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Body composition and metabolic effects of a diet and exercise weight loss regimen on obese, HIV-infected women

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Abstract

HIV has classically been a wasting disease. However, in the United States, obesity is increasingly common among HIV-infected individuals receiving effective antiviral treatment. The risks of obesity are unclear in HIV, although the increased prevalence of diabetes and cardiovascular disease in the presence or absence of obesity causes growing concern. This study aimed to assess the effects of weight loss (through energy restriction combined with aerobic and resistance exercise) on body composition, body fat distribution, resting energy expenditure, quality of life (QOL), strength and fitness, and metabolic risk factors in obese, HIV-infected women. Eighteen HIV-infected women with a body mass index of 30 or more completed a 12-week weight loss program. Before and after the intervention, body composition and fat distribution by dual energy x-ray absorptiometry and whole-body magnetic resonance imaging, resting energy expenditure by indirect calorimetry, QOL, strength, and fitness were measured. Insulin sensitivity by intravenous glucose tolerance test and circulating cardiovascular risk factors (including lipids, tissue plasminogen activator, and plasminogen activator inhibitor 1) were measured in a subset (n = 9). Daily food intake and total body weight decreased (mean ± SD) by 3195 ± 477 kJ and 6.7 ± 4.2 kg, respectively. Weight lost was 95.5% fat by dual energy x-ray absorptiometry or 6.2 L of subcutaneous adipose tissue, 0.7 L visceral adipose tissue, and 0.8 L skeletal muscle by magnetic resonance imaging. Resting energy expenditure fell approximately 419 kJ, strength and fitness increased by 28.9% ± 18.5% and 36.8% ± 41.6%, respectively, and QOL improved in 11 of 13 dimensions. There was significant insulin resistance in the subset with metabolic measurements at baseline, and at follow-up there was no improvement in fasting glucose, insulin, or insulin sensitivity, nor was there any change in fasting lipids, tissue plasminogen activator, or plasminogen activator inhibitor 1. There was no significant change in CD4 count or HIV viral load. In conclusion, moderate weight loss achieved by a short-term program of diet and exercise in obese HIV-positive women appears safe and induces loss of adiposity in both the subcutaneous adipose tissue and visceral adipose tissue regions. Despite reduced food intake, weight and fat loss, as well as improvements in strength, fitness, and QOL, the lack of improvement in metabolic parameters suggests that additional interventions may be necessary to reduce the risk of diabetes and cardiovascular disease in this population.

1. Introduction

Before the availability of effective antiretroviral agents, unintentional weight loss and depletion of fat-free mass (FFM) were common in HIV infection [1] and were associated with diminished quality of life (QOL) [2,3] and excess mortality [4,5]. Since the advent of highly active antiretroviral therapy in 1996, the incidence of malnutrition has decreased substantially and US deaths due to HIV have fallen from a peak of approximately 45 000 in 1995 to 15 000 annually since 1997. However, new abnormalities in nutritional status have arisen. Instead of returning to normal nutritional status, many HIV-infected individuals have developed a condition commonly referred to as "HIV-associated lipodystrophy" [6-8]. Morphological and pathologic aspects

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of HIV lipodystrophy include subcutaneous adipose tissue (SAT) depletion (lipoatrophy), visceral adipose tissue (VAT) accumulation, insulin resistance, and dyslipidemia. All except VAT accumulation have been definitively linked with individual antiviral agents, and combinations of medications worsen the effects [8].

An additional surprising finding is a mounting occurrence of obesity [9], often coupled with components of lipodystrophy. Obesity itself, as well as several features of lipodystrophy, have long been associated with adverse outcomes, notably premature or accelerated atherogenesis, in men [10] as well as women [11]. Many of the health risks of obesity are related to fat distribution (VAT/SAT ratio) rather than total fat content, as first observed almost 50 years ago [12]. The results of several epidemiologic studies indicate increased cardiovascular risk in the HIV-positive population [13,14]. Interventions to reduce risk of cardiovascular disease or diabetes in overweight but otherwise healthy individuals include weight loss through energy restriction, increased physical activity, or a combination of the two [15]. In people without HIV, weight loss has been effective in promoting both an improved lipid profile and increased insulin sensitivity [16].

The goals of weight loss in obese patients with insulin resistance include maintaining skeletal muscle and other lean tissues along with visceral fat reduction and improvements in metabolic parameters. In non-HIV populations, volitional weight loss through energy restriction results in loss of both fat and FFM, the proportion of which varies based upon the stringency of the diet and the baseline amount of body fat [17]. Preferential loss of visceral fat does not appear to differ based on the method of weight loss, but rather on the total amount of weight loss and the quantity and proportion of VAT before weight loss [18]. Studies in individuals without HIV indicate that increased physical exercise may mitigate losses of FFM [19,20]. In HIV-infected individuals, a pilot study suggested that exercise might be an effective method for treating fat redistribution [21]. Insulin sensitivity and cardiovascular risk were not measured in that study. A single case study in a man with lipodystrophy indicated that an exercise program combined with a moderate-fat, low glycemic index, high-fiber diet might improve aspects of lipodystrophy, including visceral fat, low-density lipoprotein cholesterol (LDL-C), and insulin resistance [22].

