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Short-term energy restriction reduces resting energy expenditure in patients with HIV lipodystrophy and hypermetabolism

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Abstract

We have previously shown that resting energy expenditure (REE) is increased in patients with HIV lipodystrophy. This hypermetabolism could be the result of an inadequate storage capacity for lipid fuel secondary to atrophy of the subcutaneous adipose tissue depot. Therefore, energy restriction may be able to alleviate this hypermetabolism. To test this hypothesis, we measured REE in HIV-infected patients with lipodystrophy and hypermetabolism and in HIV-infected and healthy controls. Measurements were taken during the overnight fasted state after 3 days on a eu-energetic diet and again after 3 days on a diet of similar composition but reduced in energy by 50%. After 3 days of eu-energetic feeding, REE was significantly higher in HIV-infected patients with lipodystrophy compared with healthy controls (139.5 ± 1.3 vs 117.2 ± 1.3 kJ/kg lean body mass, $P < .001$) and tended to be higher compared with HIV-infected subjects without lipodystrophy (139.5 ± 13 vs 127.3 ± 1.4 kJ/kg lean body mass, $P = .06$). Furthermore, energy restriction caused a significant decline in REE in patients with HIV lipodystrophy ($P < .001$). This dietary manipulation did not lead to a significant reduction in REE in either HIV-infected or healthy controls. This suggests that energy intake and REE may be uniquely coupled in patients with lipodystrophy as a means to dissipate energy that cannot be stored in a normal manner. A better understanding of this coupling would have important implications for weight regulation in general.

1. Introduction

The body fat changes and metabolic disturbances occurring in HIV-infected patients receiving potent antiretroviral therapy are typically referred to as the "HIV lipodystrophy syndrome [1]." Lipodystrophies are characterized by loss of body fat, and patients with HIV lipodystrophy experience wasting of subcutaneous fat in the face, extremities, and abdomen [2]. In contrast, the visceral fat depot is preserved or may increase in size. Metabolic disturbances, including insulin resistance and dyslipidemia, often accompany these body fat changes [1,2]. Both fat atrophy and the relative or absolute increase in visceral fat may play a causal role in these metabolic disturbances [3], but in treated patients, they can occur in the absence of clinically apparent body fat changes [4,5].

In previous work, we found that patients with HIV lipodystrophy had significantly greater resting energy expenditure (REE) and total daily energy expenditure (TEE) expressed per kilogram of lean body mass (LBM) compared with both HIV-infected and healthy controls [3,6]. This suggests that hypermetabolism may be another feature of the HIV lipodystrophy syndrome. Indeed, hypermetabolism has been described in other lipodystrophy syndromes. Increases in REE have been found to be especially marked in generalized lipodystrophy [7-9], which is characterized by an almost complete absence of body fat, and an elevated metabolic rate is held to be one of the characteristic features of this disease [9]. A variety of partial lipodystrophies have also been associated with less extreme elevations in REE [10-12]. Finally, there is evidence of increased basal metabolic rates in transgenic mouse models of generalized lipodystrophy [13,14].

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Hypermetabolism, therefore, appears to be a consistent feature of lipodystrophy syndromes. Furthermore, REE appears to be highest in those forms of lipodystrophy with the most extensive fat loss. This increase in REE may be a chronic and adaptive response to an inability to store triglyceride fuel in a normal manner. We therefore hypothesized that reducing energy expenditure in patients with HIV lipodystrophy and hypermetabolism would result in a significantly greater fall in REE in these patients compared with both HIV-infected subjects without lipodystrophy and healthy controls. To test this hypothesis, we measured REE in these groups after both short-term eu-energetic and hypo-energetic feeding periods.

2. Subjects and methods

2.1. 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, and, 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 face were wasted. Specifically, lipoatrophy was judged to be present in the extremities if these 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. Lipodystrophic subjects were also required to have a measured REE greater than 112% of that predicted by the Harris-Benedict [15] equation.

