Effects of physical exercise in the perception of life satisfaction and immunological function in HIV-infected patients: Non-randomized clinical trial

Efeito do exercício físico na percepção de satisfação de vida e função imunológica em pacientes infectados pelo HIV: Ensaio clínico não randomizado

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Abstract

Background: There is a lack of research about the relationship between exercise and the psychological well-being of HIV-infected (Human Immunodeficiency Virus) patients. Objective: The objective of this study was to investigate the influence of a physical training program on life satisfaction and on the immunological function in HIV-patients. Methods: A total of 29 HIV-seropositive patients [age: 45±2 yrs; Body Mass Index (BMI): 22.8±1.0 kg/m²; TCD4: 20.5±2.0%] were allocated to the control (CG, n=10) and to the experimental groups (EG, n=19). The EG participated in an exercise program combining aerobic, strength, and flexibility exercises for a period of 12 weeks [3 times/week of 30 min of aerobic exercise (workload corresponding to 150 bpm-PWC150); 50 min of strength exercises (3 sets of 12 repetitions in 5 exercises at 60-80% 12 RM); and 10 min of flexibility exercises (2 sets of 30 seconds at maximal range of motion of 8 exercises)]. The immunological function was assessed by flow citometry [absolute and relative TCD4 cells counting] and the life satisfaction was assessed by the Life Satisfaction Index (LSI). Results: The analysis of variance (ANOVA) showed no significant differences for relative and absolute CD4 T counts for both groups, however, a slight enhancement trend in the EG [16%, p=0.19] was observed. There was a significant improvement of LSI [approximately 15%; P<0.05] in EG, but not for CG. Conclusion: A physical activity program of moderate intensity improved life satisfaction perception in HIV-infected patients with no immunological function impairment. Article registered in the Australian New Zealand Clinical Trials Registry under the number ACTRN12610000683033.

Key words: physical activity; AIDS; physical fitness; health; HIV.

Resumo

Contextualização: Os estudos sobre a relação entre prática de exercícios e bem-estar psicológico de pacientes com vírus da imunodeficiência humana (HIV) são raros. Objetivo: Investigar a influência de programa de condicionamento físico sobre a satisfação com a própria vida e sobre a função imunológica. Métodos: Para tal análise, 29 pacientes soropositivos (idade: 45±2 anos; índice de massa corporal (IMC): 22,8±1,0 kg/m₂; TCD4: 20,5±2,0%), foram divididos em grupo controle (GC, n=10) e grupo experimental (GE, n=19). O GE participou durante 12 semanas de programa de exercícios que combinavam exercícios aeróbios, força e flexibilidade (três vezes/semana; aeróbio-30min: carga em watts equivalente a 150bpm-PWC150; força-50min: três séries de 12 repetições em cinco exercícios a 60-80% 12 RM; flexibilidade-10min: duas séries de 30s na máxima amplitude em oito exercícios). A função imunológica foi avaliada por contagem absoluta e relativa das células TCD4 (citometria de fluxo),e a satisfação de vida, por meio do Índice de Satisfação de Vida (ISV). Resultados: A análise de variância (ANOVA) não identificou alteração significativa para os linfócitos TCD4 em ambos os grupos, apesar da tendência à elevação no GE (16%, p=0,19). Houve melhora significativa no ISV (≈15%, P<0,05) para o GE, mas não para o GC. Conclusão: Um programa de condicionamento físico de intensidade moderada melhorou a percepção de satisfação de vida dos pacientes com HIV observados, sem acarretar prejuízos imunológicos.

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Palavras-chave: atividade física; AIDS; aptidão física; saúde; HIV.

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Introduction :::.

The current use of the highly active antiretroviral therapy (HAART) has provided an increase of life expectancy in patients infected with human immunodeficiency virus (HIV)^{1,2}; therefore a new prognosis has been established. Since then, the Acquired Immunodeficiency Syndrome (AIDS) has become a chronic disease, enabling the use of non-pharmacological approaches such as physical exercises^{3,4} which maintains functionality and quality of life for several years. Therefore, maintaining the physical and functional fitness of patients with HIV/AIDS has become one of the most important therapeutic targets, particularly in the case of "wasting syndrome", which is an important loss of muscle mass⁵.