We hypothesized that, in obese HIV-positive women, significant weight loss could be achieved and that the proportion of visceral to subcutaneous fat lost would be related to the baseline quantity of visceral fat as well as the quantity of total weight loss. To evaluate the effects of the diet and exercise program on glucose metabolism, we conducted frequently sampled intravenous glucose tolerance tests (FSIVGTTs) in a subset of subjects. We hypothesized that irrespective of antiviral therapy, the decrease in fat mass and VAT/SAT would correlate with improvements in insulin resistance and other measurements, including fasting lipids, clotting factors, resting metabolic rate, objective measures of physical function (muscle strength and cardiorespiratory fitness), and subjective dimensions of QOL.

2. Subjects and methods

2.1. Study design

This 12-week prospective, longitudinal pilot study of an "open-label" weight reduction intervention combined a hypoenergetic (5024 kJ) diet and a program of aerobic and resistance exercise training. Subjects were studied between January 2001 and October 2002.

2.2. Subjects

Women enrolled in this study had to be older than 18 years, HIV-positive, and obese. Obesity was defined as a body mass index (BMI; kg/m^2) greater than 30 [23], and a maximum BMI of approximately 38 kg/m^2 was established as the upper limit for which the body composition equipment could provide valid measurements. Race was by self-definition. Participants had to be clinically stable and on a stable antiretroviral drug regimen for at least 4 weeks before enrollment, and without plans to change the regimen during the study period.

Women with any active opportunistic infection or malignancy were excluded. Diabetic subjects were included only if their blood glucose was under control by medication or diet. Women were excluded if they were pregnant or breast-feeding, had uncontrolled hypertension, or any condition that would prevent them from exercising or magnetic resonance imaging (MRI) (including claustrophobia and metal implants). Additional exclusions were based on self-reported medical history, including history of an eating disorder, for example, anorexia nervosa or bulimia; history of gallbladder disease; history of renal disease; or active substance abuse or methadone treatment. Participants in the metabolic substudy additionally had to be nondiabetic and with adequate venous access for the FSIVGTT. All subjects signed informed consent, and the protocol and consent form were approved by the St Luke's-Roosevelt Hospital Institutional Review Board and Radiation Safety Committee.

2.3. Diet and exercise

Subjects were counseled individually at baseline and throughout the trial period as needed, and participated in weekly group nutrition education classes. Dietary advice was based on behavior modification and the American Diabetes Association Exchange Lists [24] for a 5024-kJ hypoenergetic diet, with 50% of energy from carbohydrate, 30% from fat, and 20% from protein. Lessons encouraged avoidance of saturated fat and intake of low glycemic index and high-fiber foods. Subjects were provided with multivitamin and mineral supplements (Jarrow Formulas, Los Angeles, CA) to ensure adequate consumption of micronutrients while dietary intake was restricted.

Participants exercised for 90 minutes under the supervision of a trainer 3 times per week in the Human Performance Laboratory of the Body Composition Unit at St Luke's Hospital. They were asked to not change their physical activity otherwise. Aerobic exercise consisted of a 5-minute warm-up and 30 minutes of moderate intensity level and graded treadmill walking at 70% to 80% of estimated maximal heart rate. Heart rate was monitored using a portable heart rate monitor (Polar Vantage, Port Washington, NY). Progressive resistance exercise was performed on a multigym apparatus (Tuff Stuff, Task Enterprises, Pomona, CA) for 7 major muscle groups. Participants performed 3 sets of 10 different exercises at 8 to 10 repetitions for each set as per guidelines provided by The American College of Sports Medicine [25]. Participants were dropped from the study if they missed more than 5 exercise sessions.

2.4. Measurements

All reported measurements were made before and after the intervention, that is, at baseline and week 12. Assessments included dietary evaluation, physical function testing of one repetition maximum (1-RM) muscle strength and cardiorespiratory endurance, resting metabolic rate, QOL, body composition testing by MRI, dual-energy x-ray absorptiometry, total body potassium 40 (^{40}K) counting, total body water (TBW) and extracellular water (ECW), and anthropometrics (height, weight, skinfolds, circumferences). In a subset of nondiabetic participants with adequate venous access, laboratory analyses at these time points included insulin sensitivity assays, fasting blood lipid profiles, and tissue plasminogen activator (tPA) and plasminogen activator inhibitor 1 concentrations.

2.4.1. Food intake

Three-day food diaries were completed and analyzed before the study, and during the first, sixth, and twelfth weeks of the intervention to assess dietary change and adherence. All diaries were analyzed by the same nutritionist using the Food Processor computer software database program (version 8.0, ESHA Research, Salem, OR).

2.4.2. One repetition maximum strength test

Isotonic muscle strength was determined for 3 major muscle groups (pectorals, latissimus dorsi, quadriceps) using the 1-RM technique [26]. In our laboratory, reproducibility of 1-RM strength in HIV-infected persons is within 4% [27]. Changes in 1-RM results were used to indicate changes in strength resulting from progressive resistance exercise.

2.4.3. Cardiorespiratory endurance

Cardiorespiratory endurance was determined using an estimation of maximal oxygen consumption ($\dot{V}O_2$max) from a modified stress test using the Balke protocol [28]. Heart rate, blood pressure, and a 12-lead electrocardiogram were recorded and monitored during a period while the subject was at rest and during the last minute of each exercise stage and recovery period. Throughout the test, subjects rated their perceived exertion based on the 20-point Borg [29] scale, a measure of exercise intensity. Fitness was assessed as length of time on the treadmill before reaching 85% of estimated maximal heart rate and perceived effort during that time.

