Increased resting energy expenditure, fat oxidation, and food intake in patients with highly active antiretroviral therapy-associated lipodystrophy

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Sutinen J, Yki-Järvinen H. Increased resting energy expenditure, fat oxidation, and food intake in patients with highly active antiretroviral therapy-associated lipodystrophy. Am J Physiol Endocrinol Metab 292: E687–E692, 2007. First published October 24, 2006; doi:10.1152/ajpendo.00219.2006.—Highly active antiretroviral therapy (HAART) is associated with metabolic adverse events such as lipodystrophy in human immunodeficiency virus (HIV)-infected patients. The objective of the present study was to evaluate the effects of HAART-associated lipodystrophy on resting energy expenditure and caloric intake. In this cross-sectional study we compared resting energy expenditure (REE) and energy intake in 30 HAART-treated patients without lipodystrophy (HAART+LD−) with 13 HAART-treated patients without lipodystrophy (HAART+LD−). REE was measured using indirect calorimetry, and energy intake was recorded as a 3-day diary of food intake. REE (5,180 ± 160 vs. 4,260 ± 150 J/min, P < 0.01) and also REE expressed per fat-free mass (86 ± 1 vs. 78 ± 2 J/kg fat-free mass−1·min−1, P < 0.01) were significantly higher in the HAART+LD+ than the HAART+LD− group. Rate of lipid oxidation was significantly higher in the HAART+LD+ than the HAART+LD− group. Total energy and fat intakes were significantly increased in the HAART+LD+ compared with the HAART+LD− group. These results imply that HAART-associated lipodystrophy is associated with increased REE and lipid oxidation and with increased caloric and fat intake.

HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) has improved the prognosis of human immunodeficiency virus (HIV)-infected patients (25). HAART is, however, associated with metabolic complications, including lipodystrophy, insulin resistance, and dyslipidemia (19). As a result of widespread use of HAART, HAART-associated lipodystrophy (HAL) has become by far the most prevalent form of human lipodystrophies (16). HAL is characterized by loss of subcutaneous fat (lipodystrophy) and a relative increase in central fat (19). Lipodystrophy has been suggested to be the dominant morphological change of HAL (56). The pathophysiology of this syndrome appears to be multifactorial, including HAART-induced inhibition of adipocyte differentiation, inflammatory changes, and mitochondrial dysfunction in adipose tissue (18). HAL also could affect energy metabolism, albeit this aspect of HAL has been sparsely studied.

When the effects of HAL on resting energy expenditure (REE) are studied, the confounding effects of HIV infection or HAART per se on REE must be taken into account. According to a very recent meta-analysis, REE expressed per fat-free mass (FFM) is significantly higher in HIV-positive subjects than in healthy controls (6). Among HIV-infected subjects, the prevalence of lipodystrophy was not associated with an increase in REE/FFM. However, in these studies lipodystrophic patients did not have significantly less subcutaneous fat compared with HAART-treated nonlipodystrophic patients (1, 6, 21, 31, 32, 43). Thus whether patients with significantly reduced amounts of subcutaneous fat have an increase in REE/FFM is still unknown. Furthermore, food intake has not been quantified in any study involving lipodystrophic patients. The aim of the current study was to evaluate the effects of HAL on both REE and energy intake by comparing two previously characterized groups of HIV-infected, HAART-treated patients with and without significant loss of subcutaneous fat.

MATERIALS AND METHODS

Subjects and Study Design

This is a cross-sectional study on energy metabolism in two groups of HIV-infected, HAART-treated patients, one group with (HAART+LD+) and the other group without lipodystrophy (HAART+LD−). As previously described, the patients were recruited from the outpatient clinic of the Helsinki University Central Hospital (29, 51–54, 61). All participants had to have been treated with combination antiretroviral therapy for at least 18 mo before enrollment and did not have any signs or symptoms of current opportunistic infections. Indirect calorimetry was performed and blood samples were drawn after an overnight fast.

