

Dysregulated Energy Expenditure in HIV-Infected Patients: A Mechanistic Review

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Metabolic abnormalities are common in patients with human immunodeficiency virus (HIV) infection and range from protein catabolism to lipodystrophy and dyslipidemia associated with the use of highly active antiretroviral therapy. One abnormality is increased resting energy expenditure, which even occurs in clinically stable HIV-infected patients. Increased resting energy expenditure may aggravate the tendency towards weight loss and wasting, which are independent predictors of mortality. Despite much investigation, the factors associated with altered resting energy expenditure remain unclear; viral load, CD4 cell count, use of antiretroviral drugs, body composition, hormones, and proinflammatory cytokines have been imputed. Mechanisms that could explain increased resting energy expenditure include the HIV accessory protein viral protein R, antiretroviral drugs that affect mitochondrial function, and futile cycling within adipocytes. Other components of energy expenditure are also important to overall energy balance and may also be affected. Identifying unifying mechanisms will be an important step to finding effective treatments for HIV-related alterations in energy expenditure and to reversing metabolic risks in patients with HIV infection.

Metabolic abnormalities in patients with HIV infection range from accelerated protein catabolism (in the pre-HAART era) to lipodystrophy and dyslipidemia associated with HAART. One feature that was observed in the pre-HAART period and that has persisted since the advent of HAART is increased resting energy expenditure (REE). Increased REE, if unmatched by increased energy intake, may aggravate loss of both weight [1] and lean body mass, which are independent predictors of mortality in HIV-infected patients [2–6]. A similar phenomenon of increased REE has been observed in other chronic diseases, such as end-stage renal disease [7], rheumatoid arthritis [8], cancer [9], and chronic obstructive pulmonary disease [10]. Interventions, such as diet counseling [11, 12], nutritional supplementation

[13–15], exercise [16, 17], and pharmacologic therapies (with megestrol acetate [18], dronabinol [19], thalidomide [20, 21], growth hormone [22–24], and testosterone [25, 26]) may prevent loss of lean body mass in HIV-infected patients. However, no intervention has proven to be effective for normalizing REE.

METHODS

We searched the PubMed database for articles published before 1 February 2006 and limited the search to articles published in the English language and involving adult human subjects. We used combinations of the terms “HIV,” “HAART,” “resting energy expenditure,” and “energy expenditure.” We only considered articles that reported outcomes of weight loss, REE, and REE per kg of fat-free mass (FFM).

We identified 85 articles with these search terms. Twenty-five articles were excluded: 5 did not include weight loss or REE as outcomes, 10 involved children, 3 lacked abstracts, and 7 had limited statistical analyses. Eighteen were review articles that provided us with additional references. We reviewed various types of literature, including case-control studies, textbooks, letters and/or editorials, and review articles about energy

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expenditure in other patient populations. Finally, 97 sources were selected, including 10 randomized, controlled trials; 18 cohort studies; 40 cross-sectional studies; 8 review articles; 2 letters; 2 meta-analyses; 12 laboratory reports; 1 textbook; 2 case-control studies; 1 case series; and 1 case report. The details of 5 cross-sectional and cohort studies are shown in the Appendix.

DEFINITION OF REE

Total energy expenditure (TEE) can be divided into 4 measurable components: REE, physical activity, thermic effect of food, and adaptive thermogenesis. REE is the largest component, comprising 60%–65% of TEE [27]. REE is defined as the amount of energy consumed during metabolic activities to maintain homeostasis at rest. Voluntary physical activity fluctuates daily but generally comprises ~30% of TEE in sedentary adults. Thermic effect of food is the energy consumed during digestion, absorption, and storage of food, comprising ~10% of TEE [27]. Adaptive thermogenesis is a variable amount of energy expended in response to environmental changes, such as cold temperature, physical stress, trauma, and overfeeding. REE has been the focus of attention among HIV-infected patients.

