Exercise Training in HIV-1–Infected Individuals with Dyslipidemia and Lipodystrophy

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ABSTRACT

TERRY, L., E. SPRINZ, R. STEIN, N. B. MEDEIROS, J. OLIVEIRA, and J. P. RIBEIRO. Exercise Training in HIV-1–Infected Individuals with Dyslipidemia and Lipodystrophy. *Med. Sci. Sports Exerc.*, Vol. 38, No. 3, pp. 411–417, 2006. **Purpose:** Highly active antiretroviral therapy has improved the prognosis of human immuno deficiency virus type 1 (HIV-1)–infected individuals, but it has been associated with the development of metabolic and fat distribution abnormalities known as the lipodystrophy syndrome. This study tested the hypothesis that aerobic exercise training added to a low-lipid diet may have favorable effects in HIV-1–infected individuals with dyslipidemia and lipodystrophy. **Methods:** Thirty healthy subjects, carriers of HIV-1, with dyslipidemia and lipodystrophy, all of whom were using protease inhibitors and/or non-nucleoside reverse transcriptase inhibitors, were randomly assigned to participate in either a 12-wk program of aerobic exercise or a 12-wk stretching and relaxation program. All subjects received recommendations for a low-lipid diet. Before and after intervention, peak oxygen uptake, body composition, CD4, viral load, lipid profile, and plasma endothelin-1 levels were measured. **Results:** Peak oxygen uptake increased significantly in the diet and exercise group (mean ± SD: $32 ± 5$ mL·kg^{-1}·min^{-1} before; $40 ± 8$ mL·kg^{-1}·min^{-1} after) but not in the diet only group ($34 ± 7$ mL·kg^{-1}·min^{-1} before; $35 ± 8$ mL·kg^{-1}·min^{-1} after). Body weight, body fat, and waist-to-hip ratio decreased significantly and similarly in the two groups. There were no significant changes in immunologic variables in either group. Likewise, plasma triglycerides, total cholesterol, and HDL cholesterol levels did not change significantly in either group. Plasma endothelin-1 levels were elevated in both groups and presented no significant changes during the study. **Conclusion:** HIV-seropositive individuals with lipodystrophy and dyslipidemia submitted to a short-term intervention of low-lipid diet and aerobic exercise training are able to increase their functional capacity without any consistent changes in plasma lipid levels. **Key Words:** AIDS, AEROBIC EXERCISE, HIGHLY ACTIVE ANTIRETROVIRAL THERAPY, CHOLESTEROL, ENDOTHELIN

In the past few years, the introduction of combination antiretroviral therapy has delayed the progression of human immunodeficiency virus type 1 (HIV-1) infection and has prolonged the survival of patients (29). However, opportunistic diseases related to HIV-1 have been replaced by metabolic and fat distribution abnormalities known as the lipodystrophy syndrome. The pathophysiologic mechanisms responsible for these abnormalities remain unclear, and a causal link to a specific drug or class of drugs is uncertain. Protease inhibitors, which effectively inhibit replication of HIV-1, were initially associated with some metabolic abnormalities, such as hyperlipidemia, insulin resistance, and body changes characterized by peripheral fat wasting and central adiposity (4,17). Recent reports have also implicated the non-nucleoside reverse transcriptase inhibitor efavirenz with the lipodystrophy syndrome (20).

Metabolic and fat distribution abnormalities that characterize the lipodystrophy syndrome represent a potential health risk. Cardiovascular complications, such as myocardial infarction and stroke, have been described in HIV-1–positive patients who are receiving active antiretroviral therapy (18). These reports have raised the question of whether there is an increased risk of atherosclerotic disease in such patients.