HAART+LD+ patients had self-reported symptoms of loss of subcutaneous fat with or without increased abdominal girth, breast size, or development of a buffalo hump. HAART+LD− patients had received antiretroviral therapy without developing symptoms of lipodystrophy. Both the presence and absence of lipodystrophy was confirmed by a single investigator before enrollment.

The purpose, nature, and potential risks of the study were explained to the patients before their written, informed consent was obtained. The protocol was approved by the ethics committee of the Helsinki University Central Hospital.

Methods

Indirect calorimetry. Respiratory gas exchange and REE were recorded for 40 min by indirect calorimetry using the Deltatrac metabolic monitor (Datex, Helsinki, Finland). Substrate oxidation rates and rates of energy expenditure were calculated from the gas exchange data as previously described (15, 60).

Food intake and physical activity. The participants kept a 3-day diary of food and fluid intake on 2 days of normal working and 1 day off from work. The patients were instructed not to change their regular diet on the days of data recording. The quality of food intake recording was confirmed, and data analysis was performed by an
experienced dietician who was unaware of the absence or presence of lipodystrophy of the participants. Food diaries were analyzed using NUTRICCA software (version 3.0; Research Centre of the Social Insurance Institution, Helsinki, Finland). Patients were asked about their physical activity during a structured interview. Physical activity was classified as light, such as walking, or strenuous, defined as any activity making patients to be out of breath or to sweat.

**Body composition.** Total body fat mass and lean body mass were determined using BIA (BioElectrical Impedance Analyzer System model BIA-101A; RJL Systems, Detroit, MI). The volumes of intra-abdominal and subcutaneous fat were measured using magnetic resonance imaging. A total of 16 T1-weighed transaxial scans extending from 8 cm above to 8 cm below the fourth and fifth lumbar interspace were analyzed (field of view, 375 × 500 mm²; slice thickness, 10 mm; breath-hold repetition time, 138.9 ms; echo time, 4.1 ms). Intra-abdominal and subcutaneous fat volumes were quantified using image analysis software (Alice 3.0; Parexel, Waltham, MA). In our hands, the reproducibility of intra-abdominal and subcutaneous fat measurements performed on two separate occasions was 5% and 3% (coefficient of variation) (50). Subcapsular skin fold thickness (mean of triplicate measurements) was performed using Harpenden calipers (John Bull British Indicators, West Sussex, UK).

**Laboratory analyses.** Serum free insulin concentrations were determined with radioimmunoassay (Phadephese Insulin RIA; Pharmacia & Upjohn Diagnostics, Uppsala, Sweden) after precipitation with polyethylene glycol (13). Plasma glucose concentrations were measured using a hexokinase method. Serum total and HDL cholesterol and triglyceride concentrations were measured using respective enzymatic kits from Roche Diagnostics. The H VIRAL load was measured using the HIV-1 Monitor Test (Roche Diagnostics Hitachi 917; Hitachi, Tokyo, Japan). Serum free fatty acid (FFA) concentrations were measured using fluorometric assay (38). Serum leptin concentrations were quantified by radioimmunoassay with a commercial kit (Human Leptin RIA kit; Linco Research, St. Charles, MO). Serum concentrations of tumor necrosis factor (TNF)-α and IL-6 were measured using commercial enzyme-linked immunoassays (Quantikine; R&D Systems, Minneapolis, MN). The HIV viral load was measured using the HIV-1 Monitor Test (Roche Diagnostics, Branchburg, NJ) with a detection limit of 50 copies/ml.

**Statistical Analysis**

The unpaired t-test was used to compare differences between the groups. Logarithmic transformation was performed on skewed data. Correlations were calculated using Spearman’s rank correlation coefficient. Categorical variables were compared using Fisher’s exact test. All data are given as means ± SE. All calculations were performed using the Systat statistical package (version 10.0; Systat, Evanston, IL) or GraphPad Prism (version 3.0; GraphPad, San Diego, CA). A P value <0.05 was considered statistically significant.