2.4.4. Resting metabolic rate

Resting metabolic rate (RMR) was determined by indirect calorimetry using a MMC Horizon metabolic cart (Sensormedics, Yorba Linda, CA).

2.4.5. Quality of life

Subjective perceptions of well-being and functional status (ie, QOL) were assessed at baseline and post-intervention using 5 standardized QOL measures, each of which has been previously validated in other groups. The Medical Outcomes Survey 36-item Short-Form Health Survey [30] was used to assess physical functioning and mental health, including physical, social, and role limitations as well as vitality (energy and fatigue). The depression and anxiety subscales of the Brief Symptom Inventory [31] were used to measure current psychological status. The 5-item Satisfaction with Life scale [32] measured overall happiness. The 13-item Sense of Coherence scale [33] has been widely used in HIV disease, including in minority women at risk for HIV [34], and describes an individual's beliefs regarding the fairness, manageability, and meaningfulness of their circumstances. The Life Distress Inventory is an 18-item questionnaire that measures self-reported distress across areas of social life and functioning [35].

2.4.6. Body composition

Anthropometric measurements were taken by expert technicians at the St Luke's Hospital Body Composition Unit using techniques recommended by Lohman [36].

Adipose tissue compartments (SAT, VAT, and intramuscular adipose tissue [IMAT]) and skeletal muscle (SM) were measured on a 1.5-T MRI scanner (General Electric, 6X Horizon, Milwaukee, WI). The method was slightly modified from that described by Ross and Rissanen [37]. Cross-sectional images of the total body were made with 10-mm slice thickness and 40-mm gaps between slices. Body size in excess of the scanner's field of view on individual slices required some (approximately 10%) to be acquired in 2 sections—left and right. In addition to whole-body results, regional values for adipose tissue and skeletal muscle were determined for the arms, legs, upper, and lower trunk. The same trained observer within the St Luke's Hospital Obesity Research Center Image Reading Center read all MRI scans. The coefficient of variation on repeated readings of the same 2 scans by this observer is 3.8% for total adipose tissue (TAT), 3.4% for SAT, 9.7% for VAT, 2.2% for SM, and an estimate 7.3% for IMAT. Images were

analyzed using VECT image analysis software (Martel, Montreal, CA) on a PC platform.

Body fat and FFM, including lean and bone mineral content, were assessed using dual energy x-ray absorptiometry (DXA; Lunar DPX, Lunar Radiation, Madison, WI) [38]. In addition to total body results, regional values for fat, lean and bone, were determined based on cut-points provided by the manufacturer. In our laboratory, the coefficient of variation (CV) for percentage of body fat is 3.3%. A negative serum pregnancy test was required within 2 weeks before each DXA scanning. Total body potassium (TBK) was measured to assess body cell mass using a 4-pi whole-body liquid scintillation counter of γ-rays produced from the natural decay of the ^{40}K radioisotope [39]. Body cell mass was calculated as milliequivalent of TBK $\times$ 0.0092 [40]. TBW and ECW were determined by tracer dilution using deuterium oxide and sodium bromide, respectively. Intracellular water (ICW), a direct measure of body cell mass (BCM), was calculated as the difference between TBW and ECW. Samples were analyzed by infrared spectrophotometry to determine TBW [41] and liquid chromatography to determine ECW [42].

2.4.7. Blood tests

Additional measurements were made in a subset of participants for a preliminary investigation of the effects of weight loss on metabolism. All blood samples were centrifuged at 4°C, aliquoted, and frozen at −80°C until assay. Glucose, insulin, total cholesterol, triglyceride, and high-density lipoprotein cholesterol concentrations were measured in serum collected while the subject was in the fasted state. Subjects were instructed to take nothing by mouth except water and required medications from midnight before all scheduled blood tests. Glucose and insulin were assayed in the Hormone and Metabolites core laboratory of the Obesity Research Center at St Luke's Hospital. Lipids were analyzed in the core laboratory of the Columbia University General Clinical Research Center. Total cholesterol and triglyceride concentrations were determined using standard enzymatic techniques (Roche Diagnostics, Basel, Switzerland). High-density lipoprotein cholesterol concentration was determined by direct measurement (Roche). Low-density lipoprotein cholesterol was calculated using the Friedewald formula [43]. Tissue plasminogen activator and plasminogen activator inhibitor 1 (PAI-1) concentrations were by enzyme-linked immunosorbent assays (Biopool International, Ventura, CA) in the Obesity Research Center core laboratory.

2.4.8. Frequently sampled intravenous glucose tolerance test

Peripheral insulin sensitivity was estimated by the FSIVGTT. The measurement was made in the fasting state and within 10 days of the onset of the menstrual cycle in women with regular cycles. The 3.5-hour test was conducted using intravenous administration of glucose (0.3 g/kg at time 0) and insulin (0.03 U/kg body weight) and frequent blood sampling through an intravenous catheter [44]. We used a minimum model of glucose disposal and insulin secretion and the MINMOD computer program [45].

2.5. Safety

At baseline and monthly during the intervention, basic physical examinations were performed, medical histories were taken, and blood was drawn for a fasting basic metabolic panel and complete blood count with differential analyzed in the clinical laboratory of St Luke's Hospital. CD4 lymphocyte counts and plasma HIV RNA (viral load) values were requested from the primary care physician of each study participant before and after the study.