There is generally a linear relationship between REE and FFM in healthy, nonobese adults [28, 29]. This relationship may be modeled using organ and tissue masses measured by MRI, assuming there to be stable, specific resting metabolic rates of individual organs and tissues [28, 30]. The most metabolically active organs are the liver, kidneys, heart, and brain, which together account for 5%–6% of body mass [28]. Skeletal muscle and adipose tissue, which constitute a large proportion of body mass, have some of the lowest metabolic rates [28]. FFM, particularly in the skeletal muscle and liver, explains 85% of the variance in REE [30].

Because FFM varies with age and sex, REE should be adjusted for FFM when comparing individuals. Body composition can be assessed by the following different methods to obtain a measure of FFM: bioelectrical impedance analysis, dual-energy X-ray absorptiometry, skinfold thickness, underwater weighing, and MRI or CT imaging. Bioelectrical impedance analysis and dual-energy X-ray absorptiometry are frequently used measurements and are highly correlated among control subjects with regard to FFM [48, 55], but bioelectrical impedance analysis does not adequately measure fat distribution. Because obesity is generally associated with increases in both fat mass and FFM, obese individuals have greater REE [31, 32] and TEE [32, 33] than nonobese patients.

Techniques to measure REE include indirect calorimetry, direct calorimetry, and double-labeled water analysis. Indirect calorimetry measures the rates of oxygen consumed (VO_2) and carbon dioxide produced (VCO_2) in a hood enclosing the head

of an individual at rest and uses this information to calculate the respiratory quotient (RQ) according to the formula $RQ = VCO_2/VO_2$. REE can be calculated [29]:

$$REE \approx VO_2 \times [4.686 + (RQ - 0.707) \times 0.361/0.293],$$

where 4.686 is the caloric equivalent of a liter of oxygen when the RQ is 0.707, 0.707 is the RQ when fat is oxidized, 0.361 is the difference in the caloric equivalent of the liter of oxygen when the RQ is between 1.000 and 0.707, and 0.293 is the difference between the RQ for carbohydrate and fat oxidation.

Indirect calorimetry measures REE quite accurately and is easy to perform, but it requires the subject to remain still, awake, and undistracted while the measurements are obtained. Indirect calorimetry does not measure energy expenditure due to anaerobic processes or permit analysis of the specific type of fuel metabolized. Direct calorimetry uses the same principle, except the subject is placed completely within a sealed chamber. Direct calorimetry is very accurate and can track changing energy expenditure while a subject performs activities, but it is not widely available because of the expense of installing and maintaining a whole-body metabolic chamber. In the double-labeled water method, $^2H_2^{18}O$ is administered orally, and the loss of 2H_2 and ^{18}O is measured in saliva, urine, or blood over time by mass spectrometry. Oxygen and carbon dioxide exchange—and thus, energy expenditure—can be calculated from the changing isotope levels. This technique permits measurements of energy expenditure in a free-living subject, but it involves the expense of the stable isotopes and mass spectrometry. The majority of studies of REE in HIV-infected patients have used indirect calorimetry.

REE IN UNTREATED HIV-INFECTED PATIENTS

Early research focused on REE, because it was thought to contribute to “AIDS wasting syndrome” [34]. Reports in the pre-HAART era [35–37] were conflicting with regard to whether REE per kg of FFM is elevated in HIV-infected patients. Importantly, REE per kg of FFM is increased even in asymptomatic HIV-infected patients [38, 39], suggesting that HIV infection, per se, is associated with increased REE. Viral load is correlated with REE per kg of FFM, and CD4 cell count may also be associated with changes in REE [40]. Patients with AIDS experience greater increases in REE per kg of FFM than patients with HIV infection who do not have AIDS; patients with AIDS and secondary or opportunistic infection experience even greater increases [41–44]. However, malabsorption [45] and cachexia [36] may be associated with a decrease in REE. Therefore, because of the varied complications of HIV infection, there is an extraordinarily wide range in REE, which could account

for inconsistencies among the results of different metabolic studies [46].