**RESULTS**

**HIV-Related Characteristics**

The mean time since the diagnosis of HIV was 8.2 ± 0.6 vs. 8.6 ± 1.3 yr (not significant, NS) in the HAART+LD+ compared with the HAART+LD− group. None of the patients had symptoms or signs of an acute opportunistic infection at the time of the study, but eight patients (27%) in the HAART+LD+ and one patient (8%) in the HAART+LD− group (NS) had a history of a previous AIDS-defining illness. The groups were comparable regarding the viral load (1.87 ± 0.15 vs. 1.65 ± 0.25 log₁₀ copies/ml, HAART+LD+ vs. HAART+LD−, NS), CD4 count (572 ± 54 vs. 516 ± 70 × 10⁹/l, respectively, NS), and the duration of combination antiretroviral therapy (4.2 ± 0.2 vs. 3.8 ± 0.4 yr, respectively, NS). All participants in both groups were receiving nucleoside reverse transcriptase inhibitors as part of the combination therapy. Of the thymidine analogs, zidovudine was used by 7 patients (23%) in the HAART+LD+ group and 10 patients (77%) in the HAART+LD− group (P < 0.01), whereas stavudine was used by 21 (70%) and 3 patients (23%), respectively (P < 0.01). Thirty-three percent of the patients in the HAART+LD+ group and 38% of those in the HAART+LD− group (NS) used nonnucleoside reverse transcriptase inhibitors, and 73 and 69%, respectively (NS), used protease inhibitors.

**Body Composition and Biochemical Characteristics**

As previously described (29, 51–54, 61), the age, body mass index, and total body fat mass values were comparable between the HAART+LD+ and the HAART+LD− groups. The HAART+LD+ group had, however, significantly less subcutaneous fat (1,100 ± 200 vs. 1,800 ± 300 cm², P < 0.05) and more intra-abdominal fat (1,900 ± 200 vs. 900 ± 300 cm², P < 0.01) than the HAART+LD− group (Table 1). The HAART+LD+ group also had higher fasting serum insulin and triglyceride concentrations and lower HDL cholesterol concentrations than the HAART+LD− group. Serum FFA concentrations were slightly but not significantly increased in the HAART+LD+ group compared with the HAART+LD− group. Serum leptin concentration was not significantly different between the two groups. Serum TNF-α (1.6 ± 0.1 vs. 1.5 ± 0.2 pg/ml, HAART+LD+ vs. HAART+LD−, NS) and IL-6 (2.2 ± 0.3 vs. 1.9 ± 0.6 pg/ml, respectively, NS) concentrations were not significantly different between the groups.

**Energy Metabolism**

REE (kJ/min) was 21%, REE adjusted for body weight was 13%, and REE adjusted for FFM was 11% greater in the HAART+LD+ than the HAART+LD− group (Table 2). The increase in energy expenditure also remained significant if women were excluded from the analysis (data not shown). REE (kJ/day) correlated closely with FFM in both groups (r = 0.5 ± 0.01).

**Table 1. Body composition and metabolic characteristics of patients with and without HAART-associated lipodystrophy**

<table>
<thead>
<tr>
<th></th>
<th>HAART+LD+</th>
<th>HAART+LD−</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males/females</td>
<td>25/5</td>
<td>9/4</td>
<td>NS</td>
</tr>
<tr>
<td>Age, yr</td>
<td>43 ± 2</td>
<td>39 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>23.6 ± 0.5</td>
<td>22.4 ± 1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>73.1 ± 2.1</td>
<td>68.9 ± 3.5</td>
<td>NS</td>
</tr>
<tr>
<td>Subcapsular skin fold, mm</td>
<td>20 ± 2</td>
<td>13 ± 2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Total fat-free mass, kg</td>
<td>60.1 ± 1.4</td>
<td>55.5 ± 2.6</td>
<td>NS</td>
</tr>
<tr>
<td>Total body fat mass, kg</td>
<td>13.1 ± 1.1</td>
<td>13.4 ± 1.9</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma glucose, mg/dl</td>
<td>99 ± 5</td>
<td>90 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Serum insulin, μU/ml</td>
<td>11.1 ± 1.2</td>
<td>6.5 ± 1.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Serum triglycerides, mg/dl</td>
<td>301 ± 35</td>
<td>106 ± 9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum HDL cholesterol, mg/dl</td>
<td>42 ± 4</td>
<td>62 ± 41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum free fatty acids, μmol/l</td>
<td>561 ± 36</td>
<td>470 ± 55</td>
<td>NS</td>
</tr>
<tr>
<td>Serum leptin, ng/ml</td>
<td>4.0 ± 0.6</td>
<td>5.1 ± 1.9</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>67 ± 2</td>
<td>65 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>125 ± 2</td>
<td>121 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>78 ± 1</td>
<td>77 ± 2</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are means ± SE. HAART+LD+, highly active antiretroviral therapy-treated patients with lipodystrophy; HAART+LD−, HAART-treated patients without lipodystrophy; NS, non significant.
Energy expenditure in HIV-lipodystrophy