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 have been no significant changes in body habitus since starting antiretroviral therapy. These subjects, as well as healthy controls, also had to have an REE no greater than 102% of that predicted by the Harris-Benedict equation. These energy expenditure criteria were based on our previous work [3,6] and on a review of data collected from healthy volunteers using the same metabolic cart system. Of 17 patients with HIV lipodystrophy who were screened for the study, 15 qualified based on the REE criteria. One subject dropped out after 1 day of the eu-energetic diet because he felt this level of food intake was far below his daily needs. Three others did not enter the dietary phases because of scheduling difficulties. Ten HIV-infected patients without lipodystrophy were screened for the study, and all qualified. One subject in this group did not complete the dietary studies because of scheduling difficulties. Finally, 10 healthy control subjects were screened and qualified for the study, and completed all testing.

All HIV-infected patients were on potent antiretroviral therapy, and regimens did not differ significantly between the groups with and without lipodystrophy. Subjects were excluded if they had HIV-1 RNA levels greater than 1000 copies per milliliter, an active opportunistic infection or malignancy, hepatitis C, abnormal thyrotropin, or a history of congestive heart failure or pulmonary disease because all these conditions have been associated with altered energy expenditure. All subjects were studied at the General Clinical Research Center (GCRC) at the University of Colorado at Denver Health Sciences Center.

2.2. Body composition and body fat distribution

Body weight was measured on a calibrated scale. Each subject wore only a hospital gown. Total fat and lean mass were measured by dual-energy x-ray absorptiometry using model Delphi W, version 11.2 (Hologic, Bedford, MA). Estimates of the amount of fat in the trunk and extremities were made. The trunk was defined as the region extending from an upper horizontal border at the lower edge of the chin, lateral borders that were delineated by vertical lines bisecting 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, whereas the leg included the entire hip, thigh, and lower leg.

2.3. Study design

Eleven subjects with HIV lipodystrophy, 10 HIV-infected subjects without lipodystrophy, and 9 healthy controls took part in the study. Subjects were studied under 2 dietary conditions: 3 days of eu-energetic feeding followed by 3 days of hypo-energetic feeding. Energy requirements for the eu-energetic dietary period for each subject were based on measured REE multiplied by an activity factor, which was typically 1.3, as subjects were requested to abstain from significant physical activity during the study. During the hypo-energetic period, subjects consumed half the energy they did during the eu-energetic period. Dietary composition during both periods was 55% carbohydrate, 30% fat, and 15% protein. All food for the dietary conditions was provided by the GCRC kitchen.

On the morning after the third day of both eu-energetic and hypo-energetic feeding, respiratory gas exchange was measured by indirect calorimetry (Sensormedics 2900, Yorba Linda, CA). At least 20 minutes of testing was done in the overnight (12 hours) fasted state after subjects rested quietly for 30 minutes. The oxygen and carbon dioxide concentrations in the expired air were used to calculate whole-body energy expenditure [16]. 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

Table 1
Subject characteristics

	HIV-LD (11)	HIV-C (10)	Healthy controls (9)
Age (y)	50.7 ± 1.2	36.1 ± 2.3*	37.9 ± 3.2†
Male/female	9/2	7/2	7/3
BMI (kg/m^2)	22.4 ± 0.9	22.9 ± 0.6	24.4 ± 0.8
CD4 cell count (×10^6/L)	586 ± 84	486 ± 76	Not done
HIV-1 RNA levels	<20 (<20, 230)	<20	Not done
REE (kJ/d)	7264 ± 222	6858 ± 301	6510 ± 394
Percentage predicted REE	119 ± 2.4	98 ± 1.3*	92 ± 2.9†

Data are means ± SEM expect for HIV-1 RNA levels, which are median values with the 25th and 75th percentiles in parentheses. HIV-LV indicates HIV-infected patients with lipodystrophy; HIV-C, HIV-infected controls.

