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Decreased respiratory quotient in relation to resting energy expenditure in HIV-infected and noninfected subjects

Kathleen V. Fitch[a], Lauren M. Guggina[a], Hester M. Keough[a], Sara E. Dolan Looby[a], Colleen Hadigan[a,c], Ellen J. Anderson[b], Jane Hubbard[b], James G. Liebau[a], Stine Johnsen[a], Jeffery Wei[a], Hideo Makimura[a], Takara L. Stanley[a], Janet Lo[a], Steven K. Grinspoon[a,*]

[a]*Program in Nutritional Metabolism, Massachusetts General Hospital, Boston, MA 02114, USA*
[b]*General Clinical Research Center, Massachusetts General Hospital, Boston, MA 02114, USA*
[c]*National Institute of Health, National Institute of Allergy and Infectious Disease, Bethesda, MD 20892, USA*

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Abstract

The purpose of this study was to evaluate the relationship of respiratory quotient (RQ), a surrogate marker of substrate oxidation, as well as body composition and dietary intake to resting energy expenditure (REE) among HIV-infected patients in the current era of highly active antiretroviral therapy and among non–HIV-infected control subjects. Resting energy expenditure is increased in HIV-infected patients; but little is known regarding the potential contribution of altered substrate metabolism, body composition, and dietary intake to increased energy expenditure in this population. Respiratory quotient, REE, body composition, and dietary intake parameters were assessed in 283 HIV-infected patients and 146 community-derived HIV-negative controls who were evaluated for metabolic studies between 1998 and 2005. Respiratory quotient was lower (0.83 ± 0.00 vs 0.85 ± 0.01, $P = .005$), whereas REE adjusted for fat-free mass (FFM) was higher (31.8 ± 0.3 vs 29.8 ± 0.3 kcal/[d kg], $P \leq .0001$), in HIV-infected compared with control subjects. In multivariate modeling among HIV-infected patients, including age, sex, and parameters of immune function, FFM ($\beta = 24.811334$, $P < .0001$), visceral adiposity ($\beta = .7182746$, $P = .008$), and total body fat ($\beta = 8.0506839$, $P = .041$) were positively associated with REE, whereas RQ was negatively associated with REE ($\beta = -528.4808$, $P = .024$). Overall r^2 was equal to 0.705 and P was less than .0001 for the model. In control subjects, by contrast, only visceral adiposity ($\beta = 1.0612073$, $P = .004$), total body fat ($\beta = 15.805547$, $P = .010$), and FFM ($\beta = 22.613005$, $P < .0001$) were significant predictors of REE; and there was no relationship with RQ. Overall r^2 was equal to 0.825 and P was less than .0001 for the model. These data suggest that alterations in substrate metabolism may contribute to increased REE in HIV-infected patients compared with control subjects.

1. Introduction

Little is known regarding factors that contribute to increased resting energy expenditure (REE) among individuals with HIV. Several studies have described elevated REE in HIV-infected individuals in the pre–highly active antiretroviral therapy (HAART) era, and suggest that REE may contribute to wasting [1] and may be increased in association with viral load and CD4 count [2]. Recent studies have evaluated REE in HIV-infected patients with lipodystrophy. These studies have reported conflicting results with regard to the effects of HIV on REE [3,4]. In a recent meta-analysis, the authors concluded that REE, when adjusted for fat-free mass (FFM), was higher in HIV-positive patients when compared with the healthy controls [5]. The purpose of this study is to evaluate the relationship of respiratory quotient (RQ), a surrogate marker of substrate oxidation, as well as body composition, metabolic parameters, and dietary intake to REE among HIV-infected patients in the current era of HAART, in comparison with non–HIV-infected control subjects.

The authors' responsibilities were as follows—KF, SDL, CH, JH, JL, and JL: responsible for subject recruitment and data acquisition; HK and JW: responsible for data entry; KF, LG, and SG: responsible for the data analysis and interpretation; KF and SG: responsible for the statistical analysis; KF and SG: responsible for the draft of the manuscript; KF, KF, SDL, CH, EA, JL, JH, SJ, HM, TS, JL, and SG: responsible for the critical revision of the manuscript and its important intellectual content; SG: responsible for obtaining funding; and SG: responsible for study supervision. None of the authors reported a conflict of interest.

* Corresponding author. Tel.: +1 617 724 9109; fax: +1 617 724 8998.
E-mail address: sgrinspoon@partners.org (S.K. Grinspoon).

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2. Subjects and controls

Data were prospectively collected from 1998 to 2005 in 283 HIV-infected patients participating in metabolic studies at the Massachusetts General Hospital (MGH) and Massachusetts Institute of Technology (MIT) and 146 HIV-negative subjects simultaneously recruited from the community as controls for these studies [6-20]. Human immunodeficiency virus–infected patients with wasting (body mass index [BMI] <20 kg/m^2) were not included in the analysis. Human immunodeficiency virus–infected patients were recruited from newspaper advertisement, community, and referral-based practices. The subjects were 18 to 60 years old with documentation of HIV status. For subjects receiving antiretroviral therapy, a stable regimen for a minimum of 6 weeks before evaluation was required. Subjects were excluded if they had a history of diabetes mellitus; were receiving concurrent therapy with insulin, antidiabetic agents, glucocorticoids, growth hormone, supraphysiologic testosterone replacement, or anabolic steroids; were current substance abusers; had a major opportunistic infection within the 6 weeks before the study; had a thyroid disorder; or were pregnant or breast-feeding within the past year. The HIV-negative controls were recruited through hospital and local advertisements using similar exclusion criteria and tested negative for HIV disease by enzyme-linked immunosorbent assay and Western blot. For both HIV-infected and control groups, baseline data were obtained before any intervention. All participants provided informed consent. The studies were approved by the Institutional Review Boards at both the MGH and MIT. These data represent a subset of a larger data set, which demonstrated differences in dietary fat intake [21] and relationship of visceral and subcutaneous adipose tissue area (VAT and SAT, respectively) to BMI [22]. Data on the relationship of RQ, body composition, and dietary intake to REE have not previously been published from the data set. Patients were not recruited based on lipodystrophy status; but lipodystrophy was characterized by investigators on the basis of evidence of fat accumulation in the trunk, breast, or neck and loss of fat in the face or extremities on physical examination as previously described [23].