Table 2. Resting metabolic rate and substrate use in patients with and without HAART-associated lipodystrophy

<table>
<thead>
<tr>
<th></th>
<th>HAART+LD+</th>
<th>HAART+LD-</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Resting energy expenditure</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1/min</td>
<td>5.180±160</td>
<td>4.260±150</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>J·kg⁻¹·min⁻¹</td>
<td>71±1</td>
<td>62±1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>J·kg⁻¹·FFM⁻¹·min⁻¹</td>
<td>86±1</td>
<td>78±2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Nonprotein respiratory quotient</td>
<td>0.78±0.01</td>
<td>0.83±0.02</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Substrate oxidation rates, mg·kg⁻¹·FFM⁻¹·min⁻¹</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>1.28±0.18</td>
<td>1.80±0.19</td>
<td>NS</td>
</tr>
<tr>
<td>Lipid</td>
<td>1.29±0.07</td>
<td>0.94±0.10</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Protein</td>
<td>0.86±0.11</td>
<td>0.71±0.10</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are means ± SE. FFM, fat-free mass.

DISCUSSION

In the present study, REE was significantly higher in HIV-infected, HAART-treated patients with lipodystrophy than in HIV-infected, HAART-treated patients without lipodystrophy. The higher dietary energy intake in the HAART+LD+ group is consistent with the higher energy expenditure. Patients with HAL also had higher lipid oxidation rates in both relative and absolute terms than patients without lipodystrophy.

Since HIV-infection itself has been associated with higher REE (20, 24, 35) and HAART with a decrease in REE (42), we compared two groups of HIV-infected, HAART-treated patients, one group with and the other without lipodystrophy. This comparison makes it possible to differentiate between effects of lipodystrophy from those of HIV infection and HAART per se. However, although all patients in the current study were using HAART, their antiretroviral combinations were not identical. Therefore, the possibility cannot be fully excluded that the differences in patients’ antiretroviral regimens may have contributed to the differences in energy metabolism between the groups also by a direct drug-induced effect, which was not mediated by lipodystrophy. The use of different control groups, such as HIV-negative subjects or HIV-positive but untreated patients, may explain some of the discrepancies in the literature, such as a decreased REE in patients with HAL compared with HIV-infected but untreated.

Table 3. Dietary intake in patients with HAART+LD+ and HAART+LD–

<table>
<thead>
<tr>
<th></th>
<th>HAART+LD+</th>
<th>HAART+LD–</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total energy intake, kJ/day</td>
<td>9,580±360</td>
<td>7,790±630</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Fat intake, g/day</td>
<td>99±6</td>
<td>67±7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Carbohydrate intake, g/day</td>
<td>227±10</td>
<td>195±17</td>
<td>NS</td>
</tr>
<tr>
<td>Protein intake, g/day</td>
<td>93±5</td>
<td>66±5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>%Total energy intake from fat</td>
<td>39±1</td>
<td>32±2</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>%Total energy intake from carbohydrate</td>
<td>40±1</td>
<td>43±3</td>
<td>NS</td>
</tr>
<tr>
<td>%Total energy intake from protein</td>
<td>17±1</td>
<td>14±1</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are means ± SE.
patients (58). In this comparison, the observed difference may not exclusively reflect a decrease in REE in HAL but also an increase in REE in the control group due to untreated HIV infection (6, 24).

