Short-term overfeeding increases resting energy expenditure in patients with HIV lipodystrophy[1–3]

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ABSTRACT

Background: HIV lipodystrophy and other lipodystrophy syndromes are characterized by extensive loss of subcutaneous adipose tissue. Lipodystrophy syndromes are also associated with increased resting energy expenditure (REE). This hypermetabolism may be an adaptive response to an inability to store triacylglycerol fuel in a normal manner.

Objective: This study was done to determine whether REE increases significantly after short-term overfeeding in patients with HIV lipodystrophy.

Design: REE was measured in HIV-infected patients with lipodystrophy ($n = 9$) and in HIV-infected ($n = 10$) and healthy ($n = 9$) controls after 3 d on a eucaloric diet and again after 3 d on a diet of similar composition but increased in calories by 50%.

Results: After 3 d of eucaloric feeding, REE was significantly higher in patients with HIV lipodystrophy [33.2 ± 0.27 kcal/kg lean body mass (LBM)] than for both HIV-infected and healthy controls (29.9 ± 0.26 and 29.6 ± 0.27 kcal/kg LBM, respectively; $P < 0.01$). Furthermore, after 3 d of overfeeding, REE increased significantly in patients with HIV lipodystrophy but not in the control groups (33.2 ± 0.27 vs 34.7 ± 0.27 kcal/kg LBM; $P < 0.01$). Finally, postprandial thermogenesis did not differ among the groups after a "normal" test meal but tended to be higher in patients with HIV lipodystrophy than in healthy controls after a large test meal.

Conclusions: Adaptive thermogenesis in the resting component of total daily energy expenditure and in the postprandial period may be a feature of the HIV lipodystrophy syndrome and may be due to an inability to store triacylglycerol fuel in a normal manner. *Am J Clin Nutr* 2007;86:1009–15.

KEY WORDS HIV lipodystrophy, resting energy expenditure, overfeeding, metabolic rate, caloric intake, thermic effect of food

INTRODUCTION

Lipodystrophy syndromes are by definition characterized by loss of adipose tissue (1). HIV lipodystrophy, first reported in 1998, is an acquired lipodystrophy characterized by loss of subcutaneous adipose tissue in the face, trunk, extremities, and buttocks (2). It is also associated with insulin resistance, diabetes mellitus, and elevated triacylglycerol concentrations, the same metabolic disturbances present in congenital and other acquired forms of lipodystrophy (1).

Lipodystrophy syndromes share another feature, namely an increased resting metabolic rate (3–6). It also appears that both resting energy expenditure (REE) and the metabolic disturbances discussed above are greater the more extensive the fat loss. For example, REE 20–73% above normal was described in persons with congenital generalized lipodystrophy, which is characterized by almost complete absence of adipose tissue (3, 7). In familial forms of partial lipodystrophy, there are reduced amounts of adipose tissue in the extremities but normal to increased amounts of fat in the trunk and face. In this disorder, REEs 15–35% above normal were found (4, 8). In patients with HIV lipodystrophy, we have found REE, corrected for lean body mass (LBM), to be ≈17 higher than in HIV-infected controls and 25% higher than in healthy controls (6). Recently, other investigators have also found that REE per kilogram of fat-free mass is higher in patients with HIV lipodystrophy than in HIV-infected controls (9).

Importantly, we have previously shown that short-term caloric restriction (72 h) results in a significant fall in REE in patients with HIV lipodystrophy but not in HIV-infected or healthy controls (10). Normally, such short-term caloric restriction does not lead to significant reductions in REE because LBM, which accounts for ≈80–85% of the variation in REE, does not decrease significantly during this period of time (11, 12). Therefore, the reduction in REE in the patients with lipodystrophy on short-term caloric restriction suggests that their elevated metabolic rates may be a form of adaptive thermogenesis invoked to dissipate calories that cannot be stored in a normal manner. Significant reductions in REE in response to short-term caloric restriction were also described in persons with congenital generalized lipodystrophy (7, 13).

In the current study, we overfed a "mixed" diet to 3 groups of subjects. HIV-infected patients with lipodystrophy and HIV-infected and healthy controls were overfed for 72 h during which time they consumed 50% more calories than in the eucaloric

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[2] Supported by NIH (grants HL 59331 and HL 04226) and Public Health Services (research grant M01 RR00051) from the Division of Research Resources.

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Received February 20, 2007.