All subjects were studied after an overnight fast of 12 hours. Each individual had a complete medical history and a physical examination. Triglycerides, cholesterol, high-density lipoprotein (HDL), and glucose were measured using standard techniques [14]. Complete blood count, CD4 count, and HIV viral load were obtained.

Dual-energy x-ray absorptiometry (Hologic QDR-4500A; Hologic, Waltham, MA) was used to determine fat mass and FFM. The dual-energy x-ray absorptiometry technique has a precision error of 3% for fat mass and 1.5% for FFM [24]. Cross-sectional abdominal computed tomography (CT) scans were performed to assess SAT and VAT [25]. After an overnight fast, REE was measured by indirect calorimetry (Deltatrac or Vmax29; Sensormedics, Yorba Linda, CA). Subjects sat quietly in a thermal neutral room for approximately 15 minutes before the study began. Oxygen consumption and carbon dioxide production were measured continuously. Measurements were recorded for 20 minutes, and the final 15 minutes of recording was analyzed. Respiratory quotient is the ratio of CO_2 production and O_2 consumption. The reference range of RQ in humans is 0.67 to 1.2 [26]. Metabolic rates were further validated by calculating percentage predicted basal metabolic rate (BMR). The BMR was calculated using the Harris-Benedict [27] equation.

Self-reported levels of physical activity were assessed with the Modifiable Activity Questionnaire [28]. Activity questionnaires were available in 207 HIV-infected subjects and 36 control subjects. Physical activity level was calculated as the product of the duration and frequency of each activity (in hours per week), weighted by an estimate of the metabolic equivalent of that activity (MET) and summed for all activities performed, with the result expressed as the average MET hours per week.

Dietary intake was obtained via 4-day food records (3 weekdays and 1 weekend day) in 282 HIV-infected subjects and 93 controls, and via multiple-pass 24-hour recall in an additional 53 controls. For the 4-day food records and 24-hour recall, participants were instructed by trained research dietitians to record completely all food and drink consumed. Dietary intake data were analyzed using Nutrition Data System for Research software versions 4.02_30 through 2004 developed by the Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN. Anthropometric determinations were made in triplicate using an inelastic tape measure for circumferences and a wall-mounted stadiometer (Holtain, Crymych, United Kingdom) and digital scale for height and weight, respectively. Waist and hip circumferences were determined using standard methods. All measurements were completed by trained research dietitians.

2.1. Statistical analysis

Comparison of demographic, body composition, energy, and metabolic parameters was made by HIV status using the t test for continuous variables and the χ^2 test for categorical variables. P values were also determined using analysis of variance, controlling for age and BMI. Within each group, HIV and control, separate multivariate regression models were constructed using REE as the dependent variable and age, BMI, sex, carbohydrate and fat intake, VAT, FFM, RQ, triglyceride level, and activity level as the independent variables for the HIV-infected patients. Immune function parameters were also included in the model for HIV-infected patients. Covariates for inclusion were based on results of univariate regression analysis. For multivariate and stepwise regression analyses, estimates equal change in REE (in kilocalories per day) per 1 unit of change in the independent variable. In addition, forward stepwise regression models were conducted, with a criteria of P less than .1 to enter the

Table 1
Demographics in HIV-infected and non–HIV-infected subjects

Variable	HIV+[a] (n = 283)	Control[a] (n = 146)	*P* value[b]
Demographics			
Age (y)	42 ± 0	40 ± 1	.005
BMI (kg/m^2)	26.9 ± 0.4	29.1 ± 0.5	.0004
Sex (%)			.81
Male	48.8	50.0	
Female	51.2	50.0	
Race (%)			.44
White	51.2	59.6	
African American	33.2	27.4	
Hispanic	9.2	7.5	
Other	6.4	5.5	
HIV parameters			
CD4 (/mm^3)	442 ± 16	–	–
Log_{10} viral load (copies/mL)	2.7 ± 0.1	–	–
Duration HIV (y)	8.8 ± 0.3	–	–
Currently taking PI (%)	61.7	–	–
Currently taking NRTI (%)	92.5	–	–
Currently taking NNRTI (%)	37.9	–	–

[a] Results expressed as mean ± SEM.
[b] *P* values for the differences between HIV-infected and control subjects derived from χ^2 testing for categorical variables and *t* test for continuous variables.

model, to establish the hierarchy by which factors contributed to REE and the marginal contribution of each factor.

All values are expressed as mean ± SEM unless otherwise indicated. Statistical analyses were performed using SAS JMP software, version 5.0.1 (SAS Institute, Cary, NC).