2.6. Statistical analysis

The pre- to posttreatment effects for dependent variables were analyzed by Student t test for paired comparisons. Nominal data were analyzed by χ^2 or Fisher exact test. Hypotheses were tested by regression analysis. To test the hypothesis that a higher amount of visceral fat in relation to subcutaneous fat would be associated with greater insulin resistance and would blunt the improvement in metabolic parameters associated with this program of hypoenergetic feeding and exercise, we performed regression analysis with insulin resistance as the dependent variable and body fat compartments as the main independent variables.

The hypothesis that the relative loss of VAT and SAT during weight loss was related to the amount of baseline VAT irrespective of fat distribution was tested by plotting the relative changes in VAT and SAT as a function of baseline values. The primary end point was the selectivity index (SI) as described by Smith and Zachwieja [18]—% change in VAT/% change in fat. A number (confidence) significantly greater than 1 is considered to reflect preferential loss of VAT, whereas a number significantly less than 1 is considered to reflect preferential sparing of VAT. In addition, the mean result from all subjects for baseline L4 through L5 VAT/SAT was compared with SIs from studies reviewed by the same authors.

Analyses were performed using SAS statistical software (versions 8.2 and 9.1; SAS Institute, Cary, NC). Data are presented as mean $\pm$ SD. Significance for all comparisons was set at $P < .05$.

3. Results

3.1. Subjects

Of 45 women screened, 39 were eligible for the protocol and underwent some or all of the baseline testing. Ten women withdrew from the study during the baseline testing period, primarily because of scheduling conflicts and distaste for the testing involved, including previously unidentified claustrophobia, plus investigator decisions

Table 1
Baseline characteristics of participants who completed or did not complete the 12-week study intervention, plus characteristics of the subset of participants who had metabolic measurements at baseline and week 12

	Completed intervention	All noncompleters	*P* (completers vs noncompleters)
n	18	21	
Age (y)	41.8 ± 7.5	41.3 ± 7.2	.80[a]
Menstrual status, n (%)[b]			.06[c]
Premenopausal	7 (47)	13 (65)	
Perimenopausal	4 (27)	3 (15)	
Postmenopausal	4 (27)	4 (20)	
Race, n (%)			.04[c]
White	3 (16.7)	2 (8.7)	
Black	10 (55.6)	15 (73.9)	
Hispanic	4 (22.2)	4 (17.4)	
Other	1 (5.6)	0	
Smoker, n (%)[b]			.08[c]
Never	3 (19)	5 (25)	
Past	5 (31)	5 (25)	
Current	8 (50)	10 (50)	
CD4 count (cells/mm^3)[b]	519 ± 228	813 ± 387	.08[a]
HIV viral load, n (%) undetectable[b]	8 (53)	4 (40)	NS[d]
Current antiretrovirals, n (%)[b]			[c]
NRTI	12 (92)	11 (100)	.54
NNRTI	7 (54)	6 (55)	.32
PI	7 (39)	7 (41)	.27
BMI (kg/m^2)	35.6 ± 3.3	33.7 ± 2.8	.06[a]
Waist-hip ratio	0.87 ± 0.06	0.90 ± 0.08	.24[a]
Body fat (% of body weight)	42.7 ± 8.2	43.5 ± 4.9	.74[a]

Data are expressed as mean ± SD unless otherwise noted. NS indicates not significant; NRTI, nucleoside reverse transcriptase inhibitor, NNRTI, nonnucleoside reverse transcriptase inhibitor, PI, protease inhibitor.

[a] Computed by Student *t* test for means.
[b] Data not available for all subjects.
[c] Computed by 1-tailed Fisher exact test.
[d] Computed by χ^2 test.

based on subjects' lack of adherence to appointments. Among the 28 women who began the diet and exercise program there was a dropout rate of 36%, which is similar to the 35% rate seen in a prior exercise study in our laboratory with malnourished women [2]. Missed visits were the major factor in dropouts during the intervention period. Only one woman dropped out because of an unrelated adverse event, an ear infection.

Characteristics of the women who participated in the study intervention are shown in Table 1. There was no difference between completers and noncompleters in age, waist-hip ratio, or percentage of body fat. There was a trend toward a higher BMI in the women who completed the study. There was a significant difference in race between completers and noncompleters by 1-tailed Fisher exact test, with a smaller proportion of black women completing the intervention than beginning it. There was no difference between groups in current antiretroviral therapy, and the proportion of women with undetectable HIV viral loads was not statistically different, but there was a trend toward higher CD4 counts in those who did not complete the trial. There was no difference between groups in any measure of strength or cardiovascular fitness at baseline (data not shown, all $P > .10$). The subset of 9 nondiabetic women with adequate venous access, who had FSIVGTTs and other blood tests before and after the intervention, included a higher proportion of Hispanic women and had higher CD4 counts, but did not differ otherwise.

3.2. Food intake and resting metabolic rate

Average food intake decreased from 8709 ± 3228 at baseline to 5514 ± 2751 kJ/d after the 12-week intervention. The composition of food intake changed from baseline to be more consistent with dietary instruction. Carbohydrate intake rose from 46% of total energy expenditure to 48% and protein intake from 17% to 22%, whereas fat fell from 36% to 31% of total intake. Resting metabolic rate fell significantly between baseline and week 12 (7025 ± 909 vs 6569 ± 976 kJ, $P = .006$). There was no relationship between the drop in metabolic rate and race nor any change in energy intake, body weight, body composition, or strength (data not shown, all $P \geq .10$).

