San Raffaele Scientific Institute

Brisk Walking Improves Inflammatory Markers in cART-Treated Patients

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Background

HIV infection and antiretroviral therapy (cART) are associated with low-grade inflammation and persistent immune activation, which can may contribute to the development of metabolic problems and chronic diseases, such as cardiovascular disease, which are often present also in a general old population . It has been reported that in the general population the physical activity, including moderate intensity activity, reduce all-cause mortality and the risk of developing cardiovascular disease, stroke and type 2 diabetes. The aim of this study is to evaluate the benefit of brisk walking as moderate intensity exercise, with or without strength exercise, on metabolic and inflammatory parameters in cART-treated patients.

Methods

We enrolled 49, HIV-infected cART-treated, sedentary subjects in a 12-week exercise program, consisting of 3 outdoor sessions/week of 60 min walking at 65-75% of HR (Heart Rate) max with ("walk/strength" group) or without ("walk" group) 30 min circuit training at 65% of 1-RM (Repetition Maximum) (**Figure 1**). Subjects were assessed at baseline (BL) and 12 weeks (W12) by 6-minute walking test (6MWT) and 1-RM test, morphometric measures (BMI, waist, hip and leg circumferences), blood examination (cytometry, fasting total, HDL and LDL cholesterol, triglycerides, glucose, insulin, AST/ALT, gGT, CPK, HbA1c, CD4 and CD8 cells, plasma HIV-RNA). We measured traditional soluble markers of chronic immune activation (IL-6, d-dimer, sCD14 and hCRP), and IL-18 and myostatin, as potential negative regulators of adipose tissue and muscle homeostasis, respectively. We also assessed the expression of CD38+ and HLA-DR+ on CD4+ and CD8+ T cells. Statistical analysis were performed by Wilcoxon-signed paired rank test and Spearman's correlation.