In normal individuals, regular physical activity is associated with favorable changes in certain blood lipids, in particular increased plasma HDL cholesterol, and reduction in plasma triglyceride as well as the ratio of total cholesterol

to HDL cholesterol (9). Based on this information, current guidelines recommend exercise training as first-line nondrug therapy for HIV-1–positive individuals with dyslipidemia who receive highly active antiretroviral therapy (7). However, most controlled trials on the effects of aerobic exercise training in HIV-1–infected individuals were conducted before the widespread use of antiretroviral therapy (13,16,23,25). The few studies that have focused on the effects of aerobic and resistance exercise training on hyperlipidemia associated with antiretroviral therapy suggest that these interventions may be effective in improving the lipid profile, but none of these studies included a control group to account for co-intervention (12,26,28). Therefore, we conducted the present randomized trial to examine the effects of the addition of aerobic exercise training to a low-lipid diet on variables associated with hyperlipidemia, functional capacity, immune function, and body composition in HIV-1–infected individuals with lipodystrophy and dyslipidemia. Our hypothesis was that aerobic exercise training would improve the lipid profile, functional capacity, and body composition, without compromising the immune system.

METHODS

Patients. Study participants were patients of the Hospital de Clínicas de Porto Alegre, a national reference center for acquired immunodeficiency syndrome in southern Brazil. This institution provides care for approximately 800 HIV-infected adults. A total of 42 patients, 26 men and 16 women, carriers of the HIV-1 virus, were recruited for the study. All met the Centers for Disease Control and Prevention modified criteria for immunodeficiency syndrome (5). They were physically inactive for at least 6 months before entry, had no contraindications for exercise training, and were currently following a combination antiretroviral therapy regimen, including one or two protease inhibitors (ritonavir, indinavir, saquinavir, nelfinavir, amprenavir, lopinavir-ritonavir) and/or a non-nucleoside reverse transcriptase inhibitor, efavirenz, for at least 6 months before enrollment. Participation was limited to patients who had hyperlipidemia associated with lipodystrophy syndrome who were not on lipid-lowering therapy and not taking any other medications, including anabolic steroids. The criteria for selection were total cholesterol level between 200 and 400 mg·dL^{-1} and/or triglyceride level between 200 and 700 mg·dL^{-1}. Patients with diagnosis other than lipodystrophy syndrome, using medication other than combination antiretroviral therapy, drug users, or those with physical disability or history suggestive of clinical deterioration were not recruited. The protocol was approved by the committee for ethics in research of the Hospital de Clínicas de Porto Alegre, and all subjects signed a written informed consent.

Protocol. Eligible patients had medical history, physical examination, and 12-h fasting blood samples. Those who met the inclusion criteria were then randomized to participate in the diet and exercise group or the diet-only group for

12 wk. The randomization was made by blocks of four subjects (11). Before and after the intervention, 12-h fasting venous blood samples were collected for the following measurements: number of CD4 T lymphocytes, plasma HIV-1 RNA, triglycerides, total and HDL cholesterol, endothelin-1, hemoglobin, albumin, and glucose. Likewise, before and after intervention, measurements of height, body weight, skin fold thickness, and waist and hip circumferences were performed, and a maximal cardiopulmonary exercise test was conducted.

All patients met a 3-d food record (two weekdays and one weekend day) before the program. Dietary intake was assessed using computerized food record analysis (version 2.5, Escola Paulista de Nutrição, São Paulo, Brazil). A registered dietitian reviewed each subject's 3-d food record and provided detailed dietary and behavioral counseling during the 3 months of the study. As indicated for HIV-positive patients (10), recommendations were given to achieve a daily caloric intake of 30 kcal·kg^{-1} of body weight for women and 40 kcal·kg^{-1} of body weight for men, with a protein intake of 2.0 g·kg^{-1} of body weight for women and 2.5 g·kg^{-1} of body weight for men. Fifty-seven percent of calories were given as carbohydrates, 23% as fat, and 15% as saturated fat. The daily recommended intake of cholesterol was 200 mg.