Accepted for publication June 14, 2007.

period. We hypothesized that a short-term increase in caloric intake would lead to a significant increase in REE in patients with HIV lipodystrophy but not in HIV-infected and healthy controls. We also hypothesized that postprandial thermogenesis (PPT) would increase more in subjects with lipodystrophy after a single large meal than in both HIV-infected and healthy controls.

SUBJECTS AND METHODS

Subjects

HIV-infected subjects were recruited from local HIV primary care practices. Healthy controls were recruited through advertisement. Subjects gave written informed consent under a protocol approved by the institutional review board at the University of Colorado at Denver and Health Sciences Center. HIV lipodystrophy remains a clinical diagnosis; therefore, HIV-infected subjects were classified as having lipodystrophy if the subject, the subject's primary care provider, and the primary investigator agreed that the subcutaneous fat of both the extremities and the face was significantly reduced. Specifically, lipoatrophy was judged to be present in the extremities if they were characterized by venous prominence and a pseudomuscular appearance. Lipoatrophy of the face was judged to be present if the cheeks had a sunken appearance and the nasolabial folds were prominent. Fat accumulation was not used as criteria for the diagnosis of HIV lipodystrophy. To be included in the HIV-infected control group, the subject, the primary care provider, and the primary investigator had to agree that the subject showed no signs of fat atrophy in any depot and that there had been no significant changes in body habitus since starting antiretroviral therapy.

All HIV-infected patients were on potent antiretroviral therapy (for details, see "Study design"). Subjects were excluded if they had HIV-1 RNA concentrations $>$ 1000 copies/mL, an active opportunistic infection or malignancy, hepatitis C, abnormal thyroid-stimulating hormone (TSH), or a history of congestive heart failure or pulmonary disease because all these conditions are associated with altered energy expenditure (EE). All subjects were studied on the General Clinical Research Center.

Body composition and body fat distribution

Body weight was measured on a calibrated scale with subjects wearing only a hospital gown. Total fat and lean mass were measured by dual-energy X-ray absorptiometry with the use of model Delphi W, version 11.2 (Hologic, Bedford, MA). Estimates were made of the amount of fat in the trunk and extremities. The trunk was defined as the region extending from an upper horizontal border at the lower edge of the chin, lateral borders by vertical lines that bisected the axilla oriented obliquely to include the waist, hip, buttock, and thigh tissue to a lower border formed by the intersection of oblique lines extending from the level of the superior aspect of the iliac crest and passing through the hip joint. The arm included the entire shoulder, arm, and forearm, and the leg included the entire hip, thigh, and lower leg.

Study design

Nine subjects with HIV lipodystrophy, 10 HIV-infected subjects without lipodystrophy, and 9 healthy control subjects took part in the study. Antiretroviral agents were recorded as nonnucleoside reverse transcriptase inhibitors (NNRTIs), nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs), or protease inhibitors (PIs). Among the 9 patients with HIV lipodystrophy, 5 were on NNRTIs plus NRTIs, and the other 4 were on NNRTIs plus PIs plus NRTIs. Among the 10 HIV-infected controls, 5 were on NNRTIs plus NRTIs, 3 were on PIs plus NRTI, and 2 were on PIs only.

Subjects were studied under 2 dietary conditions: 3 d of eucaloric feeding followed by 3 d of overfeeding. Caloric requirements for the eucaloric dietary period for each subject were based on measured REE, multiplied by an activity factor of 1.3 because subjects were in general sedentary and were also required to abstain from significant physical activity during the study. During the overfeeding period, subjects consumed 50% more calories than during the eucaloric period. Dietary composition during both periods was 55% carbohydrate, 30% fat, and 15% protein, and all food for the dietary conditions was provided by the General Clinical Research Center kitchen.

On the morning after the third day of both the eucaloric and overfeeding periods, respiratory gas exchange was measured by indirect calorimetry (Sensormedics 2900; Sensormedics, Yorba Linda, CA). At least 20 min of testing was done in the overnight (12 h) fasted state after subjects rested quietly for 30 min. The oxygen and carbon dioxide concentrations in the expired air were used to calculate whole-body EE (14). Criterion for a valid metabolic rate was a minimum of 15 min of steady state, defined as $<$10% fluctuation in minute ventilation and oxygen consumption and $<$5% fluctuation in respiratory quotient (RQ). Blood samples were taken after these REE measurements were completed.