3. Results

Among the 283 HIV-infected and 146 non–HIV-infected subjects, there were no statistically significant differences in sex or race between the HIV-infected and control subjects. Body mass index was significantly lower in the HIV-infected population compared with the control population (26.9 ± 0.4 vs 29.1 ± 0.5 kg/m^2, $P = .0004$), and HIV-infected subjects were slightly older than HIV-uninfected controls (42 ± 0 vs 40 ± 1 years, $P = .005$) (Table 1).

The HIV-infected subjects demonstrated higher REE/FFM (31.8 ± 0.3 vs 29.8 ± 0.3 kcal/[d kg], $P < .0001$, HIV vs control), lower RQ (0.83 ± 0.00 vs 0.85 ± 0.01, $P = .005$), and lower activity levels (55 ± 5 vs 106 ± 22 MET hours, $P = .001$) compared with the control subjects. Percentage of predicted BMR was 108% ± 1% vs 98% ± 1% (HIV vs

Table 2
Body composition, energy, and metabolic parameters in HIV-infected and non–HIV-infected subjects

Variable	HIV+[a] (n = 283)	Control[a] (n = 146)	*P* value[b]	*P* value adjusted for age and BMI
Body composition parameters				
Waist (cm)	94.8 ± 0.8	97.2 ± 1.5	.13	.0003
Hip (cm)	100.4 ± 0.7	108.0 ± 1.2	<.0001	<.0001
Waist-to-hip ratio	0.94 ± 0.00	0.90 ± 0.01	<.0001	<.0001
CT VAT (cm^2)	121.5 ± 4.1	130.8 ± 7.9	.25	.020
CT SAT (cm^2)	231.3 ± 9.1	319.3 ± 17.3	<.0001	.64
Total body fat (kg)	21.1 ± 0.6	26.4 ± 1.2	<.0001	.011
FFM (kg)	54.7 ± 0.7	56.5 ± 1.1	.12	.85
Energy parameters				
REE (kcal/d)	1730 ± 22	1705 ± 40	.56	.027
% Predicted BMR[c]	108 ± 1	98 ± 1	<.0001	<.0001
REE/FFM (kcal/[d kg])	31.8 ± 0.3	29.8 ± 0.3	<.0001	<.0001
RQ	0.83 ± 0.00	0.85 ± 0.01	.005	.025
Activity (MET h)[d]	55 ± 5	106 ± 22	.001	.002
Dietary parameters				
Total calories (kcal/d)	2156 ± 46	2123 ± 60	.66	.85
Total dietary carbohydrates (g/d)	262 ± 6	257 ± 8	.60	.97
% Dietary carbohydrates	48.9 ± 0.5	49.0 ± 0.9	.92	.60
Total dietary fat (g/d)	85 ± 2	81 ± 3	.28	.27
% Dietary fat	35.3 ± 0.4	34.0 ± 0.7	.090	.041
Total dietary SFA (g/d)	29.9 ± 0.8	27.3 ± 1.2	.068	.044
Total dietary protein (g/d)	87 ± 2	88 ± 3	.81	.75
Metabolic parameters				
Triglycerides (mg/dL)	203 ± 12	130 ± 11	<.0001	.0006
Serum cholesterol (mg/dL)	189 ± 3	178 ± 3	.011	.005
HDL (mg/dL)	42 ± 1	48 ± 1	<.0001	<.0001
Fasting glucose (mg/dL)	90 ± 1	89 ± 1	.52	.45
FFA (mEq/L)	0.52 ± 0.03	0.52 ± 0.02	.91	.56

SFA indicates saturated fatty acids.
[a] Results expressed as mean ± SEM.
[b] *P* values for the differences between HIV-infected and control subjects determined by *t* test and mixed-effects analysis of variance controlling for age and BMI.
[c] Harris-Benedict equations used to calculate predicted BMR: Women: BMR = 66.5 + (13.8 × weight[kg]) + (5.0 × height[cm]) − (6.8 × age[y]) Men: BMR = 655 + (9.6 × weight[kg]) + (1.8 × height[cm]) − (4.7 × age[y]).
[d] Determined by the Modifiable Activity Questionnaire and recorded as MET; n =36.

control, $P < .0001$). These differences remained significant in adjusted analyses accounting for age and BMI. Resting energy expenditure was not different in unadjusted analyses, but was significantly different in the adjusted analysis (1730 ± 22 vs 1705 ± 40 kcal/d, $P = .027$) (Table 2).

Hip circumference (100.4 ± 0.7 vs 108.0 ± 1.2 cm, $P < .0001$), total body fat (21.1 ± 0.6 vs 26.4 ± 1.2 kg, $P < .0001$), and HDL cholesterol (42 ± 1 vs 48 ± 1 mg/dL, $P < .0001$) were significantly lower in the HIV-infected subjects when compared with the HIV-uninfected subjects, whereas triglycerides (203 ± 12 vs 130 ± 11 mg/dL, $P < .0001$) and total cholesterol (189 ± 3 vs 178 ± 3 mg/dL, $P = .011$) were higher among HIV-infected subjects (Table 2). There were no statistically significant differences in waist circumference; FFM; and total caloric, carbohydrate, fat, and protein intake among the HIV-infected and non–HIV-infected subjects, although percentage fat intake and saturated fat intake were higher in the HIV group, after adjusting for age and BMI, as previously reported [22] (Table 2).