Aerobic exercise and stretching programs. The aerobic exercise program consisted of 36 sessions of 1 h each, performed three times per week. Each session was supervised by one of the investigators (L.T.) and included a 15-min stretching warm-up period, followed by 30 min of aerobic exercise at the target intensity, and ended with 15 min of stretching exercises to cool down. The aerobic exercise part of each session was continuous. The exercise group ran at a speed that resulted in a HR of 70–85% of the HR$_{max}$ obtained in the maximal exercise test. The target exercise intensity was monitored and recorded for each individual by a HR watch (Cardiosport Heartsafe-T). The watch alarms were set to the upper and lower limits of the corresponding target intensity for each subject to help with compliance to the intensity. After each session, HR data for each individual were downloaded to a computer to access compliance to the target exercise intensity.

To account for cointervention, the control group also had sessions three times per week supervised by one of the investigators (L.T.). Each session included 45 min of soft stretching and relaxation routines, without significant elevation of HR. Our goal with the control group sessions was to ensure a minimum of drop out rate and to keep subjects interested in order to guarantee compliance.

Laboratory measurements. Venous blood samples were collected after an overnight 12-h fast, before and after interventions, at least 48 h after the last exercise session. Plasma glucose was measured by the glucose hexokinase method, and plasma levels of total cholesterol and triglycerides were measured by enzymatic procedures (Mega-Merck, Merck, Darmstadt, Germany) (1,19). HDL cholesterol was measured by selective inhibition (27). For endothelin-1 analysis, blood samples were drawn in an

ethylenediaminetetraacetic acid–containing tube after a 30-min resting period in the supine position. Samples were centrifuged, and plasma was stored frozen at $-70°C$ for subsequent analysis. Extraction of endothelin-1 was performed using a centrifugal evaporator after plasma solvent dilution (water, hydrochloric acid, and acetone). Assays were carried out immediately after extraction. Endothelin-1 was measured in duplicate samples by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN) (sensitivity <1.0 pg·mL^{-1}, mean intra- and interassay coefficient of variation 4.2% and 5.1%, respectively) (21). The number of CD4+ T lymphocytes was measured by flow cytometry using monoclonal antibodies (Simultest CD4, Becton Dickinson), as previously described (25), and plasma HIV-1 RNA was measured by the NASBA Nuclisens method (ORGANON TEKNIKA) (lower limit of detection 80 copies per milliliter).

Anthropometry. Weight, height, circumferences, and skinfold thickness were measured by one experienced investigator, before and after the protocol, for the estimation of the body density and percent body fat by the formulas of Durnin and Womersley (8) and Siri (22), respectively. Body weight was measured to the nearest 0.1 kg and height to the nearest 1 cm. Body mass index was calculated as the weight in kilograms divided by the height squared in meters. Waist circumference was measured as the narrowest circumference between the costal margin and the iliac crest at the end of a gentle expiration. Hip measurement was the maximum circumference at the level of the femoral trochanter. The circumferences were measured with a nonstretchable tape to the nearest 1 cm with the subject standing upright to calculate waist-to-hip ratio.

Peak oxygen uptake. Maximal cardiopulmonary exercise testing was conducted before and after intervention under the supervision of a cardiologist. Subjects exercised on a motor-driven treadmill (IMBRAMED, KT 4000, Porto Alegre, Brazil) with an initial speed of 3 km·h^{-1} and a 2% incline, with continuous increments in speed and incline, following a ramp protocol adjusted to the subjects' predicted functional capacity, to reach volitional fatigue in approximately 10 min. Blood pressure was measured every 3 min using a standard arm sphygmomanometer, 12-lead ECG was continuously monitored (Micromed-Biotecnologia, Brasília, Brazil), and respiratory gases were analyzed by a previously validated commercial system (Total Energy Expenditure Measurements, Aerosport, Ann Arbor, MI) (15).