In addition, PPT was measured after subjects consumed breakfast on the last day of the eucaloric feeding period and after breakfast on the first day of the overfeeding period. The latter breakfast was 50% larger than the former, and each breakfast represented $\approx$33% of food intake for that particular day. For the measurement of PPT, REE was measured after an overnight fast, then subjects consumed their breakfast meal within a 30-min period after which EE was measured for 15–20 min every hour during the next 5 h. PPT was calculated from the postmeal increment in metabolic rate, ie, the incremental area under the curve (postprandial metabolic rate $-$ REE) with the use of the trapezoidal rule.

Blood sample analysis

Blood samples for analysis of serum triacylglycerols, insulin, glucose, thyroid function tests, free fatty acids (FFAs), and adiponectin were collected in the fasting state at the end of the eucaloric and overfeeding periods. TSH was measured by a sandwich assay, and free thyroxine and total triiodothyronine were measured by competitive assays (Beckman, Irvine, CA). Triacylglycerol and FFA concentrations were measured by enzymatic assay. Glucose was measured by a glucose hexokinase assay, and insulin was measured by competitive radioimmunoassay (Pharmacia, Piscataway, NJ). Insulin sensitivity was estimated by the homeostasis model assessment (15). The formula for insulin resistance is [fasting insulin (μU/mL) $\times$ fasting glucose (mmol/L)/22.5]. Adiponectin was measured by radioimmunoassay (Linco Research, Inc, St Charles, MO), and the interassay and intraassay CVs were both $<$7%.

Statistical analysis

One-factor analysis of variance (ANOVA) was used to compare group characteristics. Two-factor repeated-measures

TABLE 1
Patient characteristics at screening[1]

	Patients with HIV LD ($n = 9$)	HIV-infected controls ($n = 10$)	Healthy controls ($n = 9$)
Age (y)	48.0 ± 5.1[2]	38.4 ± 9.3[3]	30.1 ± 9.5[4]
Sex (*n*)			
Male	6	9	8
Female	3	1	1
Ethnicity (*n*)			
African American	0	3	0
Hispanic	1	2	1
White	8	5	8
BMI (kg/m^2)	22.7 ± 3.7	24.0 ± 2.8	24.9 ± 2.3
CD4 cell count (× 10^6/L)	883 ± 281	530 ± 201[3]	Not done
HIV-1 RNA (copies/mL)	<50	<50	Not done
Antiretroviral regimen (*n*)			
NNRTI + NRTI	5	5	NA
NNRTI + NRTI + PI	4	0	NA
PI + NRTI	0	3	NA
PI only	0	2	NA
REE (kcal/d)	1683 ± 157	1649 ± 285	1672 ± 221
REE (kcal/kg LBM)	33.7 ± 3.2	29.5 ± 2.4[5]	29.0 ± 1.9[5]
RQ	0.81 ± 0.02	0.83 ± 0.06	0.81 ± 0.05

[1] LD, lipodystrophy; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside or nucleotide reverse transcriptase inhibitor; PI, protease inhibitor; REE, resting energy expenditure; LBM, lean body mass; RQ, respiratory quotient; NA, not applicable. There were no significant differences between the HIV-infected controls and the healthy controls.
[2] $\bar{x}$ ± SD (all such values).
[3–5] Significantly different from patients with HIV LD (one-factor ANOVA): [3] $P < 0.05$, [4] $P < 0.001$, [5] $P < 0.01$.

ANOVA was used to determine the effect of group and diet on both EE and metabolic indicators. Tukey's test was used for post hoc analysis of the repeated-measures ANOVA when the latter showed that the interaction between groups and diet were significant. All statistical analyses were performed with SIGMASTAT (version 2.03; SPSS, Chicago, IL).

RESULTS

Baseline characteristics

Subject characteristics and REE values at the baseline visit are shown in **Table 1**. Most subjects were men, and subjects with HIV lipodystrophy were significantly older than both the HIV-infected subjects without lipodystrophy and the healthy controls ($P < 0.05$ and $P < 0.001$, respectively). Body mass index (in kg/m^2) was not significantly different among the groups. Mean CD4 cell count was significantly higher in the patients with lipodystrophy than in the HIV-infected controls ($P < 0.05$), but HIV-1 RNA concentrations did not differ significantly between the 2 HIV-infected groups. Unadjusted REE did not differ among the groups at the baseline visit. However, REE expressed per kilogram of LBM was significantly greater in the patients with HIV lipodystrophy than in both the HIV-infected and healthy controls ($P < 0.01$). At baseline, RQ did not differ significantly among the groups.