The VAT area was not different between the groups in unadjusted analyses, but was lower in the HIV-group after adjusting for age and BMI (121.5 ± 4.1 vs 130.8 ± 7.9 cm^2, $P = .020$). In contrast, SAT was lower in HIV vs control in unadjusted analyses, but not after adjusting for age and BMI (Table 2).

Table 3
Univariate regression analyses for REE (in kilocalories per day)

HIV-infected subjects

Parameter	*r*	*P* value
BMI (kg/m^2)	0.30	<.0001
Age (y)	−0.04	.53
RQ	−0.12	.047
Dietary fat (g/d)	0.28	<.0001
Dietary carbohydrate (g/d)	0.25	<.0001
CT VAT (cm^2)	0.35	<.0001
CT SAT (cm^2)	−0.0004	.99
FFM (kg)	0.77	<.0001
Total body fat (kg)	0.02	.68
CD4 ($/mm^3$)	0.07	.26
Triglycerides (mg/dL)	0.27	<.0001
Activity (MET h)	0.19	.007
Log_{10} viral load (copies/mL)	0.007	.93
FFA (mEq/L)	−0.03	.78

Relationships between covariates and REE in univariate regression modeling among HIV-infected subjects

Control subjects

Parameter	*r*	*P* value
BMI (kg/m^2)	0.68	<.0001
Age (y)	0.38	<.0001
RQ	−0.04	.61
Dietary fat (g/d)	0.42	<.0001
Dietary carbohydrate (g/d)	0.18	.029
CT VAT (cm^2)	0.69	<.0001
CT SAT (cm^2)	0.52	<.0001
FFM (kg)	0.88	<.0001
Total body fat (kg)	0.57	<.0001
Activity (MET h)	−0.01	.98

Relationships between covariates and REE in univariate regression modeling among control subjects.

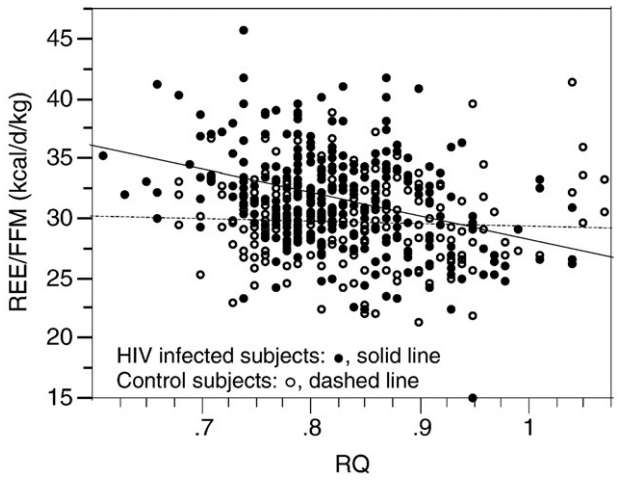

Fig. 1. Relationship between REE/FFM and RQ. For HIV-infected subjects (●, solid line; n =273): REE/FFM (in kilocalories per day per kilogram) = 47.790534 − 19.433101 (RQ) ($P < .0001$); for control subjects (○, dashed line; n =143): REE/FFM (in kilocalories per day per kilogram) = 31.330088 − 1.7998838 (RQ) ($P = .61$).

Among the HIV-infected subjects, 192 were classified with lipodystrophy and 91 were classified without lipodystrophy. There was no difference in age, race, viral load, or REE based on lipodystrophy status. Body mass index (27.4 ± 0.4 vs 25.6 ± 0.6 kg/m^2, $P = .007$), CD4 (474 ± 19 vs 372 ± 28/mm^2, $P = .003$), waist-to-hip ratio (0.97 ± 0.01 vs 0.90 ± 0.01, $P \leq .0001$), and RQ (0.83 ± 0.01 vs 0.81 ± 0.01, $P = .034$) were significantly higher in the HIV-infected subjects with lipodystrophy compared with those without lipodystrophy. In the lipodystrophic group, REE/FFM (32.1 ± 0.3 vs 31.1 ± 0.3 kcal/[d kg], $P = .063$) tended to be higher, although this did not reach statistical significance. Subanalyses were also performed based on viral load. Of the patients who had viral loads done in the study, 72 had undetectable viral loads and 82 had detectable viral loads; REE was not different between these patients (1661 ± 42.1 vs 1637 ± 39.4, $P = .680$). Patients with HIV and undetectable viral loads did have increased REE compared with healthy controls (1768 ± 28.9 vs 1705 ± 33.8, $P = .033$).

The relationship of REE to metabolic and immune parameters in HIV and control subjects is shown in Table 3. Body mass index ($r = 0.30$, $P < .0001$), RQ ($r = −0.12$, $P = .047$), dietary fat intake ($r = 0.28$, $P < .0001$), dietary carbohydrate intake ($r = 0.25$, $P < .0001$), VAT area ($r = 0.35$, $P < .0001$), FFM ($r = 0.77$, $P < .0001$), triglyceride ($r = 0.27$, $P < .0001$), and MET hours ($r = 0.19$, $P = .007$) were related to REE in univariate regression analyses among the HIV group, whereas BMI ($r = 0.68$, $P < .0001$), age ($r = 0.38$, $P < .0001$), dietary fat intake ($r = 0.42$, $P < .0001$), dietary carbohydrate intake ($r = 0.18$, $P = .029$), VAT area ($r = 0.69$, $P < .0001$), SAT area ($r = 0.52$, $P < .0001$), FFM ($r = 0.88$, $P < .0001$), and total body fat ($r =$