* $P < .001$, HIV-infected patients with lipodystrophy vs HIV-infected controls.

† $P \leq .001$, HIV-infected patients with lipodystrophy vs HIV-infected controls.

respiratory quotient (RQ). Blood samples were taken after the REE measurements were completed.

2.4. Blood sample analysis

All blood samples for analysis of serum triglycerides, insulin, glucose, thyroid function tests, adiponectin, leptin, and free fatty acids were collected in the fasting state at the end of the eu-energetic and hypo-energetic phases. Triglyceride concentrations were measured by enzymatic assay. Glucose was measured by a glucose hexokinase assay, and insulin by competitive radioimmunoassay (Diagnostic System Laboratories, Webster, TX). Leptin and adiponectin concentrations were measured by enzyme-linked immunosorbent assay and radioimmunoassay, respectively. For leptin, the inter- and intra-assay coefficients of variation were less than 6.2% and less than 7%, respectively, and for adiponectin, both were less than 7%. Insulin sensitivity was estimated by the homeostasis model assessment (HOMA) [17]. The formula for insulin resistance is as follows: fasting insulin (uU/mL) × fasting glucose (mmol/L)/22.5.

2.5. Statistical analyses

One-way analysis of variance (ANOVA) was used to compare group characteristics. If data were not normally distributed, Kruskal-Wallis 1-way ANOVA on ranks was used for comparisons. Two-way repeated-measures ANOVA was used to determine the effect of group and diet on both energy expenditure and metabolic parameters. The Tukey test was used for post hoc analysis of the repeated-measures ANOVA when the latter showed that the interaction between groups and diet was significant. All statistical analyses were performed with SigmaStat (Version 2.03, SPSS, Chicago, IL) statistical software.

3. Results

3.1. Baseline characteristics

Table 1 shows subject characteristics and REE values at the screening visit. Most subjects were male, and subjects with HIV lipodystrophy were significantly older compared with both HIV-infected subjects without lipodystrophy and healthy controls ($P \leq .001$). Body mass index was similar among the groups, and mean CD4 cell counts and median HIV-1 RNA levels did not differ significantly between the HIV-infected groups. Unadjusted REE did not differ among the groups at the time of screening. At this time, REE expressed per kilogram of LBM was significantly greater in the lipodystrophy group compared with healthy controls ($P < .05$). In the HIV lipodystrophy group, the percentage of predicted REE was significantly greater compared with both HIV-infected subjects without lipodystrophy and healthy controls ($P < .001$), whereas the percentage of predicted REE did not differ significantly between the control groups.

Table 2
Body composition

	HIV-LD (11)	HIV-C (10)	Healthy controls (9)
LBM (kg)	51.3 ± 1.9	52.5 ± 2.9	54.2 ± 4.2
% Body fat	15.9 ± 1.7	20.7 ± 2.4	23.1 ± 1.9*
Total body fat (kg)	8.8 (8.0, 11.4)	13.9 (11.5, 17.4)	15.4 (13.9, 19.5)*
% Body fat in trunk	69.4 ± 1.4	54.1 ± 2.7††	44.4 ± 2.5**,‡
% Body fat in extremities	21.2 ± 1.4	38.8 ± 2.6††	50.0 ± 2.3**,‡
Extremity body fat (kg)	1.7 (1.4, 2.5)	4.8 (4.0, 6.9)†	7.2 (6.4, 8.4)*

Data are means ± SEM except for total body fat and extremity fat mass, which are median values with the 25th and 75th percentiles in parentheses.

* $P < .05$, HIV-infected subjects with lipodystrophy vs healthy controls.

** $P < .001$, HIV-infected subjects with lipodystrophy vs healthy controls.

† $P < .05$, HIV-infected subjects with lipodystrophy vs HIV-infected controls.

†† $P < .001$, HIV-infected subjects with lipodystrophy vs HIV-infected controls.