REE IN THE HAART ERA

Many studies, conducted both before and after the widespread use of HAART, have shown that REE per kg of FFM is indeed 9%–10% (630–663 kJ/day) higher in asymptomatic HIV-infected persons than it is in HIV-negative nonobese adults [47]. The factors associated with increased REE in asymptomatic HIV-infected patients remain unclear. Most investigations have focused on men; thus, it is difficult to ascertain if sex has an independent effect on REE. Two studies of asymptomatic HIV-infected women have shown that their REE is higher than that of HIV-uninfected women, even after adjusting for body composition [48, 49]. Furthermore, there are no reports of differences in REE among HIV-infected patients of different ethnicities. However, because ethnicity may contribute to differences in energy expenditure in HIV-uninfected persons [50, 51], this is a relationship worth investigating.

REE per kg of FFM is increased even in asymptomatic HIV-infected patients who are experiencing viral suppression while receiving HAART [52–54]. The specific contribution of HAART to REE has been difficult to quantify, because many early studies did not compare asymptomatic patients receiving HAART with those not receiving HAART. However, 1 study showed that viral load exerts a persistent effect on REE, despite HAART. Among a cohort of 372 HIV-infected patients, there was a significant increase in REE of 90 kJ/day per \log^{10} copies/mL increase in HIV RNA load after adjusting for age, FFM, CD4 cell count, and HAART use [55]. Of note, viral load has not been correlated with REE in HIV-infected women [48] or in patients with lipodystrophy [56].

Some studies, as well as a recent meta-analysis, suggest that REE may not be significantly affected by HAART [47, 57], although others suggest that HAART exerts an independent effect on REE [55, 58]. An example of the latter is a longitudinal cohort study that examined the effects of initiating therapy with a protease inhibitor–based HAART regimen among asymptomatic, weight-stable, protease inhibitor–naïve HIV-infected patients [59]. After the initiation of therapy, there was a significant decrease in viral load and an increase in CD4 cell count, followed by a decrease in REE per kg of FFM. After 24 weeks, there was no difference in REE between the HIV-infected patients and the HIV-uninfected control subjects, suggesting that HAART decreases REE by decreasing viral load. However, in another study, patients with HIV-associated wasting did not experience a significant change in REE after a median of 62 days of treatment with indinavir [60]. It is likely that these patients already had a lower REE than healthy persons because of malnutrition, although this was not assessed in the study. Another study demonstrated the independent effects of viral

load and HAART on REE [55]. After adjusting for FFM and age, the mean REE (\pm SD) among HIV-infected patients receiving various HAART regimens was 250 ± 72 kJ/day greater than that among HAART-naïve patients. This difference between the 2 groups was even greater after adjusting REE for CD4 cell count and viral load. The significance of this is uncertain, because it seems to contradict the findings of other studies. It is possible that various classes of drugs influence REE differently and that duration of HAART may affect REE.

HAART has been associated with body composition changes characterized by fat “redistribution” [61–65], a term commonly used to describe some combination of fat atrophy (usually peripheral) and fat accumulation (usually central). Although lipoatrophy and lipohypertrophy coexist, the 2 processes may be independent; lipoatrophy is a more specific consequence of HIV infection [66]. Scoring systems for lipodystrophy have been developed on the basis of body composition (trunk-to-limb fat ratio), waist-to-hip ratio, cholesterol level, and demographic characteristics [67]. However, classifying patients with variable degrees of lipodystrophy remains difficult. The question is whether clinically evident lipodystrophy—characterized by lipoatrophy of face, limbs, and buttocks; gynecomastia; lipomas; dorsocervical fat pad; increased visceral adipose tissue; insulin resistance; and dyslipidemia [54, 67]—exerts an effect on REE that exceeds that of HIV infection alone. Altered body composition certainly contributes to increased REE in HIV-infected patients with lipodystrophy; REE has been significantly correlated with waist-to-hip ratio [57], FFM [48, 53, 55, 56], and fat mass [53]. However, studies investigating the effects of fat redistribution have had varying results; some revealed that HIV-infected patients with lipodystrophy had greater REE per kg of FFM than those without lipodystrophy [57, 56], others found no difference [53, 61], and 1 study suggested that REE per kg of FFM is actually lower in HIV-infected patients with lipodystrophy [68]. A detailed meta-analysis revealed no significant difference in REE per kg of FFM between HIV-infected patients with and those without lipodystrophy [47]. However, in a recent study published since that meta-analysis, HIV-infected patients with lipodystrophy had increased REE, compared with HIV-infected patients without lipodystrophy; having lipodystrophy was associated with increased lipid oxidation and increased total energy and fat intake [69].