Statistical analysis. The 8.0 version of Statistical Package for Social Sciences (SPSS) software was used for statistical analysis. Based on the results of previous studies (12,26,28), we estimated that a sample size of 15 individuals in each group would have a power of 80% to detect a 10% difference in triglyceride and cholesterol levels for $\alpha = 0.05$. Descriptive data are presented as mean ± SD. After randomization, demographic, physical, and clinical characteristics of the two groups were compared by the Student t-test or by the Fisher exact test. The effects of the two interventions on continuous variables were compared by two-way ANOVA for repeated measures. Categorical data were analyzed by the χ^2 statistic.

RESULTS

Patients and interventions. Of the 42 subjects, all infected with HIV-1, who entered the study, 30 completed the protocol, 15 in the diet and exercise group (six women) and 15 in the diet-only group (four women). Eleven individuals dropped out the study (six in the diet and exercise group, two women, and five in the diet-only group, all women) due to lack of interest, time, or economic or family problems. One additional subject from the diet and exercise group was excluded from the analysis because he did not comply with the antiretroviral therapeutic regimen, but no subject dropped out because of infection or illness. Table 1 presents the demographic, clinical, cardiovascular, and anthropometric characteristics as well as the medication use of the two groups for subjects who completed the study. All subjects were receiving combined therapy including nucleoside analogues, and 26 of them protease inhibitors and four taking efavirenz. Eight individuals were smokers, four in exercise group and four in control group (one woman); four individuals smoked 20 cigarettes per day, and the others smoked ≤10 cigarettes per day. After randomization, the groups had similar characteristics, with the exception of a small but significant difference in blood hemoglobin levels. Each of the subjects who completed the protocol participated in 36 sessions over 12.6 ± 1.1 wk. Compliance with the sessions in both groups was 100%. Figure 1 demonstrates that the target HR

TABLE 1. Demographic, physical, and clinical characteristics of the two groups after randomization.

	Diet and Exercise Group (N = 15)	Diet Group (N = 15)
Age (yr)	36 ± 5	39 ± 7
Gender (male:female)	9:6	11:4
Ethnicity (white:nonwhite)	13:2	14:1
Time since diagnosis (yr)	6.0 ± 3.0	6.0 ± 2.6
Time of antiretroviral therapy (yr)	1.7 ± 0.9	1.9 ± 0.8
Antiretroviral therapy (no.)		
Indinavir	4	8
Indinavir + ritonavir	5	1
Saquinavir + ritonavir	0	1
Amprenavir + ritonavir	0	1
Ritonavir	0	1
Nelfinavir	5	0
Biovir + efavirenz	1	3
Body weight (kg)	68.1 ± 12.4	67.1 ± 11.5
Body mass index (kg·m^{-2})	25 ± 3	24 ± 4
Waist-to-hip ratio	0.91 ± 0.05	0.94 ± 0.05
Body density (g·cm^{-3})	1.03 ± 0.02	1.04 ± 0.02
Body fat (%)	27 ± 11	23 ± 9
CD4+ (cel·mm^{-3})	563 ± 258	435 ± 154
$\dot{V}O_{2max}$ (mL·kg^{-1}·min^{-1})	32 ± 5	34 ± 7
Peak HR (bpm)	179 ± 10	175 ± 11
Triglycerides (mg·dL^{-1})	325 ± 192	338 ± 158
Total cholesterol (mg·dL^{-1})	256 ± 53	256 ± 54
HDL cholesterol (mg·dL^{-1})	42 ± 13	38 ± 8
Glucose (mg·dL^{-1})	90 ± 6	100 ± 21
Hemoglobin (g·dL^{-1})	13.4 ± 1.0	14.4 ± 1.2*
Albumin (g·dL^{-1})	4.3 ± 0.3	4.5 ± 0.4