‡ $P \leq .01$, HIV-infected controls vs healthy controls.

Table 3
Energy expenditure and RQ after eu-energetic and hypo-energetic feeding

Group	Eu-energetic	Hypo-energetic
REE (kJ/d)		
LD	7113 ± 66	6594 ± 66*
HIV-C	6682 ± 73	6619 ± 73
C	6276 ± 69	6494 ± 69
REE (kJ/kg LBM)		
LD	139.4 ± 1.31	128.9 ± 1.3*
HIV-C	127.3 ± 1.4	126.4 ± 1.4
C	117.2 ± 1.3†	121.4 ± 1.3
RQ‡		
LD	0.79 ± 0.01	0.73 ± 0.01
HIV-C	0.73 ± 0.01	0.71 ± 0.01
C	0.76 ± 0.03	0.70 ± 0.03

Data are expressed as means ± SEM. LD indicates lipodystrophy; C, control.

* $P < .001$, change within the HIV-infected subjects with lipodystrophy upon hypo-energetic feeding.

† $P < .001$, HIV-infected subjects with lipodystrophy vs healthy controls on eu-energetic diet.

‡ $P = .025$, change in RQ across all groups.

3.2. Body composition

There was no significant difference in dual-energy x-ray absorptiometry–determined LBM among the 3 groups (Table 2). The percentage of body fat, however, was significantly lower in HIV-infected patients with lipodystrophy compared with healthy controls ($P = .04$), but not compared with HIV-infected subjects without lipodystrophy. Similarly, total body fat mass was significantly lower in the lipodystrophy group compared with healthy controls ($P < .05$), but not compared with HIV-infected subjects without lipodystrophy. The percentage of total body fat located in the trunk was significantly greater in patients with lipodystrophy ($P < .001$), whereas the percentage located in the extremities was significantly lower compared with both HIV-infected and healthy controls ($P < .001$). HIV-infected subjects without lipodystrophy also had a significantly greater percentage of fat in the trunk ($P = .015$) and a significantly less percentage in the extremities ($P = .003$) compared with the healthy controls. Finally, the total fat mass of the upper and lower extremities combined was significantly lower in the lipodystrophy group compared with both control groups ($P < .05$).

3.3. Resting energy expenditure and RQ

Unadjusted REE did not differ significantly among the groups after 3 days of eu-energetic or hypo-energetic feeding (Table 3). In contrast, REE per kilogram of LBM was significantly greater in the lipodystrophy group compared with healthy controls on the eu-energetic diet ($P < .001$) and tended to be higher compared with HIV-infected subjects without lipodystrophy ($P = .06$). After 3 days of energy restriction, unadjusted REE fell significantly only in the lipodystrophy group ($P < .001$). Likewise, REE per kilogram of LBM fell significantly with energy restriction only in this group ($P < .001$). Resting energy expenditure was also measured in patients with lipodystrophy 24 hours after energy restriction (data not shown). After 24 hours of energy restriction, REE had already fallen significantly from a mean of 139.4 ± 4.2 to 130.6 ± 1.7 kJ/kg LBM ($P = .03$). Respiratory quotient was not significantly different among groups after each feeding period, and hypo-energetic feeding resulted in a significant decrease in RQ across all groups ($P = .025$). The 2 control groups did not differ significantly in any energetic parameter. Importantly, the amount of weight lost from the end of the eu-energetic period to the end of the hypo-energetic period did not differ significantly between the groups with a mean weight loss of 1.5 ± 0.2 kg in the lipodystrophy group and 1.1 ± 0.2 and 1.2 ± 0.1 kg in the HIV-infected and healthy controls, respectively.

3.4. Metabolic parameters

Metabolic parameters after the 2 dietary periods are shown in Table 4. Independent of diet, fasting glucose concentrations were significantly higher in the lipodystrophy group compared with both HIV-infected subjects without lipodystrophy ($P = .009$) and healthy controls ($P = .05$).