Table 2
Anthropometric measurements before and after the 12-week diet and exercise intervention in obese HIV-infected women (n = 18)

	Baseline[a]	Follow-up[a]	Change[b]	*P*
Weight (kg)	92.1 ± 9.6 (73.3, 107.8)	85.4 ± 10.4 (68.9, 105.6)	−6.7 ± 4.2 (−7.3 ± 4.6)	<.0001
BMI (kg/m^2)	35.6 ± 3.3 (29.7, 40.8)	33.0 ± 3.3 (27.0, 38.2)	−2.6 ± 1.7 (−7.3 ± 4.6)	<.0001
Waist circumference (cm)	103.0 ± 8.1 (92.2, 118.4)	97.0 ± 8.2 (83.0, 109.5)	−6.1 ± 5.8 (−5.8 ± 5.6)	.0003
Waist-hip ratio	0.87 ± 0.06 (0.78, 1.03)	0.86 ± 0.07 (0.71, 1.01)	−0.01 ± 0.05 (−1.2 ± 6.0)	.35
Mid-arm circumference (cm)	36.7 ± 2.9 (30.5, 40.8)	35.4 ± 3.3 (30.5, 40.7)	−1.3 ± 1.2 (−3.5 ± 3.4)	.23
Chest circumference (cm)	115.3 ± 5.7 (105.6, 125.7)	109.9 ± 5.6 (101.5, 121.2)	−5.4 ± 3.6 (−4.7 ± 3.1)	<.0001
Thigh circumference (cm)	62.6 ± 5.5 (52.9, 73.1)	60.2 ± 5.6 (51.5, 72.5)	−2.4 ± 2.3 (−3.8 ± 3.4)	.21
Triceps skinfold (cm)	2.8 ± 1.3 (0.6, 5.2)	2.4 ± 1.1 (0.3, 3.8)	−0.4 ± 0.7 (−11.5 ± 27.7)	.32
Biceps skinfold (cm)	1.7 ± 0.8 (0.3, 3.0)	1.2 ± 0.6 (0.2, 2.5)	−0.5 ± 0.3 (−26.3 ± 26.1)	.04
Abdominal skinfold (cm)	5.1 ± 1.3 (2.5, 6.5)	4.0 ± 1.3 (2.0, 6.3)	−1.1 ± 0.7 (−22.4 ± 13.9)	.01
Thigh skinfold (cm)	4.6 ± 1.6 (1.6, 6.5)	3.6 ± 1.4 (1.4, 5.6)	−1.1 ± 1.2 (−19.1 ± 27.1)	.04

[a] Data expressed as mean ± SD (minimum, maximum).
[b] Data expressed as mean ± SD (% ± SD).

Table 3
Whole-body composition before and after the 12-week diet and exercise intervention in obese HIV-infected women (n = 18)

	Prestudy	Post-study	Change	% Change	*P*
Skeletal muscle (L)[a]	22.8 ± 2.6	22.0 ± 3.1	−0.83 ± 1.0	−3.8 ± 4.2	.0035
VAT (L)[a]	3.8 ± 1.1	3.1 ± 0.9	−0.69 ± 0.51	−17.2 ± 10.6	<.0001
SAT (L)[a]	42.5 ± 9.9	36.3 ± 9.9	−6.2 ± 3.9	−14.9 ± 9.5	<.0001
VAT/SAT	0.093 ± 0.03	0.091 ± 0.03	−0.0027 ± 0.0075	−2.62 ± 8.09	.15
Intramuscular adipose tissue (L)[a]	2.56 ± 1.0	2.54 ± 1.0	−0.02 ± 0.35	0.60 ± 15.6	.79
Total adipose tissue[a]	48.9 ± 10.6	42.0 ± 10.5	−6.9 ± 4.5	−14.3 ± 9.2	<.0001
Lean (kg)[b]	49.3 ± 5.6	48.9 ± 5.0	−0.33 ± 1.5	−0.52 ± 3.0	.37
Fat (kg)[b]	39.4 ± 10.3	32.9 ± 10.1	−6.4 ± 3.7	−16.7 ± 10.3	<.0001
Fat (%)[b]	43.9 ± 8.4	39.5 ± 8.6	−4.4 ± 3.0	−10.2 ± 7.6	<.0001
Bone calcium (kg)[b]	0.93 ± 0.13	0.92 ± 0.13	0.008 ± 0.03	−0.87 ± 2.8	.23
Bone mineral (kg)[b]	2.45 ± 0.34	2.43 ± 0.35	0.02 ± 0.07	−0.86 ± 2.7	.23
Bone density (g/cm^2)[b]	1.17 ± 0.10	1.17 ± 0.11	0.01 ± 0.02	0.51 ± 1.5	.14
TBW	39.2 ± 4.1	38.8 ± 3.9	−0.3 ± 1.5	−0.60 ± 3.8	.45
Intracellular water	19.9 ± 2.7	19.6 ± 1.9	−0.3 ± 2.2	−0.70 ± 10.0	.55
TBK (mEq)	2992 ± 321	2879 ± 244	−113 ± 189	−3.4 ± 6.0	.02
BCM (kg)	24.8 ± 2.7	23.9 ± 2.0	−0.94 ± 1.6	−3.4 ± 6.0	.02

Pre- and post-study comparisons by paired *t* test. VAT indicates visceral adipose tissue; SAT, subcutaneous adipose tissue; TBW, total body water; TBK, total body potassium; BCM, body cell mass.
[a] Body composition measurement by MRI.
[b] Body composition measurement by DXA.