Data are reported as mean ± SD.
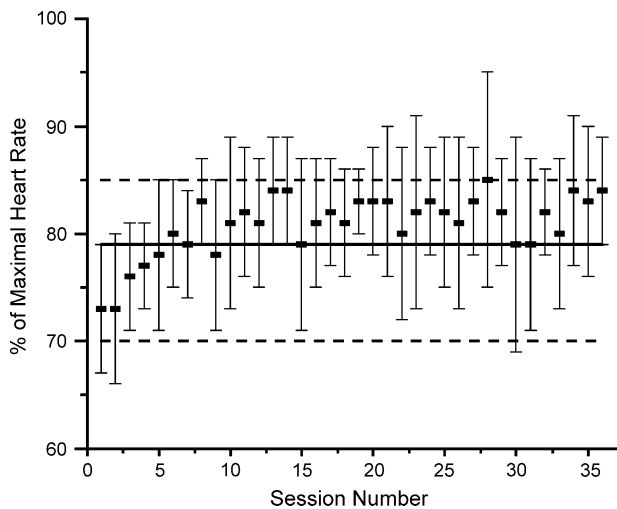* Significant difference between groups ($P < 0.02$).

FIGURE 1—Mean ± SD HR (expressed as percentage of HR_{max}) attained at the 15th minute, which represents the steady-state HR for at each exercise session for the diet and exercise group. The continuous line represents the mean HR (dashed lines for SD) for the 15 subjects considering all sessions.

was appropriately attained in each training session for the diet and exercise group.

Peak oxygen uptake. Figure 2 demonstrates that the training program resulted in a significant improvement in exercise capacity, evaluated by peak oxygen uptake ($\dot{V}O_{2max}$) on the maximal treadmill test for the diet and exercise group (32 ± 5 mL·kg^{-1}·min^{-1} before; 40 ± 8 mL·kg^{-1}·min^{-1} after) but did not change in the diet only group (34 ± 7 mL·kg^{-1}·min^{-1} before; 35 ± 8 mL·kg^{-1}·min^{-1} after).

Dietary information. Table 2 presents the 3-d dietary record measured at baseline and the dietary recommendations made by the dietitian for the diet and exercise and the diet-only groups. The 3-d caloric intake was not significantly changed by the dietary recommendation, but there was a significant reduction in the percentage of fat at the expense of small increments in protein and carbohydrate intake. The recommendations also included a reduction in saturated fatty acids and increments in monounsaturated and polyunsaturated fatty acids. There was also a significant reduction in the recommended cholesterol intake.

Anthropometric changes. Table 3 shows that body mass index, waist-to-hip ratio, body density, and body fat changed significantly in the two groups after 3 months of intervention. The values of weight, body mass index, and percentage of body fat decreased similarly from baseline to the end of the intervention in the two groups. Accordingly, estimated body density increased similarly in the two groups.

Laboratory measurements. Table 3 presents data on the responses of metabolic, immunologic, and other laboratory determinations. There were no significant changes in any of the blood tests in either group, except for a significant change in albumin at end of study in control group. Endothelin-1 was significantly elevated at baseline when compared with a sample of normal individuals previously evaluated in our laboratory to levels similar to those found in diabetic patients with dys-

lipidemia (21). There was no significant change in endothelin-1 levels after the interventions. The small difference in hemoglobin between groups at baseline was maintained to the end of the study. CD4+ T lymphocyte counts tended to decrease in the diet and exercise group and tended to increase in the diet-only group, but these changes did not reach statistical significance. Before intervention, 11 of 15 subjects in the diet and exercise group (73%) had a viral load of <80 copies per milliliter, while in the diet-only group, the ratio was eight of 15 (53%). After intervention, 13 of 15 subjects in the each group (87%) had their plasma viral load values below 80 copies per milliliter. A χ^2 cross-tabulation analysis performed on plasma viral load showed no significant effect of intervention ($P = 0.39$).

DISCUSSION

Few randomized clinical trials have evaluated the effects of aerobic exercise training on HIV-1–seropositive individuals, and they have been flawed by several methodologic limitations (12,13,16,23,26,28). This study reports the first randomized clinical trial that has evaluated the effects of aerobic exercise on hyperlipidemia associated with the use of protease inhibitors in individuals with HIV-1 that also controlled for dietary recommendation. Based on the results of previous uncontrolled studies, we hypothesized that the addition of aerobic exercise training to a low-lipid diet would result in reduction triglycerides and/or total cholesterol levels and would also improve body composition and functional capacity. However, the results of this study show that HIV-1–positive individuals with hyperlipidemia, when submitted to 3 months of aerobic exercise training and a low-lipid diet, do not experience significant changes in triglycerides, total cholesterol, or HDL cholesterol levels, but they do improve functional capacity.