After the eu-energetic diet, fasting insulin was significantly higher in the subjects with lipodystrophy compared with both control groups ($P < .001$). After energy

Table 4
Metabolic parameters after eu-energetic and hypo-energetic feeding

	Group	Eu-energetic	Hypo-energetic
Fasting glucose (mmol/L)	LD	5.0 ± 0.1*	4.7 ± 0.1*
	HIV-C	4.6 ± 0.1	4.3 ± 0.1
	C	4.6 ± 0.1	4.5 ± 0.1
Fasting insulin (μU/mL)	LD	17.20 ± 0.87***‡	10.1 ± 0.87†,§
	HIV-C	5.1 ± 1.0	4.8 ± 1.0
	C	5.9 ± 0.96	4.4 ± 0.96
HOMA-IR	LD	3.8 ± 0.20***‡	2.1 ± 0.20†,§
	HIV-C	1.0 ± 0.24	0.95 ± 0.24
	C	1.2 ± 0.21	0.90 ± 0.21
Triglycerides (mmol/L)	LD	2.85 ± 0.09**	2.49 ± 0.09**
	HIV-C	1.73 ± 0.11	148.1 ± 0.11
	C	0.91 ± 0.10	0.64 ± 0.10
Free fatty acids (mmol/L)	LD	422 ± 45	507 ± 45
	HIV-C	433 ± 52	561 ± 52
	C	372 ± 49	454 ± 49
Adiponectin (μg/dL)	LD	3.3 ± 0.43*	2.7 ± 0.43*
	HIV-C	7.1 ± 0.50	6.5 ± 0.50
	C	8.4 ± 0.47	8.9 ± 0.47

Data are means ± SEM. HOMA-IR indicates homeostasis model assessment of insulin resistance.

* $P \leq .05$, HIV-infected subjects with lipodystrophy vs both control groups.

** $P < .01$, HIV-infected subjects with lipodystrophy vs healthy controls.

*** $P < .001$, HIV-infected subjects with lipodystrophy vs HIV-infected controls.

† $P < .001$, change within the HIV-infected subjects with lipodystrophy upon hypocaloric feeding.

‡ $P < .001$, HIV-infected subjects with lipodystrophy vs healthy controls.

§ $P < .05$, HIV-infected subjects with lipodystrophy vs healthy controls on hypo-energetic diet.

restriction, fasting insulin remained significantly higher in the lipodystrophy group compared with the healthy controls ($P < .05$) and tended to be higher compared with the HIV-infected subjects without lipodystrophy ($P = .08$). Energy restriction resulted in a significant fall in fasting insulin concentrations only in the lipodystrophy group ($P < .001$). Patients with lipodystrophy were significantly more insulin resistant, as estimated by HOMA, after eu-energetic feeding compared with both control groups ($P < .001$). After the hypo-energetic feeding period, the patients with lipodystrophy remained significantly more insulin resistant than healthy controls ($P = .04$) and tended to be more insulin resistant compared with the HIV-infected subjects without lipodystrophy ($P = .07$). Finally, 3 days of energy restriction significantly improved insulin sensitivity in patients with HIV lipodystrophy ($P < .001$), but diet had no effect on insulin sensitivity in either control group.

Independent of diet, triglyceride concentrations were significantly higher in the lipodystrophy group compared with healthy controls ($P = .006$), but not compared with the HIV-infected subjects without lipodystrophy. Free fatty acid concentrations did not differ significantly among the groups at any time. Independent of diet, adiponectin was significantly lower in the lipodystrophy group compared with both HIV-infected subjects without lipodystrophy ($P = .02$) and healthy controls ($P < .001$). In contrast, leptin concentrations did not differ significantly between the groups, but energy restriction was associated with a significant fall in leptin concentrations across all groups ($P < .001$) (data not shown). Finally, thyrotropin, total triiodothyronine, and free thyroxine levels did not differ between groups or change significantly in any group upon energy restriction (data not shown).