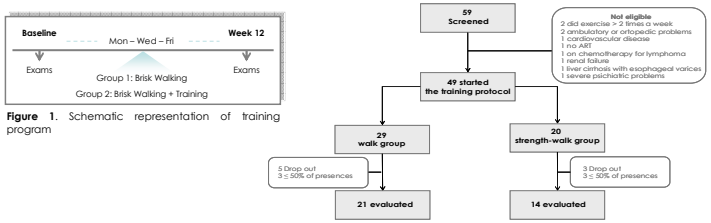


Figure 1. Schematic representation of training program

Table 1. Subject's characteristics at baseline

	Walk		Strength-Walk
	Women (N. 9)	Men (N. 12)	Men (N. 14)
Age (yrs)	47 (40-50)	49 (43-54)	50 (45-56)
Risk Group, nr. of patients (%)			
Ex-IDU	3 (33%)	4 (33%)	1 (7%)
MSM	0	7 (58%)	13 (93%)
Heterosexual	6 (67%)	0	0
Unkwnown	0	1 (8%)	0
Infection Parameters			
Nadir CD4+ (cells/mm³)	44.0 (25.7-66.0)	85.5 (69.75-108.5)	169.5 (95.0-169.5)
AIDS, nr. of patients (%)	3 (33%)	4 (33%)	2 (10%)
CD4+ (cells/mm³) *	727 (539-1040)	689 (613-766)	461 (378-577)
CD8+ (cells/mm³)	698 (550-862)	916 (783-1249)	776 (615-893)
VL<50 c/mL, nr of patients (%)	9 (100%)	12 (100%)	13 (93%)
HCV co-infection, nr of patients (%)	1 (11%)	3 (25%)	0
VACS Index	22.0 (21.0-40.0)	29.0 (16.0-31.0)	10.0 (24.0-31.0)
FIB4 Index	0.63 (0.54-0.58)	0.85 (0.65-1.16)	0.83 (0.59-1.10)
ART type, nr of patients (%)			
PI-based	2 (22%)	5 (41%)	7 (50%)
NNRTI-based	3 (33%)	4 (33%)	4 (28%)
Others	4 (44%)	3 (25%)	3 (21%)
Anti-hypertensive drugs, nr of patients (%)			
Beta blockers	1 (11%)	4 (33%)	1 (11%)
Others	0	2 (16%)	3 (21%)
Lipid-lowering drugs, nr of patients (%)			
Statins	1 (11%)	3 (25%)	6 (42%)
Fibrates	0	0	2 (14%)
Smokers, nr of patients (%)	1 (11%)	5 (41%)	3 (21%)
Metabolic Parameters			
Systolic Blood Pressure (mmHg)	118 (106-131)	121 (119-140)	127 (120-139)
Diastolic Blood Pressure (mmHg)	73 (69-86)	78 (73-82.5)	83 (76-88)
Total Cholesterol (mg/dl)	179 (155-287)	217 (174-237)	195 (155-226)
HDL Cholesterol (mg/dl)	51 (40-72)	45 (33-56)	36 (32-51)
LDL Cholesterol (mg/dl)	112 (88- 157)	147 (119- 164)	119 (94; 148)
Triglycerides (mg/dl)	93 (58; 210)	137 (101; 210)	138 (122; 208)
Glucose (mg/dl)	80 (71; 92)	86 (80; 92)	85 (78; 97)
Insulin (mIU/L)	8.1 (5.8; 16.2)	13.1 (9.8; 15.3)	13.7 (5.4; 17.4)
HOMA	2.9 (2.1; 3.3)	1.6 (0.9; 3.9)	2.8 (0.8; 3.8)
Body Composition			
Weight (kg)	65.0 (54.0; 78.7)	76.5 (68.7; 81.7)	76.0 (71.0; 81.0)
BMI (kg/m²)	26.4 (21.7; 28.8)	26.0 (24.1; 28.3)	25 (21.7; 27.4)
Waist Circumference (cm)	93 (81; 104)	92 (87.6; 99)	93.0 (82.5; 102.5)
Hip Circumference (cm)	100.0 (88.5; 108.0)	91.5 (91.0; 98.0)	97.0 (94.0; 98.0)
Leg Circumference (cm)	54.0 (48.0; 59.0)	53.5 (50.6; 57.7)	53.0 (44.0; 55.0)

Results

35/49 subjects (26 men, 9 women; median age 48 yrs) completed the 12-week program: 21 in the "walk" group and 14 in the "strength-walk" group (**Flow chart above**). At baseline there was no difference between subgroups in demographic, clinical or biochemical variables, except for higher CD4 cell count in the walk-men compared to the strength-walk group and the expected difference in lean mass between walk-women and walk-men groups (**Table 1**). The study of soluble markers, in a subgroups of 25 patients, showed a significant level reductions of IL-6 (p=0.021), d-dimer (p=0.0002), hCRP (p=0.0001), IL-18 (p=0.010) and myostatin (p=0.006) (**Figure 2**, **Panel A** and **Table 2**), with no intercorrelations between % changes at W12 of each marker (data not shown). Among all soluble tested markers the sCD14 was not significantly changed at W12.

The cellular makers, studied through the expression of HLA-DR+ and CD38+ molecules on CD4+ and CD8+ T-cells surface, revealed a significant change in the proportion of CD4+ T-cells expressing the HLA-DR+ (p=0.020) and the CD38+ (p=0.020) molecules as well as the expression of HLA-DR+ (p=0.001) and CD38+ (p=0.010) on the CD8+ T-cells surface (**Figure 2**, **Panel B** and **Table 2**).