Since the early studies on the effect of aerobic exercise training on HIV-1–positive individuals, it has been repeatedly shown that these patients are able to improve
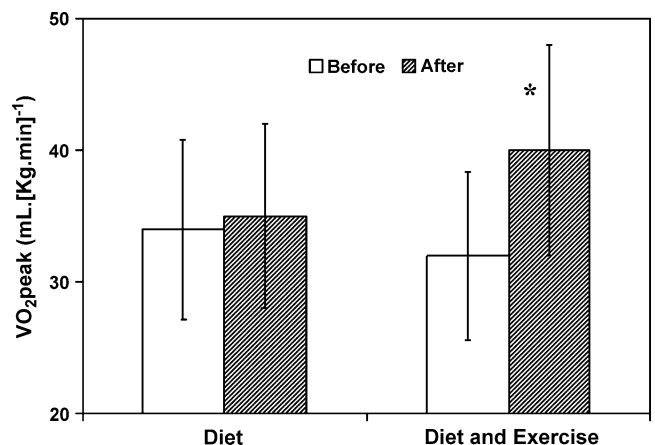

FIGURE 2—Mean ± SD peak oxygen uptake ($\dot{V}O_{2peak}$) for the diet group and the diet and exercise group, before and peak after 3 months of intervention. * ANOVA: group effect, $P = 0.204$; time effect, $P = 0.002$; interaction, $P = 0.001$).

TABLE 2. Three-day estimated nutrient intake at baseline and dietary recommendations.

	3-d Dietary Record	Dietary Recommendation	P
Diet and exercise group (N = 15)			
Caloric intake (kcal·d^{-1})	2430 ± 558	2683 ± 539	0.135
Caloric intake per nutrient (%)			
Protein (%)	17 ± 4	20 ± 1	0.0001
Carbohydrates (%)	50 ± 6	57 ± 2	0.0001
Fat (%)	33 ± 5	23 ± 2	0.0001
Saturated fatty acids (% of fat)	37 ± 6	14 ± 2	0.0001
Monounsaturated fatty acids (% of fat)	36 ± 3	52 ± 2	0.0001
Polyunsaturated fatty acids (% of fat)	26 ± 5	31 ± 3	0.0001
Cholesterol (mg·d^{-1})	484 ± 231	200 ± 47	0.0001
Diet group (N = 15)			
Caloric intake (kcal·d^{-1})	2405 ± 896	2624 ± 559	0.135
Caloric intake per nutrient (%)			
Protein (%)	16 ± 2	20 ± 1	0.0001
Carbohydrates (%)	52 ± 6	57 ± 3	0.0001
Fat (%)	32 ± 6	23 ± 4	0.0001
Saturated fatty acids (% of fat)	36 ± 6	15 ± 3	0.0001
Monounsaturated fatty acids (% of fat)	39 ± 5	51 ± 6	0.0001
Polyunsaturated fatty acids (% of fat)	24 ± 4	32 ± 6	0.0001
Cholesterol intake (mg·d^{-1})	514 ± 194	200 ± 33	0.0001

All values are expressed as mean ± SD. Nutrient intake in diet are expressed as the percentage of daily energy consumed for each nutrient. There were no significant differences between groups.

functional capacity after short-term programs of aerobic exercise (13,16,24,25). Initially, it was suggested that moderate-intensity programs could improve immune function, but that high-intensity programs could be detrimental to the immune system (13). However, more recent studies have consistently shown no significant changes in CD4+ after moderate-intensity aerobic training (16,23,25), and we found no detrimental effect of high-intensity training (25). In the present controlled trial, we confirm these observations, demonstrating a significant increase in directly measured peak oxygen uptake and no consistent changes in CD4+. In accordance with a recent report (23), we also showed no significant effect of aerobic training on viral load.