4. Discussion

Our results again suggest that REE is increased in many if not most patients with HIV lipodystrophy, which is characterized by an extensive loss of subcutaneous fat. In subjects with HIV lipodystrophy and hypermetabolism, short-term energy restriction caused a rapid and significant fall in REE, whereas the same dietary manipulation was not associated with a significant fall in REE in either HIV-infected or healthy controls. Energy restriction, therefore, tends to normalize the elevated resting metabolic rate of patients with HIV lipodystrophy.

Both body composition analysis and metabolic parameters confirmed our clinical categorization of HIV-infected subjects into groups with and without lipodystrophy. Importantly, HIV-infected controls *without* clinical evidence of lipodystrophy differed significantly from healthy controls in terms 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 [18]. Similar findings were recently published in the study of Fat Redistribution and Metabolic Change in HIV Infection [19].

Significant increases in REE have been found in other, but not all, studies of patients with HIV lipodystrophy [3,20,21]. In one study, mean REE in 6 men with HIV lipodystrophy was 128 kJ/kg LBM compared with 106 kJ/kg LBM in healthy controls [20]. In previous work, we found that mean REE was 154 kJ/kg LBM in HIV-infected patients with lipodystrophy vs 132 and 123 kJ/kg LBM in HIV-infected and healthy controls, respectively [3]. Most subjects in these studies had undetectable HIV-1 RNA levels.

Hypermetabolism has been described in other lipodystrophy syndromes. In generalized lipodystrophy, 25% to 100% increases in REE have been described [7-9]. In familial partial lipodystrophy, REE has been found to be 15% to 60% above normal [10]. Marked hypermetabolism, with REE approximately 50% above predicted values, has also been found in mandibuloacral dysplasia [11]. A mother and daughter with a unique adult-onset lipodystrophy were found to have resting metabolic rates 30% above normal when expressed per kilogram of LBM [12]. Finally, transgenic mouse models of generalized lipodystrophy also appear to have markedly increased energy expenditure [13,14].

In some cases, it has been argued that the body composition changes of lipodystrophy syndromes lead to only an *apparent* hypermetabolism when energy expenditure is expressed in terms of body weight because LBM will constitute a greater proportion of body weight in individuals with fat wasting. For example, in a recent study, 7 patients with congenital forms of lipodystrophy were found to have significantly greater TEE compared with controls [22]. When expressed per kilogram of LBM, however, there was no significant difference in TEE between groups, although it appears that there was still a tendency ($P = .11$) for those with lipodystrophy to have greater TEE.

The often extreme elevations in REE found in subjects with lipodystrophy, however, strongly suggest that true hypermetabolism is present. For example, it was estimated that each of 2 subjects with mandibuloacral dysplasia and hypermetabolism would have required an additional 20 to 25 kg of adipose tissue to render them eumetabolic when REE was adjusted for total body mass [11]. More importantly, REE in subjects with lipodystrophy has been found to be significantly greater than in controls when expressed per kilogram of LBM in several studies [3,6,8,12], thus reflecting true hypermetabolism.

It appears that there are some reasonable conclusions that can be drawn about energy expenditure in lipodystrophy syndromes. First, hypermetabolism appears to be a consistent feature of lipodystrophies characterized by extensive loss of subcutaneous fat. Because the genetic and/or environmental causes of these lipodystrophies vary greatly, it is logical to assume that increases in basal metabolism are a direct or indirect result of the loss of extensive amounts of subcutaneous adipose tissue and/or adipocyte-derived factor(s) per se. Subcutaneous adipose tissue is a large organ, making up about 85% of total body fat in lean