A few previous studies have examined effects of HAL on REE. However, none of the previous studies has compared significantly lipoatrophic HIV-1 patients with nonlipodystrophic HAART-treated patients, which may explain some of the differences in results. Our findings are in keeping with those by Kosmiski et al. (31), who found a higher REE expressed per FFM in protease inhibitor (PI)-treated patients with lipodystrophy compared with that in PI- and non-PI-treated nonlipodystrophic patients (31). These data contrast the results of three studies which found no difference in REE between lipodystrophic and weight-stable, nonlipodystrophic HIV-infected patients (1, 7, 43). In another study by Kosmiski et al. (32), total energy expenditure (TEE) consisting of REE, postprandial thermogenesis, and physical activity was higher in patients with HAL compared with HAART-treated patients without HAL and HIV-negative subjects. The increase in TEE could be attributed to an increase in REE (32).

Thyroid hormones and catecholamines increase REE (12, 17, 48). These hormones were not measured in the current study, but the patients had no signs or symptoms suggestive of excess production of either hormone, i.e., the patients were clinically euthyroid, and blood pressures and heart rates were comparable between the groups (Table 1). The available data do not suggest that hyperthyroidism would be a contributor to higher REE in HAL. In a cohort of 350 HIV-infected subjects, hypo- rather than hyperthyroidism was the most common form of thyroid dysfunction, and HAL was not associated with thyroid function abnormalities (8). In a study comparing patients with HAL to HAART-treated patients without lipodystrophy, thyroid hormone concentrations were normal and similar in both groups (43). However, the same study reported increased 24-h urinary catecholamine concentrations, which correlated with total resting metabolic rate in patients with HAL (43). A limitation of this study is that REE was not expressed per FFM. Another study has found increased plasma norepinephrine but not epinephrine concentrations in HAART-treated lipodystrophic patients compared with untreated HIV-infected patients (58). However, the same study reported a decrease in REE adjusted for lean body mass in patients with HAL independent of increased plasma norepinephrine concentration (58). The latter finding argues against a role for catecholamines in the etiology of increased REE in patients with HAL.

Increased circulating concentrations of proinflammatory cytokines TNF-α and IL-6 have been associated with hypermetabolism in AIDS patients with acute opportunistic infections (55). In the present study, serum IL-6 or TNF-α concentrations did not differ between the HAART+LD+ and HAART+LD− groups, and their concentrations did not correlate with REE. However, systemic concentrations of inflammatory cytokines may not reflect their action in target tissues. It therefore remains possible that increased local inflammation, as has been demonstrated in lipoatrophic adipose tissue (5, 26, 29, 34), may contribute to increased energy expenditure.

In vitro, nucleoside analog reverse transcriptase inhibitors are known to inhibit mitochondrial DNA polymerase γ (28), and this has been suggested to be the underlying mechanisms for HAL (9). Mitochondrial DNA is reduced in lipoatrophic adipose tissue in patients with HAL (47, 59) and in individual human adipocytes (40), which appears to impair mitochondrial function (22). It was recently shown that during standardized exercise, mitochondrial dysfunction indeed characterizes patients with HAL (10). In the latter study, a rapid increase in lactic acid concentration, an impairment in the activities of respiratory chain enzymes, and mitochondrial histoenzymatic abnormalities were observed during exercise in skeletal muscle in patients with HAL (10). Hypothetically, therefore, reduced efficacy of the respiratory chain to produce ATP may contribute to increased oxygen consumption in patients with HAL.

Another hypothetical mitochondrion-related cause for increased energy demand in HAL is an increase in the number of heat-producing brown fat cells. Uncoupling protein 1 (UCP-1) is exclusively expressed in brown adipocytes and is required for heat production. In rodents, interscapular and perirenal fat depots contain mainly brown adipocytes (23). In healthy adult humans, there are no specific brown fat depots, but occasional brown adipocytes can be detected within normal white adipose tissue (23). Interestingly, development of buffalo humps (19) and, more recently, increased perirenal fat mass (3) have been described as part of HAL syndrome. Increased UCP-1 gene expression has been demonstrated in HAL-associated buffalo humps compared with UCP-1 expression in subcutaneous adipose tissue from control subjects (44). In the current study, patients with HAL had significantly thicker subscapular skin folds than the HAART+LD− group. Therefore, an increased number of heat-producing brown adipocytes could contribute to the higher REE observed in patients with HAL. On the other hand, it can be hypothesized that patients with significant lipodystrophy loose more heat through radiation due to the lack of an insulating subcutaneous fat layer apart from the shoulder area.