3.3. Body composition changes

Body size changes are shown in Table 2. Mean body weight and BMI at baseline were 92.1 kg and 35.6 kg/m^2, respectively. The average loss after 12 weeks was 6.7 kg, or 7.3% of initial body weight. This resulted in a mean change of BMI of 2.6 kg/m^2. Four women (22%) changed from a BMI in the obesity range to an overweight BMI. There was a significant reduction in waist circumference from 103.0 ± 8.1 to 97.0 ± 8.2 cm, but no change in waist-hip ratio. Chest circumference and biceps, abdominal, and thigh skinfolds also decreased significantly.

Body composition (Table 3) at baseline averaged 49.3 ± 5.6 kg lean, 39.4 ± 10.3 kg (43.9% ± 8.4%) fat, and 2.45 ± 0.34 kg bone mineral by DXA. The composition of weight loss averaged 6.4 kg (94%) fat and 0.4 kg (6%) FFM. By MRI, baseline body composition included 3.8 ± 1.1 L (range, 2.4-5.9 L) of VAT, 42.5 ± 9.9 L (range, 23.3-60.8 L) SAT, and 22.8 ± 2.6 L (range, 19.4-31.2 L) skeletal muscle. There were highly significant losses of 0.7 L (17%) of VAT and 6 L (15%) of SAT (both $P < .0001$), whereas skeletal muscle dropped by 0.8 L (4%; $P = .0035$). There was no change in the proportion of VAT to SAT (0.093 ± 0.028 at baseline vs 0.091 ± 0.027 at week 12, $P = .15$). There was also no significant change in IMAT, in any measure of bone mineral content by DXA, nor in body water content; however, consistent with the loss of skeletal muscle there was a statistically significant reduction of 0.9 kg (3.4%) in BCM by TBK.

Regional body composition shows trends toward significant loss of skeletal muscle (MRI) only from the upper trunk ($P = .09$) and loss of lean mass (DXA) only from the arms ($P = .07$). There were no regional differences in loss of adipose tissue (MRI) or fat (DXA). No body region showed any change of bone mineral content, and there was no difference based on menopausal status.

There was significant correlation between weight loss and loss of SAT, VAT, and TAT (all $P < .001$), but not between weight change and change in SM ($P = .18$) or IMAT ($P = .11$). Change in VAT correlated directly with changes in SAT ($r = 0.75$, $P = .0003$) and IMAT ($r = 0.53$, $P = .02$), and with VAT/SAT ratio at baseline ($r = -0.59$, $P = .01$). Visceral adipose tissue loss was related to total fat loss ($r = 0.63$, $P = .0055$) and was greater in women with more VAT at baseline ($r = 0.63$, $P = .004$). The mean VAT SI [18] was 1.26 ± 0.75. Losses of both SAT and VAT correlated with reduction in waist circumference ($P < .001$ and $P = .03$, respectively), but not with change in waist-hip ratio ($P = .6$ and .5). In contrast, change in IMAT correlated with change in waist-hip ratio ($r = 0.5$, $P = .0495$), but not in waist circumference.

3.4. Exercise

Participants completed an average of 35 (22 minimum and 38 maximum) exercise sessions of aerobic and resistance training. Pectoral, latissimus dorsi, and quadriceps strength increased an average of 5.7 ± 3.6, 9.3 ± 5.7, and 9.0 ± 6.0 kg, respectively (all $P < .0001$), which is around 30% higher than at baseline. The amount of time on the treadmill before reaching 85% of estimated maximum heart rate increased from 8.8 ± 3.3 to 10.9 ± 2.4 minutes (36.8% ± 41.6%, $P = .0015$), whereas subjects' perceived exertion rating decreased from 14.9 ± 2.1 to 13.7 ± 1.5 (−7.2% ± 14.8%, $P = .03$). Changes in strength and measures of fitness did not correlate with weight change (all $P > .30$).

3.5. Quality of life

At baseline, there was no difference in any of the 13 dimensions of self-reported QOL between those who did or did not complete the trial (data not shown, all $P \geq .10$).

Table 4
Quality of life questionnaire results before and after the 12-week diet and exercise intervention in obese HIV-infected women (n = 13)

	Baseline	Week 12	*P*
Limitations in physical activity due to health problems[a]	23.0 ± 4.3	26.8 ± 4.1	.004
Limitations in role activity due to health problems[a]	6.2 ± 1.5	53.8 ± 37.4	<.0001
Bodily pain[a]	8.0 ± 2.3	9.4 ± 2.2	.027
General health[a]	16.0 ± 4.2	18.6 ± 5.0	.034
Vitality[a]	13.0 ± 4.1	17.8 ± 4.2	.0006
Limitations in social activities[a]	7.7 ± 2.7	9.0 ± 1.5	.048
Limitations in role activity due to emotional problems[a]	4.8 ± 1.4	5.6 ± 0.9	.043
General mental health[a]	22.9 ± 5.3	24.9 ± 6.0	.13
Sense of coherence composite[b]	35.2 ± 7.8	39.5 ± 5.7	.0024
Satisfaction with life[c]	17.1 ± 7.1	22.5 ± 8.2	.020
Level of distress[d]	41.1 ± 21.5	31.9 ± 22.3	.0039
BSI anxiety subscale[e]	0.56 ± 0.63	0.39 ± 0.50	.32
BSI depression subscale[e]	0.99 ± 1.2	0.32 ± 0.60	.018

Note that for most measures, the higher the score the greater the perceived QOL, but a higher score reflects greater distress, anxiety, and depression in the last 3 measures reported. Data are expressed as mean ± SD. Results were compared by paired *t* test. BSI indicates Brief Symptom Inventory.