REE AND CYTOKINES

Elevated levels of proinflammatory cytokines may contribute to cachexia and anorexia in patients with AIDS, as they do in patients with cancer [70] and rheumatoid arthritis [8]. Increased REE is correlated with serum levels of the catabolic cytokines IL-1 β and TNF α in HIV-infected men [58]. In addition, TNF α is associated with a decrease in lean body mass

[58], often in the context of acute parasitic infection [34]. However, the correlation between REE and TNF α is weak, particularly among asymptomatic HIV-infected women [49], who tend to have higher TNF α levels than HIV-infected men. The levels of soluble TNF receptor types I and II, which reflect TNF activity, increase with disease severity but do not correlate with REE in asymptomatic and symptomatic HIV-infected males [71]. Among patients with AIDS and secondary infections, increased REE per kg of FFM correlates with the inflammatory markers C-reactive protein level, erythrocyte sedimentation rate, ferritin level, IL-6 level, and soluble TNF receptor type I level [43]. Of these, C-reactive protein level is an independent predictor of REE per kg of FFM.

Elevated rates of lipolysis and protein turnover are also associated with increased REE due to unclear mechanisms [54, 72, 73]. Patients with congenital forms of lipodystrophy also have hyperglycemia, hypertriglyceridemia, and insulin resistance [74, 75], which are associated with increased lipolysis and protein turnover and elevated REE [76, 77]. The hypermetabolism of lipids and protein could be cytokine mediated. For instance, patients experiencing the early stages of cancer often have high circulating levels of cytokines, such as TNF α [70] and leukemia inhibitory factor [78], that are associated with increased lipolysis, insulin resistance, and elevated REE. Likewise, increased protein breakdown is correlated with elevated REE in HIV-infected patients and is associated with increased levels of TNF α and IL-6 [38].

Altered regulation of anabolic and adipocyte hormones has also been implicated in causing increased REE. Serum testosterone concentration [48, 58] has been positively correlated with REE, and serum leptin concentration [48] has been inversely correlated with REE, although neither has been correlated with REE per kg of FFM. However, the topic of dysregulated hormonal control of REE has not been systematically explored. Altered regulation of other hormonal axes involved in energy homeostasis, such as thyroid hormones, catecholamines, TNF α , IL-6, leptin, adiponectin, and resistin, could potentially result from chronic immune activation.

POSSIBLE MECHANISMS UNDERLYING INCREASED REE

Mitochondrial activity, through substrate oxidation and heat dissipation, is a key mechanism of energy expenditure in the basal state; thus, mitochondrial dysfunction is a likely cause of increased REE. Several factors could contribute to mitochondrial dysfunction in HIV-infected patients receiving and those not receiving HAART. First, there is a plausible role for a product of HIV itself. The HIV accessory protein viral protein R can reduce the mitochondrial membrane potential, inducing both a proton leak and apoptosis. By associating with the adenosine nucleotide translocator, viral protein R converts the mi-

tochondrial permeability transition pore complex into a non-specific channel, causing usually sequestered protons and mitochondrial cofactors to leak into the cytosol and inducing apoptosis by altering the ratio of the apoptosis-regulating regulatory proteins Bcl and Bax [79]. These effects could lead to altered energy regulation, adipocyte apoptosis, and lipotoxic insulin resistance.

Second, HAART drugs could affect mitochondrial function. Nucleoside reverse-transcriptase inhibitors inhibit DNA polymerase γ and, thus, mitochondrial transcriptional activity [80]. The action of nucleoside reverse-transcriptase inhibitors results in reduced amounts of mitochondrial DNA [80–84], which, when superimposed on abnormalities of mitochondrial ultrastructure [84, 85] and respiratory chain dysfunction [85–87], could reduce the efficiency of ATP production. Furthermore, mitochondrial DNA depletion in adipose tissue could cause apoptosis and lipotrophy [83, 88, 89].