Table 4
Multivariate regression analyses for REE (in kilocalories per day)

HIV-infected subjects, n = 183

Parameter	Estimate (β)	SE	P value
BMI (kg/m^2)	−16.33165	8.481426	.056
Age (y)	−.866462	2.252714	.70
Sex	41.237605	30.6016	.18
RQ	**−528.4808**	**231.3074**	**.024**
Dietary fat (g)	.0782477	0.546601	.89
Dietary carbohydrate (g)	.3525015	0.185404	.059
CT VAT (cm^2)	**.7182746**	**0.26755**	**.008**
FFM (kg)	**24.811334**	**2.944075**	**<.0001**
Total body fat (kg)	**8.0506839**	**3.911959**	**.041**
CD4 (/mm^3)	−.054781	0.060908	.37
Triglycerides (mg/dL)	.0773081	0.072956	.29
Activity (MET h)	.0114182	0.18809	.95

Relationships between covariates and REE in regression modeling among HIV-infected subjects (P < .0001, r^2 = 0.705). Variables in bold were significantly related to REE in the model.

Control subjects, n = 119

Parameter	Estimate (β)	SE	P value
BMI (kg/m^2)	−5.85139	9.998695	.56
Age (y)	−1.653699	2.412292	.50
Sex	.7825825	30.59653	.98
RQ	−19.85478	215.2759	.93
Dietary fat (g)	.7520528	0.501677	.14
Dietary carbohydrate (g)	−.201068	0.206064	.33
CT VAT (cm^2)	**1.0612073**	**0.355541**	**.004**
CT SAT (cm^2)	−.779323	0.41413	.063
FFM (kg)	**22.613005**	**2.677683**	**<.0001**
Total body fat (kg)	**15.805547**	**6.011043**	**.010**

Relationships between covariates and REE in regression modeling among control subjects (P < .0001, r^2 = 0.825). Variables in bold were significantly related to REE in the model.

0.57, P < .0001) were related to REE in the control subjects. Total calories per day were related to REE in the HIV-infected subjects (r = 0.33, P < .0001) and control subjects (r = 0.12, P < .0001); however, after adjusting for fat and carbohydrate intake, these relationships were no longer significant (data not shown). In the lipodystrophic group, similar relationships between metabolic variables and REE were seen. Body mass index (r = 0.32, P < .0001), dietary fat intake (r = 0.22, P = .003), dietary carbohydrate intake (r = 0.23, P = .003), VAT area (r = 0.36, P < .0001), FFM (r = 0.79, P < .0001), and triglyceride (r = 0.29, P < .0001) were related to REE in univariate analysis. Use of protease inhibitor (PI) (1769 ± 28 vs 1706 ± 40 kcal/d, P = .19), nucleoside reverse transcriptase inhibitor (NRTI) (1748 ± 25 vs 1706 ± 62 kcal/d, P = .64), and nonnucleoside reverse transcriptase inhibitor (NNRTI) (1723 ± 35 vs 1758 ± 31 kcal/d, P = .47) (current use vs nonuse, respectively, for each comparison) was not related to REE in the HIV group or in the HIV group with lipodystrophy (data not shown).

In univariate regression analysis, REE/FFM was significantly and negatively associated with RQ in HIV-infected subjects (REE/FFM [in kilocalories per day per kilogram] = 47.790534 − 19.433101 [RQ], P < .0001), whereas this relationship was not significant for control subjects (REE/FFM [in kilocalories per day per kilogram] = 31.330088 − 1.7998838 [RQ], P = .61) (Fig. 1).

Multivariate regression analysis was performed for HIV-infected subjects for REE (dependent variable) including BMI, age, sex, fat intake, total body fat and CD4 count, carbohydrate intake, visceral adiposity, RQ, FFM, triglyceride, and activity levels as independent variables. Fat-free mass (β = 24.811334, P < .0001), visceral adiposity (β = .7182746, P = .008), and total body fat (β = 8.0506839, P = .041) were positively associated with REE, whereas RQ was negatively associated with REE (β = −528.4808, P = .024). Overall r^2 was equal to 0.705 and P was less than .0001 for the model (Table 4).

By contrast, among control subjects, visceral adiposity (β = 1.0612073, P = .004), total body fat (β = 15.805547, P = .010), and FFM (β = 22.613005, P < .0001) were significant predictors of REE; and there was no relationship with RQ. Overall r^2 was equal to 0.825 and P was less than .0001 for the model (Table 4).

In forward stepwise regression modeling in the HIV-infected subjects, with REE as the dependent variable, FFM, RQ, dietary carbohydrate, and VAT were significant in stepwise modeling and accounted for 70% of the variance, with FFM (65%) contributing most in the model and with significant but smaller additional contributions from RQ, carbohydrate intake, and VAT (Table 5). In the control subjects, FFM also contributed most to REE (72%), with an additional contribution of 8% from VAT and smaller contributions from total body fat and SAT (Table 5).