Despite the metabolic abnormalities at baseline, exercise training and dietary recommendations resulted in no significant change in plasma lipid levels in our patients. There was a trend for a reduction in serum triglycerides, but the response of our patients was not consistent. Most studies on the effects of diet and aerobic exercise training in dyslipidemic individuals who do not take medication show a reduction in serum triglycerides and modest reduction in total cholesterol levels (9). Data on HIV-1–positive patients are limited, but a recent study found no significant association between fat intake and serum or body composition characteristics of lipodystrophy syndrome (2). Taken together, these observations suggest that the continuous use of protease inhibitors is a potent stimulus to the development of dyslipidemia that cannot be overcome by the favorable effects of short-term dietary recommendations and aerobic exercise training programs. The trend for an increment in blood glucose and plasma endothelin-1 (Table 3) in both groups raises the hypothesis that glucose metabolism and endothelial function may also be adversely affected with the continuous use of protease inhibitors, despite dietary recommendations and exercise training.

Our findings are in contrast with the results of previous studies on the effects of exercise training on HIV-1–positive individuals with dyslipidemia who used antiretroviral therapy. Yarasheski et al. (28) found a significant reduction in serum triglyceride levels in these individuals after 16 wk of resistance exercise training. Jones et al. (12) also found improved lipid profile after 10 wk of combined

TABLE 3. Cardiovascular, anthropometric, and clinical measurements before and after interventions for both groups.

	Diet and Exercise (N = 15)		Diet (N = 15)		ANOVA (P)		
	Before	After	Before	After	Group	Time	Interaction
Peak HR (bpm)	179 ± 10.0	179 ± 9.0	175 ± 11.0	174 ± 14.0	0.20	0.85	0.97
Body weight (kg)	68.1 ± 12.4	66.1 ± 9.1	67.0 ± 11.5	65.0 ± 9.0	0.76	0.005	0.76
Body mass index (kg·m^{-2})	25.0 ± 3.0	24.0 ± 3.0	24.0 ± 4.0	23.0 ± 3.0	0.37	0.003	0.89
Waist-to-hip ratio	0.91 ± 0.05	0.90 ± 0.05	0.94 ± 0.05	0.91 ± 0.05	0.46	0.000	0.29
Body density (g·cm^{-3})	1.03 ± 0.02	1.04 ± 0.02	1.04 ± 0.02	1.05 ± 0.02	0.25	0.000	0.56
Body fat (%)	27 ± 11	22 ± 10	23 ± 9.0	19 ± 10	0.25	0.000	0.50
Systolic blood pressure (mm Hg)	116 ± 19	117 ± 7	122 ± 16	121 ± 11	0.84	0.64	0.85
Diastolic blood pressure (mm Hg)	76 ± 8	79 ± 5	82 ± 13	80 ± 10	0.60	0.70	0.80
Triglycerides (mg·dL^{-1})	325 ± 192	296 ± 203	338 ± 158	346 ± 172	0.58	0.67	0.54
Total cholesterol (mg·dL^{-1})	256 ± 53	243 ± 47	256 ± 54	251 ± 71	0.80	0.43	0.56
HDL cholesterol (mg·dL^{-1})	42 ± 13	43 ± 12	38 ± 8	39 ± 8	0.22	0.45	0.87
Glucose (mg·dL^{-1})	90 ± 6	97 ± 12	100 ± 21	106 ± 34	0.22	0.05	0.75
Endothelin-1 (pg·mL^{-1})	1.53 ± 0.72	1.62 ± 0.65	1.75 ± 0.74	1.85 ± 0.72	0.35	0.59	0.75
Hemoglobin (g·dL^{-1})	13.4 ± 1.1	13.4 ± 1.1	14.4 ± 1.2	14.4 ± 1.3	0.02	0.93	0.69
CD4+ (cel·mm^{-3})	563 ± 258	522 ± 228	435 ± 154	483 ± 177	0.35	0.87	0.06
Albumin (g·dL^{-1})	4.3 ± 0.3	4.4 ± 0.3	4.5 ± 0.4	4.7 ± 0.4	0.01	0.24	0.22