Body composition

No significant differences were observed in the LBM measured by dual-energy X-ray absorptiometry, percentage of body fat, or total body fat mass among the 3 groups (**Table 2**). The patients with HIV lipodystrophy had a significantly greater percentage of total body fat in the trunk ($P < 0.001$) and a significantly lower percentage located in the extremities ($P <$

TABLE 2
Body composition[1]

	Patients HIV LD ($n = 9$)	HIV-infected controls ($n = 10$)	Healthy controls ($n = 9$)
Lean body mass (kg)	50.5 ± 8.4	57.3 ± 8.7	57.9 ± 9.6
Body fat (%)	17.7 ± 5.9	17.7 ± 6.9	22.8 ± 9.2
Total body fat (kg)	11.6 ± 4.9	13.1 ± 5.7	18.0 ± 7.4
Body fat in trunk (%)	68.4 ± 2.8	54.8 ± 11.9[2]	47.6 ± 4.3[2]
Body fat in extremities (%)	23.5 ± 4.1	37.5 ± 10.8[2]	46.3 ± 5.2[2,3]
Extremity body fat (kg)	2.8 ± 1.7	4.6 ± 2.5	8.5 ± 3.9[2,3]

[1] All values are $\bar{x}$ ± SD. LD, lipodystrophy.
[2] Significantly different from patients with HIV LD, $P \leq 0.001$ (one-factor ANOVA).
[3] Significantly different from HIV-infected controls $P < 0.05$ (one-factor ANOVA).

TABLE 3
Resting energy expenditure (REE) and respiratory quotient (RQ) after eucaloric and overfeeding periods by study group[1]

	Eucaloric period	Overfeeding period
REE (kcal/d)		
Patients with HIV LD ($n = 9$)	1658 ± 16.5	1729 ± 16.5[2]
HIV-infected controls ($n = 10$)	1733 ± 15.7	1744 ± 15.7
Healthy controls ($n = 9$)	1711 ± 16.5	1690 ± 16.5
REE (kcal/kg LBM)		
Patients with HIV LD	33.2 ± 0.27	34.7 ± 0.27[2]
HIV-infected controls	29.9 ± 0.26[3]	30.1 ± 0.26[4]
Healthy controls	29.6 ± 0.27[3]	29.3 ± 0.27[4]
RQ[5]		
Patients with HIV LD	0.83 ± 0.01	0.87 ± 0.01
HIV-infected controls	0.78 ± 0.01	0.80 ± 0.01
Healthy controls	0.80 ± 0.01	0.85 ± 0.01

[1] All values are $\bar{x}$ ± SEM. LD, lipodystrophy; LBM, lean body mass.
[2] Significant interaction between group and diet for REE (kcal/d) and for REE (kcal/ kg LBM), $P < 0.01$ (two-factor repeated-measures ANOVA).
[3] Significantly different from patients with HIV LD, $P < 0.01$ (one-factor ANOVA).
[4] Significantly different from patients with HIV LD, $P \leq 0.001$ (one-factor ANOVA).
[5] $P = 0.01$ for change in RQ across all groups on overfeeding.

TABLE 4
Postprandial thermogenesis (PPT) after a eucaloric meal and a single large mixed meal by study group[1]

	Eucaloric meal	Single large meal
Test meal energy (kcal)		
Patients with HIV LD ($n = 9$)	697 ± 21	1053 ± 35
HIV-infected controls ($n = 10$)	717 ± 40	1068 ± 62
Healthy controls ($n = 9$)	760 ± 39	1121 ± 61
Net PPT (kcal/5 h)		
Patients with HIV LD	56.7 ± 4.5	80.9 ± 4.4[2]
HIV-infected controls	56.2 ± 4.2	77.3 ± 4.2[2]
Healthy controls	59.4 ± 4.5	60.3 ± 4.5
Net PPT (kcal · kg LBM^{-1} · 5 h^{-1})		
Patients with HIV LD	1.2 ± 0.07	1.6 ± 0.07[2,3]
HIV-infected controls	0.9 ± 0.07	1.3 ± 0.07[2]
Healthy controls	1.0 ± 0.08	1.0 ± 0.08
PPT (% above REE)		
Patients with HIV LD	16.4 ± 1.3	23.3 ± 1.3[2]
HIV-infected controls	15.9 ± 1.2	21.0 ± 1.2[2]
Healthy controls	17.1 ± 1.3	17.2 ± 1.3

[1] All values are $\bar{x}$ ± SEM. LD, lipodystrophy; LBM, lean body mass; REE, resting energy expenditure.
[2] Significant diet-by-group interaction, $P < 0.01$ (two-factor repeated-measures ANOVA).
[3] Significantly different from healthy controls, $P < 0.05$ (one-factor ANOVA).