[a] Range of possible scores: 0 to 100.
[b] Range of possible scores: 13 to 52.
[c] Range of possible scores: 5 to 35.
[d] Range of possible scores: 18 to 126.
[e] Range of possible scores: 0 to 4.

None of the baseline scores of the QOL measures correlated with changes in energy intake or strength experienced through the intervention phase. Women with greater self-perceived limitation in ability to enact social roles (ie, perform work or other daily activities) due to health problems at baseline weighed more ($r = .48$, $P = .052$) and lost less weight over the 12 weeks ($r = -0.52$, $P = .033$). Several measures of baseline QOL functioning were related to the level of change in subjects' treadmill stress test time. This is particularly notable for the subjects' life distress score ($r = -0.54$, $P = .02$), the level of distress they feel across 18 topic areas, and their satisfaction with life scores ($r = 0.62$, $P = .006$). There was statistical improvement in 11 of 13 dimensions of self-reported QOL by week 12 (Table 4). However, there was no change in either the sum or individual aspects of general mental health measured by the Medical Outcomes Survey 36-item Short-Form Health Survey or of anxiety measured by the Brief Symptom Inventory. There was no relationship between the amount of change in any of the QOL dimensions and changes in energy intake, body weight, fitness, or strength (all $P > .10$).

3.6. Metabolism

The subset of women in whom metabolic measurements were made did not differ at baseline from other participants in body weight, BMI, VAT, SAT, SM, or fitness (data not shown, all $P \geq .20$). Although the metabolic subset exhibited greater strength (sum of 1-RM measures) at baseline ($P = .01$), change in strength over 12 weeks was not statistically different in the 2 groups, nor were changes in body weight, body composition, or fitness (all $P \geq .10$). In the metabolic subset as in the entire group, there was a significant loss of 6% of total body weight, including total fat, SAT, and VAT, but no change in IMAT or SM.

After weight loss, there were no changes in mean fasting glucose (99.9 ± 13.9 vs 95.8 ± 9.2, $P = .36$), fasting insulin (26.4 ± 19.3 vs 26.5 ± 21.7, $P = .97$), or insulin sensitivity index during FSIVGTT ($P = .80$). There was no correlation between change in any marker of glucose metabolism and any change in weight, percentage of body fat, total or regional SM, SAT, VAT, or IMAT (all $P \geq .10$). By the nonparametric Wilcoxon 2-sample test, there was no relationship between change in insulin sensitivity and current protease inhibitor or nonnucleoside reverse transcriptase inhibitor therapy (both $P = .61$).

There was no significant change in mean fasting lipid, tPA, or PAI-1 concentrations after the intervention (data not shown). There was no correlation between changes in weight and changes in lipids, tPA, or PAI-1, except LDL-C change correlated negatively with changes in weight ($r = -0.67$, $P = .07$) and SAT ($r = -0.74$, $P = .037$). There was no correlation between change in triglycerides and change in VAT.

3.7. Safety

There were few adverse events and no serious adverse events during this study. There was no significant change in CD4 count (573 ± 255 vs 539 ± 173, $P = .61$) or HIV viral load in the 10 women for whom these measurements are available before and after the study.

4. Discussion

This is the first report of a diet and exercise intervention study designed to promote weight loss in obese HIV-infected women. Obesity has become an unexpected health problem in HIV-infected women. The positive effects of highly active antiretroviral therapy, including increased life expectancy, combined with physical inactivity and overcon-

sumption of high-energy dietary supplements, support this trend. Some women stop using illicit drugs when HIV is diagnosed, which also promotes weight gain [46]. There continues to be fear of "wasting," and some patients take active measures to increase body weight and avoid weight loss as prophylaxis against wasting. We have shown that a diet and exercise program can be implemented for, and promote significant weight loss and body composition changes in, HIV-positive women in an urban environment. Weight, body composition, strength, and fitness all improved as predicted based on previous studies in HIV-uninfected individuals. Changes in BMI and body composition are also similar to those seen in the case study of an HIV-infected man reported by Roubenoff et al [22].

An important finding in a subset of participants in this study was a lack of improved insulin sensitivity and other surrogate markers of cardiovascular risk (lipids, tPA, PAI-1) in HIV-infected women despite weight and body fat loss. These results are inconsistent with the significant impact of diet and exercise in non–HIV-infected obese populations who lose similar relative amounts of weight [47,48]. There has been only one case report of an individual who improved LDL-C and insulin sensitivity after weight loss by exercise [22]. In that case, serum insulin fell from 7.9 to 4.4 μIU/mL over 4 months, whereas mean insulin concentration in the women reported here went from 26.4 to 26.5 μIU/mL over 3 months. The difference may be related to the fact that our subjects began with more insulin resistance, which may be related to their relative obesity, with a mean BMI at baseline of 35.8 in the metabolic subset vs his 29.9 kg/m^2. A minor nonsignificant (186.3 $\pm$ 42.2 vs 168.1 $\pm$ 33.0 mg/dL, P = .12) decrease in mean cholesterol was seen in this study, but there was inadequate power (power = 0.39) to detect a significant difference of this size with our small sample. Other potential reasons for the lack of metabolic response in the HIV group include the effects of antiviral agents. Both nucleoside reverse transcriptase inhibitors and protease inhibitors have been shown to promote insulin resistance, the former via mitochondrial toxicity and the latter by a direct effect of the GLUT4 glucose transport molecule [49]. The implication of these findings is that the effects of lifestyle changes, such as diet and exercise, may be reduced in HIV compared with non-HIV conditions. In this case, pharmacologic strategies for insulin resistance might be more effective than diet and exercise alone. The value of combination interventions was highlighted by Driscoll et al [50] who reported that metformin in combination with exercise training increased insulin sensitivity more than metformin alone.