All values are expressed as mean ± SD. Probabilities for two-way ANOVA for repeated measures are reported considering the group effect, the effect of interventions (time) and the interaction between the two effects.

aerobic and resistance training in six HIV-1–positive individuals. Likewise, Thoni et al. (26) recently found a significant reduction in total cholesterol/HDL cholesterol ratio and triglyceride/HDL cholesterol ratio after 16 wk of aerobic exercise in HIV-1–positive patients, most of them with lipodystrophy. However, none of these previous studies had a control group or dietary intervention, which limits the value of these observations. In accordance with our data, a recent well-designed trial demonstrated that exercise training in combination with metformin improved insulin sensitivity and decreased thigh muscle adiposity when compared to metformin alone in HIV-infected patients with fat redistribution and hyperinsulinemia, but showed no change in blood lipids (6).

The metabolic abnormalities of our patients were associated with elevated plasma endothelin-1 levels compatible with endothelial dysfunction. Dyslipidemia may induce endothelial dysfunction, which can be demonstrated by elevated plasma endothelin-1 levels (21). Likewise, Zhong et al. (30) recently demonstrated that human endothelial cells treated with the protease inhibitor ritonavir present mitochondrial DNA damage and cell death. Indeed, baseline endothelin-1 levels of our patients were abnormally elevated when compared with a group of healthy individuals without dyslipidemia and similar to those of diabetic patients with dyslipidemia previously studied in our laboratory (21). Thus, despite the recommendations for a low-lipid diet and aerobic exercise training, two interventions that may improve endothelial function, we were not able to detect any significant changes in plasma endothelin-1 levels, suggesting that these interventions cannot reverse the endothelial dysfunction most likely induced by antiretroviral therapy and/or dyslipidemia. However, these preliminary observations must be confirmed by more direct measurements of endothelial function.

We studied a group of individuals with hyperlipidemia and physical signs consistent with the lipodystrophy syndrome (4). We hypothesized that dietary recommendations and aerobic exercise would be a more potent stimulus for changes in body composition than diet alone. However, both groups improved similarly in body composition. Therefore, despite the lack of a group who was followed without dietary or exercise intervention, it is likely that the changes in body composition could be attributable mainly to the dietary intervention, with little contribution of aerobic exercise. This interpretation is supported by the results of a meta-analysis that showed that 15 wk of diet or diet plus aerobic exercise program produced almost the same weight loss (14). However, since lipodystrophy presents as subcutaneous lipoatrophy and visceral adiposity, neither adequately measured by skinfold thickness measurements, we cannot rule out the possibility that changes in visceral adiposity could have resulted from the intervention.

Since our study evaluated a diet and exercise program that lasted only 12 wk, we cannot rule out the possibility that long-term or more intensive programs could have resulted in clinically relevant beneficial effects on dyslipidemia. However, in patients with dyslipidemia who are not on retroviral therapy, 12 wk of diet and exercise intervention is usually enough to result in favorable effects on lipid profile (9). Moreover, a recent uncontrolled study demonstrated that 12 months of aerobic exercise training failed to improve the lipid profile in HIV-1–positive individuals (3). In conclusion, HIV-1–seropositive individuals with lipodystrophy and dyslipidemia submitted to short-term intervention of dietary recommendation and aerobic exercise training are able to increase their functional capacity without any consistent changes in plasma lipid levels. We speculate that continuous use of protease inhibitors seems to be a potent stimulus for the development of dyslipidemia that cannot be overcome by the favorable effects of short-term dietary recommendation and aerobic exercise training programs.

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