Another possibility that could contribute to the higher REE in patients with HAL is futile triglyceride/fatty acid cycling. Rates of lipolysis have been found to be elevated in patients with HAL compared with HIV-negative subjects (46). The increased rate of lipolysis was associated with higher plasma concentrations of glycerol, palmitate, and total FFA (46). An increased rate of lipolysis has been demonstrated in HAL-associated buffalo humps compared with UCP-1 expression in subcutaneous adipose tissue from control subjects (44). In the current study, patients with HAL had significantly thicker subscapular skin folds than the HAART+LD− group. Therefore, an increased number of heat-producing brown adipocytes could contribute to the higher REE observed in patients with HAL. On the other hand, it can be hypothesized that patients with significant lipodystrophy loose more heat through radiation due to the lack of an insulating subcutaneous fat layer apart from the shoulder area.

In addition to higher REE, we also found a significantly reduced RQ in the patients with HAL, implying higher oxidation of lipids relative to that of carbohydrates. Lipid oxidation was also higher in absolute terms in the HAART+LD+ group. This finding is consistent with the data of Sekhar et al. (46), who reported increased whole body fatty acid oxidation in patients with HAL compared with healthy controls. On the other hand, Kosmiski et al. (31) did not observe a difference in RQ when comparing patients with HAL to those without HAL.

The cause for the increased lipid oxidation in the HAART+LD+ group cannot be determined in this cross-sectional study. High FFA concentrations may promote lipid oxidation via mass action. In the current study, the HAART+LD+ group tended to have higher FFA concentra-
tions than the HAART+LD− group, but the difference did not reach statistical significance. Several other studies have reported significantly increased FFA concentrations in patients with HAL (37, 46, 57). The significant positive correlation between fasting serum FFA concentration and lipid oxidation rate among patients with HAL is in keeping with this possibility (Fig. 2). In the current study, both absolute and relative dietary fat intake was increased in the HAART+LD+ group, which could contribute to the increased lipid oxidation rate (45, 49).

The HAART+LD+ group had significantly higher dietary energy intake than the HAART+LD− group. This is an expected finding in the view of the higher energy expenditure but stable body weight. Leptin is a known regulator of satiety and food intake in mice, but its role as a satiety factor in humans is controversial (2, 27). In the current study, serum leptin concentrations were somewhat decreased in the HAART+LD+ group compared with the HAART+LD− group, although the difference was not statistically significant. In non-HIV-lipodystrophic patients with severe hypoleptinemia, leptin treatment has decreased energy intake and REE (36, 41). However, the role of leptin in HAL is not clear: HAL has been associated with decreased (14), unchanged (11, 39), and even increased (30) leptin concentrations. Therefore, it seems unlikely that slightly decreased leptin concentration in the HAART+LD+ group would drive the observed hyperphagia in the current study. Increased ghrelin concentrations in patients with non-HIV lipidodystrophy have been suggested to contribute to increased energy intake (36). This is, again, an unlikely explanation for the higher food intake in the current study, since ghrelin concentrations have been decreased and not increased in patients with HAL (33). One simple possibility for the increased food and fat intake in patients with HAL is patients’ conscious or unconscious attempt to compensate for the fat atrophy.

In conclusion, REE was significantly higher in HIV-infected patients with HAART-associated lipodystrophy compared with HIV-infected HAART-treated patients who had not developed lipodystrophy, implying that lipodystrophy per se is associated with increased energy expenditure. Lipid oxidation is favored over carbohydrate oxidation in these patients. Both increased REE and lipid oxidation are linked with increased food and fat intake in patients with HAL.

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