Finally, increased futile cycling could increase energy expenditure. Metabolic processes are regulated at several levels (e.g., gene transcription, protein translation, and posttranslational modifications), resulting in multiple mechanisms of substrate use to produce energy. These mechanisms can be envisioned as a set of cyclic events, generally occurring in series. Alterations in this system could induce redundancies, which would result in inefficient substrate use, generating heat rather than energy [90]. Patients with HIV-associated lipodystrophy have distinct metabolic abnormalities in lipid turnover. The rates of total and net lipolysis in the fasting state are markedly elevated, together with a marked increase in adipocyte reesterification [54]. These kinetic abnormalities indicate an increase in futile cycling within the adipocyte. Patients also have elevated plasma and whole-body lipid oxidation rates, as well as increased hepatic fatty acid reesterification [54]. Moreover, in the fed state, there is severe retardation of lipid clearance from chylomicrons, because the disposal of dietary fat is markedly prolonged by a defect in the entrapment function of lipoprotein lipase, leading to impaired fat storage [91]. Thus, the severe hypertriglyceridemia characteristic of HIV-associated lipodystrophy is a result of impaired clearance of triglyceride-rich lipoproteins in both fasting and fed states. These defects likely have a direct impact on energy expenditure. While fasting, increased futile cycling could elevate energy expenditure; while in the fed state, markedly delayed clearance of triglyceride-rich lipoproteins could contribute to increased diet-induced thermogenesis and further increase energy expenditure.

COMPARISON OF REE AND TEE

REE is only a piece of the puzzle why HIV-infected patients tend to maintain a negative energy balance and lose weight. As some investigators have indicated, there does not seem to be a definite relationship between REE and weight change [44,

92]. In the absence of opportunistic infections, many patients are able to maintain a stable weight, even when not receiving HAART. TEE, which takes physical activity and diet-induced thermogenesis into account, is the true determinant of energy balance and weight change. To maintain weight, TEE must equal caloric intake.

Activity-related energy expenditure, TEE minus REE, contributes to most of the variance in TEE [93]. Physical activity, the largest component of activity-related energy expenditure, may be partially responsible for the negative energy balance that occurs during episodes of weight loss. However, studies have found that episodes of rapid weight loss associated with opportunistic infections are usually accompanied by fatigue and decreased physical activity, resulting in an overall decrease in TEE [44, 93]. This decrease in TEE may help to conserve lean body mass by counterbalancing increased REE. Diet-induced thermogenesis may not be as important quantitatively, although 1 study demonstrated that the level of diet-induced thermogenesis in HIV-infected patients was elevated, compared with that in HIV-uninfected control subjects [94].

When compared with a healthy HIV-uninfected control group, both asymptomatic HIV-infected patients [95, 96] and HIV-infected patients with secondary infections who were untreated with HAART [44] appeared to have decreased or normal TEE; this may represent an adaptive phenomenon, because many of these patients had decreased caloric intake. Decreased caloric intake, rather than increased REE, significantly correlates with the rate of weight loss [41, 44, 93]. Energy intake can be compromised by anorexia associated with opportunistic infections, adverse effects of antiretroviral drugs, upper gastro-

intestinal disease, malabsorption, or abnormal intermediary metabolism of carbohydrates, protein, and fat [44]. In weight-stable, asymptomatic HIV-infected patients untreated with HAART, increased caloric intake compensates for increased REE and accelerated protein turnover [38].

A subset of HIV-infected patients was found to have increased TEE. HIV-infected, men experiencing viral suppression with lipodystrophy had increased TEE, compared with that of both HIV-infected subjects without lipodystrophy and healthy control subjects—likely because of increased REE [56]. The factors underlying elevated REE and TEE in patients with lipodystrophy are poorly understood, but loss of body fat may be a contributor [56].