Among the HIV-infected patients, use of PI (0.82 ± 0.01 vs 0.84 ± 0.01, P = .26), NRTI (0.83 ± 0.01 vs 0.82 ± 0.02, P = .44), and NNRTI (0.83 ± 0.01 vs 0.83 ± 0.01, P = .44) (current use vs nonuse, respectively, for each comparison) was not related to RQ. On univariate regression, RQ was related to BMI (r = 0.12, P = .042), CD4 T-cell count (r =

Table 5
Forward stepwise regression analyses for REE (in kilocalories per day)

HIV-infected subjects, n = 259

Parameter	Estimate (β)	R^2	P value
FFM (kg)	25.2079461	0.649	<.0001
RQ	−654.23617	0.665	.004
Dietary carbohydrate (g)	.43184009	0.674	.027
CT VAT (cm^2)	.68024196	0.689	.004

Relationships between covariates and REE in stepwise regression modeling among HIV-infected subjects.

Control subjects, n = 119

Parameter	Estimate (β)	R^2	P value
FFM (kg)	22.6017946	0.722	<.0001
CT VAT (cm^2)	.99145624	0.806	<.0001
Total body fat (kg)	12.541516	0.812	.048
CT SAT (cm^2)	−.6914458	0.818	.051

Relationships between covariates and REE in stepwise regression modeling among control subjects.

0.16, $P = .007$), VAT area ($r = 0.13$, $P = .029$), FFM ($r = 0.14$, $P = .019$), and MET hours ($r = -0.16$, $P = .026$); but none of these variables remained significant in multivariate regression analyses adjusting simultaneously for all covariates (data not shown). Respiratory quotient was not related to dietary carbohydrate intake ($r = -0.04$, $P = .49$), dietary fat intake ($r = -0.04$, $P = .50$), HIV viral load ($r = -0.11$, $P = .18$), SAT area ($r = 1.0$, $P = .087$), free fatty acids (FFA) ($r = -0.08$, $P = .44$), or triglycerides ($r = 0.07$, $P = .27$).

Among control subjects, RQ was related to VAT area ($r = 0.30$, $P = .0008$) and triglycerides ($r = 0.18$, $P = .033$) in univariate regression analysis. Respiratory quotient was not related to carbohydrate intake ($r = 0.02$, $P = .84$), dietary fat intake ($r = 0.04$, $P = .63$), FFA ($r = -0.13$, $P = .17$), BMI ($r = 0.02$, $P = .79$), SAT area ($r = 0.17$, $P = .066$), FFM ($r = 0.02$, $P = .79$), or MET hours ($r = 0.29$, $P = .090$) in the control subjects.

4. Discussion

To our knowledge, this is the largest study to date investigating REE and RQ in HIV-infected subjects and provides novel data regarding the relationship between RQ and REE in this population. Several studies examining REE in HIV-infected subjects have shown that FFM contributes to REE in this population [3,29,30]; however, no study thus far has shown that RQ is associated with REE among HIV-infected patients. The results of this study demonstrate lower RQ and higher REE adjusted for FFM in HIV-infected patients compared with the noninfected control subjects. Although REE and REE adjusted for FFM were significantly associated with RQ in HIV-infected subjects, this was not the case in HIV-negative control subjects.

In general, the HIV-infected subjects were infected with the HIV virus for longer than 8 years; most were on HAART and had a mean CD4 count greater than 400. These subjects demonstrated a number of the metabolic abnormalities consistent with the use of HAART, including increased triglyceride levels and reduced HDL. Subjects demonstrated a relative fat redistribution, but demonstrated lower levels of SAT, but not VAT, when compared with non–BMI-matched controls, consistent with Fat Redistribution and Metabolic Change in HIV Infection Study (FRAM) [31,32].

The REE/FFM, percentage predicted BMR, and BMI-adjusted REE were all significantly higher in HIV than controls. Calculation of percentage predicted BMR was useful to characterize the differences observed between HIV and non-HIV patients. Indeed, we observed a 10% difference with non-HIV controls in percentage predicted BMR (108% ± 1% vs 98% ± 1%, $P < .0001$), which is in the range of that seen in prior smaller studies [29,33]. The mechanism to explain elevated REE in the setting of HIV infection is still unclear. Shevitz et al [30] suggested that antiviral medications might directly stimulate metabolism or that metabolic demand might increase from a rejuvenated immune system in subjects on HAART. More recently, it has been postulated that mitochondrial dysfunction may contribute to increased REE and that the effects of HAART or the HIV virus may lead to altered energy regulation [34].

In our study, we did not see a relationship between use of PI, NRTI, and NNRTI and REE, or between immune parameters and REE. In contrast, we demonstrated the expected strong relationship with FFM and a smaller but significant contribution of lower RQ to increased REE not seen in the control subjects. Dietary carbohydrate intake and VAT area also contributed to increased REE in regression modeling. The significant relationship we observed between VAT and REE corroborates data from Kosmiski et al [3] demonstrating a similar relationship in a smaller study of 32 patients. Among the HIV-infected patients, triglyceride levels and activity levels were related to REE on univariate regression analyses, but not on multivariate regression analyses. Activity levels in MET hours were lower in the HIV-infected patients, suggesting that increased REE was not a function of increased activity levels.

In addition to an elevated REE, we also found a significantly lower RQ among the HIV-infected subjects. In smaller studies among subjects with HIV-associated lipodystrophy, it has been suggested that elevated FFA may contribute to increased lipid oxidation and hypertriglyceridemia [35,36]. In our study, neither triglycerides nor FFA were associated with RQ. A relative increase in dietary fat intake might contribute to an increase in lipid oxidation in the HIV-infected patients, as increased fat oxidation has been shown to be an adaptation to diets that are higher in fat [37,38] among non–HIV-infected patients. However, we did not see a relationship between dietary fat intake and RQ in the study, arguing against a significant effect of dietary fat intake on substrate oxidation in HIV-infected patients.

