndromes, but the mechanism is unknown.

The increase in REE and TEE in the patients with lipodystrophy is not explained by this study. Although insulin sensitivity was significantly correlated with both measures of EE, differences in insulin sensitivity are unlikely to account for the magnitude of the differences observed.[27] It is also possible that significant atrophy of the subcutaneous fat depot could lead to increased heat loss from the body's surface and therefore to increased EE in patients with lipodystrophy. Again, however, this mechanism is unlikely to account for such large differences in EE. Finally, we did not measure cytokine levels in this study. Interferon alfa levels have been shown to be elevated in HIV-infected patients with lipodystrophy,[28] and this cytokine has been shown to significantly increase REE in healthy subjects.[29]Therefore, it is possible that cytokine perturbations may explain the hypermetabolism of HIV lipodystrophy. Regardless of the mechanism, the hypermetabolism of HIV lipodystrophy may put patients at increased risk for significant weight loss during periods of intercurrent illness or relative anorexia.

The present study also found that carbohydrate oxidation was increased in patients with lipodystrophy as compared to healthy controls and tended to be higher in these patients as

compared to HIV-infected controls. Increased carbohydrate oxidation has also been shown in HIV-uninfected patients with congenital generalized lipodystrophy[30] and in patients with a form of partial lipodystrophy called mandibuloacral dysplasia syndrome.[24] Another study of HIV-uninfected patients with partial and generalized lipodystrophy syndromes found that mean baseline RQ was 0.95 compared to 0.77 for healthy controls.[31] In aggregate, these data suggest that increased carbohydrate oxidation is a general feature of various lipodystrophy syndromes and this may be related to the hypermetabolic state per se of patients with lipodystrophy. Further studies are needed to understand fuel oxidation and storage in patients with HIV lipodystrophy.

In summary, TEE and carbohydrate oxidation are increased in patients with stable HIV infection in the setting of the lipodystrophy syndrome. The hypermetabolism in this form of lipodystrophy may originate in the LBM, but the underlying mechanism is unknown.

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