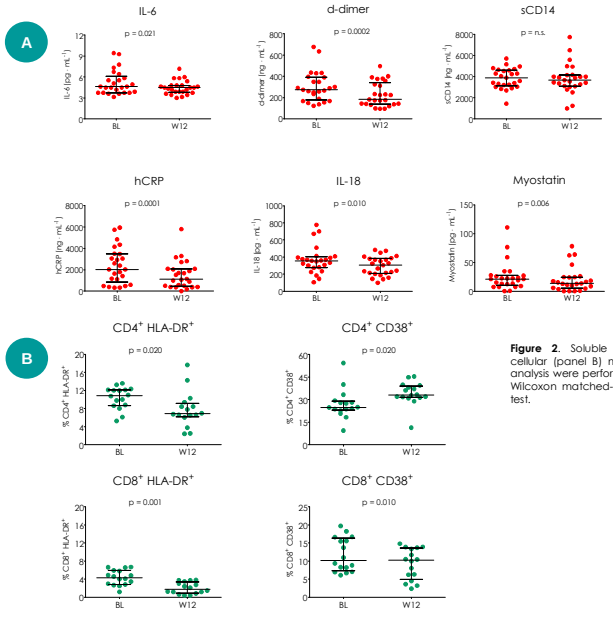


Figure 2. Soluble (panel A) and cellular (panel B) markers. Statistical analysis were performed by using the Wilcoxon matched-pairs signed rank test.

	BL	W12	p value
Soluble			
IL-6 (pg·mL⁻¹)	4.63 (3.73-6.12)	4.47 (3.81-4.78)	0.021
IL-18 (pg·mL⁻¹)	354 (276-401)	304 (208-383)	0.010
sCD14 (ng·mL⁻¹)	3887 (3123-4618)	3666 (3099-4147)	n.s.
d-Dimer (ng·mL⁻¹)	272 (177-392)	181 (137-340)	0.0002
Myostatin (pg·mL⁻¹)	20.92 (10.45-27.39)	13.48 (5.08-24.37)	0.006
hCRP (ng·mL⁻¹)	2017 (842-3483)	1136 (446-2082)	0.0001
Cellular			
CD4⁺CD3⁺HLA-DR⁺ (%)	10.87 (8.67-12.14)	6.85 (6.17-9.16)	0.024
CD4⁺CD3⁺CD38⁺ (%)	24.81 (22.95-28.98)	32.99 (31.41-39.01)	0.028
CD8⁺CD3⁺HLA-DR⁺ (%)	4.34 (2.86-5.91)	1.79 (0.93-3.37)	0.001
CD8⁺CD3⁺CD38⁺ (%)	10.19 (7.30-16.38)	10.23 (4.94-13.59)	0.010

Table 2. Median values (IQR range) of the measured soluble and cellular markers before and after 12 week training in the whole group of 25 patients.

After 12 weeks of training participants showed significant improvement of performance at 6MWT (P<0.0001) and in all strength exercises, of BMI (p=0.038), waist (p=0.050) and hip (p=0.041 circumferences, as well as total (p=0.005) and LDL cholesterol (p=0.004) (**Figure3, Table 3**). No significant differences were observed in all other data listed above (Table 2).

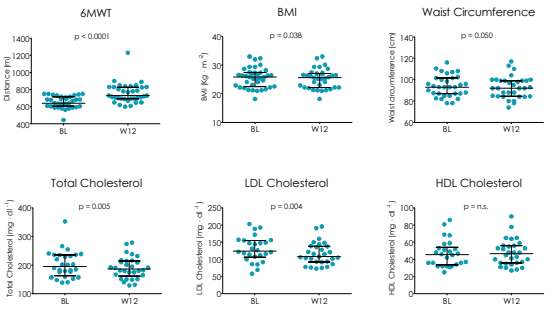


Figure 3. Physical parameters at BL and W12. Statistical analysis were performed by using the Wilcoxon matched-pairs signed rank test.

Table 3. Median values (IQR range) of the measured parameters before and after 12 week training in the whole group of 35 patients.