A novel finding in this study was that RQ was significantly associated with REE in HIV-infected patients. Respiratory quotient is a surrogate marker of substrate oxidation; and in the general population, those with morbid obesity tend to have a lower RQ in addition to higher metabolic rates [39,40]. In this study, HIV-infected patients had a lower BMI than controls, arguing against this as an explanation for lower RQ. Furthermore, RQ remained lower in the HIV patients adjusting for BMI. There are conflicting results in the few studies that have evaluated RQ among HIV-infected patients, and most of them have examined RQ in the context of smaller studies of lipodystrophy [3,35]. In a study with 43 subjects, Sutinen and Yki-Jarvinen [35] observed that subjects on HAART with lipodystrophy have a lower RQ when compared with subjects on HAART without lipodystrophy, whereas Kosmiski et al [3] found no difference among patients with lipodystrophy. A lower RQ may result in a greater postprandial decrease in glycogen stores, resulting in a suppression of satiety, an increase in appetite, and therefore an increased food intake [41].

This study has some limitations. Causality cannot be determined from a cross-sectional study. Furthermore, we did not measure substrate oxidation directly, but were able to

include data on intake of macronutrients, activity level, and detailed measures of body composition and metabolic parameters. We demonstrate clear relationships between metabolic parameters, REE, and RQ in a large study of well-phenotyped HIV-infected patients compared with controls, which extends our knowledge of altered energy metabolism in the HIV population. It is possible that factors driving increased REE may also be driving increased fat oxidation, but further studies are needed to directly assess this relationship and fat oxidation rates. Finally, although RQ was statistically lower in the HIV group, the biological significance of this difference remains unclear.

In conclusion, we evaluated the relationship between REE and RQ in a large study of HIV-infected men and women compared with control subjects. Decreased RQ is related to REE in HIV-infected patients and may play a role in metabolic abnormalities experienced by this population. Longitudinal studies are needed to follow these relationships over time to better establish the relationship between RQ, substrate oxidation, and REE in HIV-infected patients.

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References

[1] Hommes MJ, Romijn JA, Godfried MH, et al. Increased resting energy expenditure in human immunodeficiency virus-infected men. Metabolism 1990;39(11):1186-90.

[2] Mulligan K, Tai VW, Schambelan M. Energy expenditure in human immunodeficiency virus infection. N Engl J Med (letter) 1997;336:70-1.

[3] Kosmiski LA, Kuritzkes DR, Lichtenstein KA, et al. Fat distribution and metabolic changes are strongly correlated and energy expenditure is increased in the HIV lipodystrophy syndrome. AIDS 2001;15(15): 1993-2000.

[4] van der Valk M, Reiss P, van Leth FC, et al. Highly active antiretroviral therapy-induced lipodystrophy has minor effects on human immunodeficiency virus–induced changes in lipolysis, but normalizes resting energy expenditure. J Clin Endocrinol Metab 2002;87(11):5066-71.

[5] Batterham MJ. Investigating heterogeneity in studies of resting energy expenditure in persons with HIV/AIDS: a meta-analysis. Am J Clin Nutr 2005;81(3):702-13.

[6] Dolan SE, Frontera W, Librizzi J, et al. The effects of a supervised home-based aerobic and progressive resistance training regimen in HIV-infected women: a randomized trial. Arch Intern Med 2006;166: 1225-31.

[7] Hadigan C, Corcoran C, Basgoz N, Davis B, Sax P, Grinspoon S. Metformin in the treatment of HIV lipodystrophy syndrome: a randomized controlled trial. JAMA 2000;284(4):472-7.

[8] Koutkia P, Canavan B, Breu J, Grinspoon S. Effects of growth hormone–releasing hormone on bone turnover in human immunodeficiency virus–infected men with fat accumulation. J Clin Endocrinol Metab 2005;90(4):2154-60.

[9] Rietschel P, Hadigan C, Corcoran C, et al. Assessment of growth hormone dynamics in human immunodeficiency virus–related lipodystrophy. J Clin Endocrinol Metab 2001;86(2):504-10.

[10] Dolan SE, Kanter JR, Grinspoon S. Longitudinal analysis of bone density in human immunodeficiency virus–infected women. J Clin Endocrinol Metab 2006;91(8):2938-45.

[11] Hadigan C, Kamin D, Liebau J, et al. Depot-specific regulation of glucose uptake and insulin sensitivity in HIV-lipodystrophy. Am J Physiol Endocrinol Metab 2006;290(2):E289-E298.

[12] Bernstein LE, Berry J, Kim S, Canavan B, Grinspoon SK. Effects of etanercept in patients with the metabolic syndrome. Arch Intern Med 2006;166(8):902-8.

[13] Hadigan C, Yawetz S, Thomas A, Havers F, Sax PE, Grinspoon S. Metabolic effects of rosiglitazone in HIV lipodystrophy: a randomized controlled trial. Ann Intern Med 2004;140(10):786-94.

[14] Fitch KV, Anderson EJ, Hubbard JL, et al. Effects of a lifestyle modification program in HIV-infected patients with the metabolic syndrome. AIDS 2006;20(14):1843-50.

[15] Driscoll SD, Meininger GE, Lareau MT, et al. Effects of exercise training and metformin on body composition and cardiovascular indices in HIV infected patients. AIDS 2004;18(3):465-73.