We hypothesized that the proportion of visceral to subcutaneous fat lost would be related to the baseline quantity of visceral fat as well as the quantity of total weight loss, rather than to the baseline ratio of visceral and subcutaneous fat. Our results are consistent with those from non-HIV weight loss studies reviewed by Smith and Zachwieja [18], with the quantity of VAT loss related to total fat loss and greater loss in women with more VAT at baseline. The mean VAT SI [18] in the current study was 1.26 $\pm$ 0.75, indicating a preferential loss of VAT over SAT, and the relationship between SI and baseline VAT/SAT was similar to that seen in other studies.

Weight loss by dietary restriction alone results in a notable reduction in RMR in non–HIV-infected individuals [51]. However, when restricted food intake is combined with exercise, many studies observe preservation of RMR [52,53]. In contrast, the HIV-positive subjects in this study experienced significant reductions in RMR despite exercise and improvements in strength and fitness. Further studies are needed to determine whether this reduction in RMR is long-lasting or due to immediate energy restriction.

Most investigations of the effects of exercise in HIV-infected patients have been with malnourished men and women before and after 8 to 14 weeks of resistance training. Reported results include increased muscle strength [2,54-56] and cardiopulmonary performance [57]. The results of the current study support the finding that HIV does not prevent these positive effects of exercise. Other findings in HIV malnutrition treated with exercise include increased fat free and BCM [2,55] as well as QOL [2]. Many studies [19,52,58] in obese HIV-uninfected women indicate a role of exercise in weight loss, with greater loss of fat and less of FFM vs diet alone. Garrow and Summerbell [20] performed a meta-analysis of 28 concurrent diet-exercise studies (pooled n = 258 women) finding that, with a diet-induced 10-kg reduction in body weight, the addition of exercise decreased the absolute loss of FFM from 2.2 to 1.7 kg. Another meta-analysis [19] found that, in dieting women, the addition of exercise significantly reduced relative FFM loss from 24% to 11%. In this study, despite the potential catabolic effects of chronic HIV infection, FFM accounted for only 6% of total weight loss.

There are relatively few studies of the effects of exercise upon regional body fat distribution. Studies in HIV-negative women have had divergent results. Ross and Rissanen [37] found that moderate energy restriction combined with either resistance or aerobic exercise treatment produced significant reductions in both VAT and SAT, as assessed by MRI, in obese women. Two studies looked at exercise without energy restriction. In the first, older women of normal weight performing resistance exercise experienced no change in body weight or total fat mass, but a significant decrease in intra-abdominal fat, observed on computed tomography scans [58]. In the other study, aerobic training induced significant total fat loss (computed tomography scan) in obese women, with the greatest fat reduction observed as subcutaneous abdominal fat [59].

In the obese HIV-infected women in this study, baseline VAT/SAT was relatively low and did not appear to reflect a preponderance of excess visceral fat or loss of subcutaneous fat. We found that, on average, only 10% of total adipose tissue loss was from the visceral compartment. Based on the low VAT/SAT ratio at baseline, this relatively small amount

of VAT loss is consistent with the results of weight loss studies in uninfected men and women [18]. The lack of a greater fall in VAT, as well as the lack of change in another adipose tissue compartment related to insulin sensitivity, specifically IMAT, could help explain why insulin resistance did not improve after diet and exercise.

Concentrations of tPA and PAI-1 are primarily used for research purposes, are associated with obesity, insulin resistance, and inflammation, and are considered indicative of cardiovascular risk [60-62]. Both have previously been found to be elevated in HIV-infected patients with fat redistribution, and concentrations fell during treatment with metformin [63]. Concentrations of tPA also fell during antiretroviral therapy with indinavir or amprenavir in previously untreated individuals, despite increased insulin resistance with indinavir [64]. However, consistent with our other metabolic findings, this study found no change in these or other more traditional circulating indicators of cardiovascular risk in response to our intervention.

Limitations of the current study include its small number of subjects and short-term nature, which prevent us from conclusively reporting our results. However, strengths of this study include sophisticated measurements of body composition and fat distribution changes, measurements of strength and fitness, as well as direct measurements of insulin sensitivity by FSIVGTT. Given the increasing prevalence of obesity and abdominal fat distribution in HIV-infected individuals, it is of tremendous importance that larger, controlled studies be conducted to confirm our findings.

In summary, desired body weight and fat loss were safely promoted through dietary restriction and an exercise program in a multiracial urban population of obese, HIV-infected women. This program largely maintained skeletal muscle and significantly improved strength and fitness. The process also had a significant positive effect on participants' self-reported QOL, especially a reduction in perceived limitations in ability to work or perform daily activities due to health problems, but also including improved vitality and life satisfaction. In contrast, there was an unexpected inability to improve metabolic parameters.

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