0.001) than did both HIV-infected and healthy controls. HIV-infected subjects without lipodystrophy also had a significantly smaller percentage of fat in the extremities than did the healthy controls ($P < 0.05$). Finally, the total fat mass of the upper and lower extremities together was significantly lower in the lipodystrophy group than in the healthy control group ($P < 0.001$) but not compared with the HIV-infected control group. HIV-infected controls without clinical evidence of lipodystrophy also had significantly less extremity fat than did the healthy controls ($P < 0.05$).

Effect of diet on REE and RQ

Unadjusted REE did not differ significantly among the groups after 3 d of eucaloric feeding or after 3 d of overfeeding (**Table 3**). In contrast, REE per kilogram of LBM was significantly greater in the HIV lipodystrophy group than in both the HIV-infected and the healthy control groups on both the eucaloric diet ($P < 0.01$) and after 3 d of overfeeding ($P < 0.001$). A significant interaction was observed between group and diet for REE: after 3 d of overfeeding, both unadjusted REE and REE per kilogram of LBM increased significantly in the HIV lipodystrophy group ($P < 0.01$) but did not change significantly in the control groups.

RQ was not significantly different among groups after each feeding period, and 3 d of overfeeding resulted in a significant increase in RQ across all groups ($P = 0.01$). The amount of weight gained from the end of the eucaloric period to the end of the overfeeding period did not differ significantly among the groups with a mean weight gain of 1.0 ± 0.8 kg in the HIV lipodystrophy group and a mean weight gain of 0.8 ± 1.2 and 0.3 ± 0.6 kg in the HIV-infected and healthy control groups, respectively.

Postprandial thermogenesis

Data on PPT are presented in **Table 4**. The amount of energy consumed during the 2 test meals did not differ significantly among the groups. No significant difference was observed among groups in PPT after the normal breakfast meal, no matter how the data were expressed. After the single large meal, incorporating 50% excess calories, patients with HIV lipodystrophy expended more calories in the postprandial period than did healthy controls when PPT was expressed as kcal·kg LBM^{-1}·5 h^{-1} ($P < 0.05$). In addition, when expressed as absolute kcal/5 h or as a percentage increase above REE, subjects with HIV lipodystrophy tended to have higher PPT than did healthy controls. ($P = 0.10$ and $P = 0.08$, respectively). No difference was observed in PPT in the HIV lipodystrophy group compared with the HIV-infected control group.

A significant interaction was observed between group and diet for PPT: both the subjects with HIV lipodystrophy and the HIV-infected controls had a significant increase in PPT expressed as absolute increase in energy after the large meal compared with the normal meal ($P < 0.01$), but this was not the case for the healthy controls. Likewise, when PPT was expressed as kcal·kg LBM^{-1}·5 h^{-1} or as the percentage rise above REE, patients with HIV lipodystrophy and HIV-infected controls experienced a significant increase in PPT after consumption of the larger meal ($P < 0.01$) compared with the normal meal.

Metabolic indicators

Metabolic indicators after 3 d of eucaloric feeding and after 3 d of overfeeding are shown in **Table 5**. No significant interaction was observed between group and diet for any of the metabolic indicators listed in the table, except for FFAs that were significantly lower after the overfeeding period than after the eucaloric period in both the patients with HIV lipodystrophy and the healthy controls ($P < 0.05$). Glucose, insulin, and triacylglycerol concentrations did not change significantly with overfeeding in any group. On the eucaloric diet, fasting FFA concentrations

TABLE 5
Metabolic indicators after eucaloric and overfeeding periods by study group[1]