[16] Schurgin S, Canavan B, Koutkia P, Depaoli AM, Grinspoon S. Endocrine and metabolic effects of physiologic r-metHuLeptin administration during acute caloric deprivation in normal-weight women. J Clin Endocrinol Metab 2004;89(11):5402-9.

[17] Meininger G, Hadigan C, Laposata M, et al. Elevated concentrations of free fatty acids are associated with increased insulin response to standard glucose challenge in human immunodeficiency virus–infected subjects with fat redistribution. Metabolism 2002;51(2): 260-6.

[18] Fleischman A, Johnsen S, Systrom DM, et al. Effects of a nucleoside reverse transcriptase inhibitor, stavudine, on glucose disposal and mitochondrial function in muscle of healthy adults. Am J Physiol Endocrinol Metab 2007;292(6):E1666-E1673.

[19] Dolan SE, Huang JS, Killilea KM, Sullivan MP, Aliabadi N, Grinspoon S. Reduced bone density in HIV-infected women. AIDS 2004;18(3):475-83.

[20] Hadigan C, Borgonha S, Rabe J, Young V, Grinspoon S. Increased rates of lipolysis among HIV-infected men receiving highly active antiretroviral therapy. Metabolism 2002;51:1143-7.

[21] Joy T, Keogh HM, Hadigan C, et al. Relationship of body composition to BMI in HIV-infected patients with metabolic abnormalities. JAIDS 2007;47:174-84.

[22] Joy T, Keough HM, Hadigan C, et al. Dietary fat intake and relationship to serum lipid levels among HIV-infected subjects with metabolic abnormalities in the era of HAART. AIDS 2007;21: 1591-600.

[23] Hadigan C, Rabe J, Meininger G, Aliabadi N, Breu J, Grinspoon S. Inhibition of lipolysis improves insulin sensitivity in protease inhibitor–treated HIV-infected men with fat redistribution. Am J Clin Nutr 2003;77:490-4.

[24] Mazess RB, Barden HS, Bisek JP, Hanson J. Dual-energy x-ray absorptiometry for total-body and regional bone-mineral and soft-tissue composition. Am J Clin Nutr 1990;51(6):1106-12.

[25] Dolan SE, Hadigan C, Killilea KM, et al. Increased cardiovascular disease risk indices in HIV-infected women. J Acquir Immune Defic Syndr 2005;39(1):44-54.

[26] Haugen HA, Chan LN, Li F. Indirect calorimetry: a practical guide for clinicians. Nutr Clin Pract 2007;22(4):377-88.

[27] Harris JA, Benedict FG. A biometric study of basal metabolism in man. Washington, DC: Carnegie Institute of Washington; 1919.

[28] Kriska A, Knowler W, LaPorte R. Development of a questionnaire to examine the relationship of physical activity and diabetes in Pima Indians. Diabetes Care 1990;13:401-11.

[29] Grinspoon S, Corcoran C, Miller K, et al. Determinants of increased energy expenditure in HIV-infected women. Am J Clin Nutr 1998;68 (3):720-5.

[30] Shevitz AH, Knox TA, Spiegelman D, Roubenoff R, Gorbach SL, Skolnik PR. Elevated resting energy expenditure among HIV-seropositive persons receiving highly active antiretroviral therapy. AIDS 1999;13(11):1351-7.
[31] Fat distribution in women with HIV infection. J Acquir Immune Defic Syndr 2006;42(5):562-71.
[32] Bacchetti P, Gripshover B, Grunfeld C, et al. Fat distribution in men with HIV infection. J Acquir Immune Defic Syndr 2005;40(2):121-31.
[33] Batterham MJ, Garsia R, Greenop P. Prevalence and predictors of HIV-associated weight loss in the era of highly active antiretroviral therapy. Int J STD AIDS 2002;13(11):744-7.
[34] Chang E, Sekhar R, Patel S, Balasubramanyam A. Dysregulated energy expenditure in HIV-infected patients: a mechanistic review. Clin Infect Dis 2007;44(11):1509-17.
[35] Sutinen J, Yki-Jarvinen H. Increased resting energy expenditure, fat oxidation, and food intake in patients with highly active antiretroviral therapy-associated lipodystrophy. Am J Physiol Endocrinol Metab 2007;292(3):E687-E692.
[36] Sekhar RV, Jahoor F, White AC, et al. Metabolic basis of HIV-lipodystrophy syndrome. Am J Physiol Endocrinol Metab 2002;283 (2):E332-E337.
[37] Smith SR, de Jonge L, Zachwieja JJ, et al. Fat and carbohydrate balances during adaptation to a high-fat. Am J Clin Nutr 2000;71(2): 450-7.
[38] Schrauwen P, van Marken Lichtenbelt WD, Saris WH, Westerterp KR. Changes in fat oxidation in response to a high-fat diet. Am J Clin Nutr 1997;66(2):276-82.
[39] Segal KR, Edano A, Blando L, Pi-Sunyer FX. Comparison of thermic effects of constant and relative caloric loads in lean and obese men. Am J Clin Nutr 1990;51(1):14-21.
[40] Meylan M, Henny C, Temler E, Jequier E, Felber JP. Metabolic factors in the insulin resistance in human obesity. Metabolism 1987;36(3): 256-61.
[41] Valtuena S, Salas-Salvado J, Lorda PG. The respiratory quotient as a prognostic factor in weight-loss rebound. Int J Obes Relat Metab Disord 1997;21(9):811-7.