	BL	W12	p value
Physical Fitness			
6MWT, distance (m)	642.5 (605.0-715.0)	730.0 (695.0-830.0)	<0.0001
6MWT, HR_{max} (bpm)	119 (106-132)	137 (116-152)	<0.0001
6MWT, HR_{max} (bpm)	125 (112-142)	145 (132-166)	<0.0001
6MWT, Δ(La) (mmol·L⁻¹)	0.9 (0.1-2.2)	2.9 (1.5-5.3)	0.0003
6MWT, ΔRPE	1.0 (0.0-1.0)	0.5 (0.0-2.0)	n.s.
Crunch Test (nr.) *	19.5 (16.75-22.50)	30.0 (24.75-33.75)	0.0002
Lat Machine (kg) *	50.0 (43.75-55.00)	57.5 (47.50-61.25)	0.0002
Chest Press (kg) *	55.0 (47.50-61.25)	77.5 (60.00-80.00)	0.0007
Leg Extension (kg) *	40.0 (38.75-45.00)	50.0 (45.00-51.25)	0.014
Sitting Calf (kg) *	52.5 (42.50-55.00)	70.0 (58.75-75.60)	0.0004
Leg Press (kg) *	207.5 (146.3-242.5)	240.0 (187.5-300.0)	0.002
Metabolic parameters **			
Weight (kg)	75.00 (65.00-79.5)	72.00 (63.50-77.50)	0.003
BMI (kg·m⁻²)	25.8 (22.20-27.50)	25.00 (21.55-26.93)	0.038
Waist Circumference (cm)	93.00 (85.50-101.9)	92.00 (84.63-99.00)	0.050
Hip Circumference (cm)	95.00 (91.00-99.75)	93.50 (90.00-98.75)	0.041
Leg Circumference (cm)	53.00 (49.78-56.75)	53.00 (49.00-55.75)	n.s.
Total Cholesterol (mg·dl⁻¹)	195.5 (161.5-214.5)	186.0 (161.5-214.5)	0.005
HDL (mg·dl⁻¹)	45.50 (33.50-54.25)	46.50 (35.75-56.00)	n.s.
LDL (mg·dl⁻¹)	124.0 (106.0-155.3)	108.0 (92.5-138.5)	0.004
Triglycerides (mg·dl⁻¹)	142.5 (110.5-200.8)	131.0 (93.00-199.5)	n.s.
Glucose (mg·dl⁻¹)	85.0 (78.0-92)	82.0 (79.0-92.5)	n.s.
Insulin (mg·dl⁻¹)	11.8 (7.9-16.5)	12.9 (8.0-16.8)	n.s.
HOMA index	2.8 (1.6-3.4)	2.6 (1.6-4.1)	n.s.
Hb1c (%)	5.3 (5.1-5.8)	5.5 (5.3-5.6)	0.040
AST (UI⁻¹)	23.0 (17.7-29.4)	21.5 (16.0-35.0)	n.s.
ALT (UI⁻¹)	37.5 (22.8-52.50)	32.0 (20.8-47.0)	0.049
Ultrasonography			
Superficial Fat (mm)	17.00 (11.75-28.25)	16.00 (12.00-30.50)	n.s.
Visceral fat (mm)	60.00 (52.50-75.50)	64.00 (49.75-27.75)	n.s.
Total Fat (mm)	82.00 (70.25-97.59)	80.00 (72.50-92.50)	n.s.
Body DEXA			
Arm Fat (%)	22.4 (15.4-29.3)	23.3 (11.2-31.4)	n.s.
Leg Fat (%)	17.5 (11.1-26.4)	17.1 (11.5-25.9)	n.s.
Trunk Fat (%)	30.8 (24.2-38.9)	31.8 (22.2-38.9)	n.s.
Tot Fat (%)	25.1 (19.7-36.0)	25.8 (15.3-32.7)	n.s.
Trunk-to-limb fat ratio	1.7 (1.1-2.1)	1.6 (1.1-2.5)	n.s.

Conclusions

Moderate intensity exercise improved aerobic fitness and metabolic markers in cART-treated patients, and it was associated with improvement of soluble and cell immune activation markers.

Acknowledgements