CONCLUSIONS

Increased energy expenditure represents a persistent metabolic abnormality in HIV-infected patients. Increased REE contributes to nutritional imbalance and wasting. The causes of increased REE likely include viral factors, effects of secondary infections or complications, and effects of specific antiretroviral drugs. As part of the approach towards reducing metabolic risks in HIV-infected patients, it will be important to specify unifying mechanisms and find effective treatments for the alterations in energy expenditure.

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APPENDIX

SELECTED CROSS-SECTIONAL AND COHORT STUDIES.

| Study, by subject group | Sample | Outcome measure | Correlates | Independent predictor(s) of outcome |
|--|---|---|---|--|
| HIV-infected subjects not treated with HAART: Melchior et al. [42] | 165 HIV-infected subjects (129 were asymptomatic, and 36 had secondary infection) and 31 healthy control subjects | REE: REE in asymptomatic HIV-infected subjects was 11% greater than that in control subjects, and REE in HIV-infected subjects with secondary infection was 34% greater than that in control subjects | FFM: asymptomatic HIV-infected subjects ($r = 0.77$; $P < .001$); HIV-infected subjects with secondary infection ($r = 0.70$; $P < .001$); control subjects ($r = 0.78$; measured by BIA and SFT) | FFM |
| HIV-infected subjects receiving HAART | | | | |
| Batterham et al. [53] | 70 HIV-infected male subjects (62 were receiving HAART, 30 had lipodystrophy, and 17 of 30 experienced weight loss) and 16 healthy male control subjects | REE | Waist-to-hip ratio ($r = 0.236$; $P = .049$); FFM ($r = 0.75$; $P < .001$; measured by BIA); age: none; CD4 cell count: none; FM (measured by BIA) | FFM, FM; regression model: REE = $912 + 102(\text{FFM}) + 57(\text{FM})$; (SEE, 757.29; $r^2 = 0.63$) |
| Grinspoon et al. [48] | 33 premenopausal HIV-infected women who experienced weight loss 3 months before the study (61% were characterized as wasting by the CDC guidelines) and 26 premenopausal control subjects matched for weight and BMI (61% were receiving HAART) | REE per kg of FFM | Viral load ($r = 0.239$; $P = .06$) | FFM, free testosterone; regression model: REE = $230.8(\text{FFM}) + 395.9(\text{free testosterone}) - 3304(\text{variance}, s^2 = 0.49)$ |
| Shevitz et al. [55] | 530 hospital visits by 372 participants in a cohort study of HIV-seropositive men ($n = 324$) and women ($n = 48$), with approximately one-half having reported HAART use | REE | HIV RNA level: no association before adjustment for HAART use; HAART: adjusted REE was 339 kJ/day higher in those reporting HAART than in those not reporting HAART use (95% CI, 177–501 kJ/day; $P = .0001$); FFM: unknown (measured by SFT and BIA; validated against DXA); age: unknown | HIV RNA level (after adjustment for FFM, age, CD4 cell count, and HAART use); there was a mean (\pm SD) increase in REE of 90 ± 37 kJ/day per \log_{10} copies/mL (95% CI, 16–164 kJ/day; $P = .02$) |
| Kosmiski et al. [57] | 14 PI-treated patients with lipodystrophy and 13 PI-treated and 5 PI-naive patients without lipodystrophy; 94% were male | REE | WHR ($r = 0.69$; $P < .001$); waist circumference ($r = 0.44$; $P < .001$); VAT ($r = 0.57$; $P < .01$; measured by CT); insulin sensitivity ($r = -0.65$; $P < .001$); percent body fat: none (measured by DXA) | FFM (measured by DXA), insulin sensitivity; no regression model available |
| | | REE per kg of LBM | Insulin sensitivity ($r = -0.685$; $P < .005$). | |

NOTE. BIA, bioelectrical impedance analysis; BMI, body mass index; CDC, Centers for Disease Control and Prevention; DXA, dual-energy X ray absorptiometry; FFM, fat-free mass; FM, fat mass; LBM, lean body mass; PI, protease inhibitor; REE, resting energy expenditure; SEE, sleeping metabolic rate; SFT, skinfold thickness; VAT, visceral adipose tissue; WHR, waist-to-hip ratio.

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