	Eucaloric period	Overfeeding period
Glucose (mg/dL)		
Patients with HIV LD ($n = 9$)	100 ± 3.0	94 ± 3.0
HIV-infected controls ($n = 10$)	95 ± 2.0	92 ± 2.0
Healthy controls ($n = 9$)	89 ± 3.0	87 ± 3.0
Insulin (μU/mL)		
Patients with HIV LD[2]	14.0 ± 1.8	19.8 ± 1.8
HIV-infected controls	12.5 ± 1.8	10.9 ± 1.8
Healthy controls	6.7 ± 1.9	7.7 ± 1.9
HOMA		
Patients with HIV LD[2]	3.4 ± 0.5	4.5 ± 0.5
HIV-infected controls	3.1 ± 0.5	2.5 ± 0.5
Healthy controls	1.5 ± 0.5	1.4 ± 0.5
Triacylglycerol (mg/dL)		
Patients with HIV LD[2]	266 ± 10	286 ± 10
HIV-infected controls[3]	215 ± 9	232 ± 9
Healthy controls	90 ± 10	83 ± 10
FFA (meq/L)		
Patients with HIV LD	517 ± 40	398 ± 40[4]
HIV-infected controls	306 ± 43[5]	376 ± 43
Healthy controls	439 ± 38	312 ± 38[4]
Adiponectin (μg/mL)		
Patients with HIV LD[6]	3.3 ± 0.5	3.0 ± 0.4
HIV-infected controls	8.0 ± 1.2	7.8 ± 0.9
Healthy controls	7.9 ± 1.1	7.4 ± 0.8

[1] All values are $\bar{x}$ ± SEM. LD, lipodystrophy; HOMA, homeostasis model assessment; FFA, free fatty acid.
[2,3] Significantly different from healthy controls independent of diet (one-factor ANOVA): [2] $P < 0.01$, [3] $P < 0.05$.
[4] Significant diet-by-group interaction, $P < 0.05$ (two-factor repeated-measures ANOVA).
[5] Significantly different from patients with HIV LD, $P = 0.01$ (one-factor ANOVA).
[6] Significantly different from both control groups independent of diet, $P < 0.01$ (one-factor ANOVA).

were significantly higher in patients with HIV lipodystrophy than in HIV-infected controls ($P = 0.01$) but not compared with healthy controls. FFA concentrations did not differ significantly among the groups on the overfeeding diet.

As a group, patients with lipodystrophy were significantly more insulin resistant as judged by fasting insulin concentrations and homeostasis model assessment than were healthy controls ($P \leq 0.01$), and they tended to be more insulin resistant than were the HIV-infected controls ($P = 0.10$ and $P = 0.08$, respectively). Independent of diet, adiponectin concentrations were significantly lower in the patients with HIV lipodystrophy than in both control groups ($P < 0.01$), and no change in adiponectin after overfeeding was observed in any group.

Independent of diet, triacylglycerol concentrations were significantly higher in the patients with HIV lipodystrophy than in the healthy controls ($P < 0.01$) but not in the HIV-infected subjects without lipodystrophy. HIV-infected subjects without lipodystrophy also had significantly higher triacylglycerol concentrations than did the healthy controls ($P < 0.05$). Finally, TSH, total triiodothyronine, and free thyroxine did not differ among the groups or change significantly in any group on overfeeding (data not shown).

DISCUSSION

In summary, we found that short-term overfeeding of a mixed diet was associated with a significant rise in REE in patients with HIV lipodystrophy but not in HIV-infected or healthy controls. This is especially impressive, given that the lipodystrophy group already had significantly higher REE before overfeeding. Nevertheless, in patients with lipodystrophy, increased caloric intake was associated with even greater REE. In addition, PPT after consumption of a single large meal tended to be greater in patients with HIV lipodystrophy than in healthy controls.

Body composition analysis and metabolic indicators again confirmed our clinical categorization of HIV-infected subjects into groups with and without lipodystrophy, with the subjects with lipodystrophy having a significantly greater percentage of fat in the trunk and a significantly smaller percentage of fat in the extremities than did both control groups. HIV-infected controls without clinical evidence of lipodystrophy also differed significantly from healthy controls in some indexes of body fat distribution. These results again suggest that there is a continuum of body fat changes in the HIV-infected population on antiretroviral therapy as opposed to a condition that is either present or absent (16, 17).

In previous work, we showed that short-term caloric restriction (72 h) leads to a significant fall in REE in patients with HIV lipodystrophy but not in HIV-infected or healthy controls (10). In the general population, such short-term changes in caloric intake and even short-term fasting do not lead to reductions in REE in either lean or obese subjects because LBM does not decrease significantly during this period of time.