individuals [23]. According to multiple lines of evidence, this depot acts as an important "metabolic sink" or buffer [24-26]. If this buffering capacity is compromised, fat accumulation in nonadipose tissues such as the liver and skeletal muscle occurs with detrimental metabolic consequences, especially insulin resistance. Triglyceride accumulation in nonadipose tissues has been well documented in lipodystrophy syndromes, including HIV lipodystrophy [27,28]. Thus, the increase in REE observed in patients with HIV and other lipodystrophies could be a chronic and adaptive response to an inability to store triglyceride fuel in a normal manner. In this study, the amount of extremity fat was significantly lower in the lipodystrophy group as compared with both control groups. Total body fat in the lipodystrophy group was also significantly lower than in healthy controls but not compared with the HIV-infected controls. These data suggest that the relative loss of subcutaneous adipose tissue is the most important determinant of hypermetabolism in lipodystrophy syndromes.

The rapid and sustained fall in REE observed in our patients with HIV lipodystrophy suggests that energy intake and basal metabolism may be uniquely coupled in the setting of an abnormal storage capacity for lipid fuel. Resting energy expenditure did not fall significantly in either the HIV-infected or healthy controls, which is consistent with studies in the general population where short-term energy restriction and even 72 hours of fasting do not significantly alter REE [29]. The energetic response of patients with HIV lipodystrophy to underfeeding concurs with data from patients with generalized lipodystrophy. Reduced energy consumption and fasting have been shown to rapidly improve hypermetabolism in these patients as well [7,30]. In one study, a patient with generalized lipodystrophy had a baseline metabolic rate of 272 to 314 kJ/h per square meter, which fell to 188 kJ/h per square meter on the first day of a 3-day fast and to 130 kJ/h per square meter on the third day [7]. Another investigation showed that metabolic rates normalize in patients with generalized lipodystrophy when they consume reduced amounts of food that correlate with *predicted* energy needs [30].

The mechanism responsible for the significant decline in REE upon short-term energy restriction in patients with lipodystrophy is unknown. The decline is almost certainly not due to a change in LBM. Resting energy expenditure is primarily dependent on and linearly related to the size of the LBM, but this does not significantly diminish with short-term changes in energy intake. In a recent study, patients with generalized lipodystrophy were given recombinant leptin therapy, which reduced energy expenditure by approximately 1000 kcal/d and REE by 20% [31]. Leptin therapy resulted in a mean weight loss of 3.6 kg, but half of this was attributed to a decrease in the volume of fatty livers. Given this minimal weight loss, the reduction in energy intake was likely responsible for the reduction in energy expenditure. However, studies of energy restriction without leptin therapy in these same patients are not available.

Recent data from an *overfeeding* study in patients with congenital forms of lipodystrophy also support the notion that energy expenditure and REE may be uniquely coupled in lipodystrophy syndromes [32]. Lipodystrophic subjects and healthy controls were studied during two 40-hour dietary periods in a whole-room calorimeter. Each subject 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 resting and total energy expenditure. The increased energy expenditure in the lipodystrophy group was accompanied by a 29% increase in fat oxidation.

There are limitations to this study. Subjects with lipodystrophy were significantly older than the controls. However, increasing age is associated with a *decline* in REE. This is mostly due to the decline in lean body mass that occurs with aging, and only in advanced age is there a reduction in REE when adjusted for LBM [33]. Therefore, the age differences in our study would tend to bias against our findings of increased REE in the lipodystrophy group. In addition, currently available data suggest that aging is associated with an *attenuated* reduction in REE upon energy restriction [33] rather than an enhanced one as we found in our older lipodystrophy group.

It appears, therefore, that subjects with lipodystrophy uniquely respond to both short-term energy restriction and excess with significant changes in *resting* energy expenditure. This could represent an adaptive response to an inability to store ingested energy. This apparent flexibility of REE in lipodystrophy syndromes may ultimately represent a defense mechanism to protect nonadipose tissues from further lipid accumulation. Questions as to the tissue(s) or organ(s) responsible for the hypermetabolism associated with HIV lipodystrophy and the effect of macronutrient intake on energy expenditure are some we hope to answer in future studies.

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