Both this study and another recent study have found that short-term overfeeding leads to a significant increase in REE in subjects with lipodystrophy. In the latter study, subjects with congenital forms of lipodystrophy and healthy controls were studied during two 40-h dietary periods in a whole-room calorimeter (18). Each received an energy-balanced diet followed by a diet incorporating 30% excess energy as fat. Unlike the healthy controls, lipodystrophic subjects responded to this short-term overfeeding with significant increases in REE and total EE. The increased EE in the lipodystrophy group was accompanied by a 29% increase in fat oxidation. In the current study, subjects were overfed a mixed diet rather than a high-fat diet. Nevertheless, the increased fat intake that accompanied this diet may have been responsible for the rise in REE observed in the subjects with lipodystrophy. In future studies, we plan to compare the effects of high-carbohydrate with high-fat overfeeding on energetic indicators and macronutrient oxidation rates in patients with HIV lipodystrophy.

Persons with lipodystrophy accumulate triacylglycerol in nonadipose tissues, such as skeletal muscle and the liver (19–23). This ectopic fat accumulation is most severe in persons with generalized lipodystrophy. Patients with this form of lipodystrophy can develop fatty livers so massive that the livers extend into the pelvis, something not seen in even the most obese of patients. This nonadipose tissue steatosis has important consequences, including severe insulin resistance. Persons with generalized lipodystrophy develop diabetes mellitus in their teenage years and can require thousands of units of insulin per day (24). Transgenic mouse models of generalized lipodystrophy are also characterized by severe triacylglycerol accumulation in skeletal muscle and liver and by severe insulin resistance with diabetes (25,

26). Interestingly, these mouse models also display increased EE.

Lipodystrophy is associated with 2 abnormalities that lead to ectopic fat accumulation, namely loss of a significant portion of the adipose organ and low concentrations of adipocytokines that normally act to limit ectopic fat accumulation. In lipodystrophy syndromes, leptin and adiponectin concentrations are typically low (27–29). Obese mice and humans, however, also have nonadipose steatosis, but this appears to be relatively limited by both a large capacity to store triacylglycerol in the adipose organ and high leptin concentrations. With defects in both lipid storage and adipocytokine protection from nonadipose steatosis, patients with lipodystrophy may invoke a higher REE to dissipate fuel that cannot be stored in a normal manner. This idea is supported by this study and others that show short-term changes in caloric intake are accompanied by significant changes in REE in lipodystrophy syndromes. This energetic adaptation to short-term changes in caloric intake is, to our knowledge, unique to lipodystrophy.

To our knowledge, this is the first study to measure PPT in a lipodystrophy syndrome. On a eucaloric mixed diet, PPT did not differ among the groups. With overfeeding of a single large meal, both subjects with HIV lipodystrophy and HIV-infected controls had a significant increase in PPT. This is the expected finding because multiple studies have shown that the magnitude of PPT is related to the energy load of the test meal (30). However, we cannot explain why the healthy controls did not have a significant increase in PPT after consuming the larger meal.

After the single large meal, patients with HIV lipodystrophy tended to expend more energy in the postprandial period than did the healthy controls despite similar caloric intake. This suggests that there could also be adaptive thermogenesis in this component of total daily EE. This issue is complex because it is difficult to compare PPT in groups that differ significantly in baseline REE.

There are limitations to this study. Subjects with lipodystrophy were significantly older than controls. However, increasing age is associated with a decline in REE. This is mostly due to the decline in LBM that occurs with aging, and only in advanced age is there a reduction in REE when adjusted for LBM (31). Therefore, the age differences in our study would tend to bias against our findings of increased REE in the lipodystrophy group. The effect of aging on PPT is less clear, with some studies showing that PPT correlates negatively with age in male subjects (32), whereas others report that age does not affect absolute PPT but may be associated with a delay to peak postmeal thermogenesis (33).

In conclusion, it appears that subjects with lipodystrophy uniquely respond to short-term caloric excess with significant increases in REE. Lipodystrophy may also be associated with a more robust thermogenic response to caloric intake in the postprandial period. The apparent flexibility of REE in lipodystrophy syndromes may ultimately represent a defense mechanism to protect nonadipose tissues from further lipid accumulation. The mechanisms responsible for both the increased resting metabolic rate and its responsiveness to short-term changes in caloric intake in lipodystrophy syndromes should be the subject of further study.

The author's responsibilities were as follows—LAK, TJH, and DHB: study design, data analysis, and writing of the manuscript; SAS: data collection; JRK: played a major role in subject recruitment and in determining eligibility of participants. None of the authors had a conflict of interest.

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