On the other hand, HIV-infected patients suffer with multiple social stressors that may accelerate the progression of this disease. These conditions may be related to the diagnosis, to the presence of events of uncontrolled nature related to the disease⁶, and also to the reduced functional capacity related to the overall physical losses⁷. Therefore, although life expectancy has increased, psychological problems seem to affect seropositives subjects and their quality of life⁸.

There is evidence that mental health may improve by the regular practice of physical activities. Thus, the regular practice of exercises may be an interesting approach to deal with the psychological problems related to the HIV infection. Some studies have shown that subjects enrolled in programs of aerobic or strength training may present improved well-being⁹ and reduction of depressive symptoms¹⁰. However, the psychological aspects have been neglected by the investigations with regards to the practice of physical activity and the HIV-infection.

In fact, there are few studies considering this matter, especially after the introduction of the HAART. Studies regarding this topic would be important since the side effects of these drugs may also result in psychological disturbances. Therefore, it would be important to understand better about the impact that programs of regular physical exercises have on the general condition of the HIV-infected subjects. Ideally, physical activity would led to favorable adaptations on functionality and well-being perception, without causing negative impact on clinical and immunological conditions of patients.

Therefore, this study tested the influence of a program of physical fitness in the psychological well-being of seropositive subjects. It was hypothesized that HIV – infected subjects enrolled in a supervised program of exercises would exhibit more favorable modifications in their quality of life perception in relation to sedentary subjects, even receiving the HAART. In addition, the immunologycal function was compared in both

groups of active and sedentary participants through the counting of CD4+T cells.

Methods

Sample

The sample was composed by 29 HIV-infected patients, with a mean age of 45±2 years, body mass index (BMI): 22.8±1,0 kg/ m²; CD4+T: 20.5±2,0%, all assisted by doctors. Subjects were allocated in to two groups: experimental (EG, n=19; 12 men and 7 women), which participated on the exercises program, and control (CG, n=10; 5 men and 5 women), which remained with their normal activities. All the participants from this study signed a consent form and the research protocol was approved by the Ethics Committee of Research from the Universidade do Estado do Rio de Janeiro (UERJ), Rio de Janeiro (RJ), Brazil (Process n° 1942-CEP).

Due to ethical reasons, the allocation of the groups was not randomly: The EG was composed by those willing to join the training sessions. The CG was composed by the subjects who dropped out from the program, that where those selected among the subjects whom attended less than 25% of the total sessions and those subjects who were on the waiting list to join the program. To be included in the study, subjects could not have had opportunistic diseases until, at least, three months before the training start and should be taking antiretroviral drugs. In addition, they should not have been regularly exercising for at least 6 months prior to the begging of the training program. There were no drops out in both groups during the training program.

Training program

The exercises program included aerobic, strengthening and flexibility activities, 3 times a week (in alternate days) over 12 weeks. The training sessions consisted in 30 min of aerobics (treadmill or cycloergometer), with intensity that could not exceed the heart rate of 150 beats per minutes (bpm) (*physical work capacity*-PWC 150), in order to avoid an immune depression induced by high intensity exercises ^{11,12}. Then, a set of strengthening exercises were performed: leg press, horizontal supine, knee extension on an leg extension machine, low rowing (supinated grip) and partial abdominal flexion. For all exercises, three sets of 12 repetitions were performed using workloads of 60% to 80% derived from 12 maximal repetitions (12MR). The workloads used were estimated based upon tests of 12MR performed at each two weeks, to guarantee a progressive increase of loads. In these

tests, subjects performed 12 repetitions of the exercises with the highest load possible until the performance become impossible without an external support. At the end of each session, eight flexibility exercises for trunk, hip, knee, shoulder and elbow were performed, maintaining the maximal range of motion. These exercises were performed in three sets of 30 seconds for each position.

CD4 T-cell counting

In order to verify the presence of immunological impairment due to the exercise, the lymphocyte CD4 T-cell were quantified, since they are the most important marker of disease progression. To determine the absolute and relative CD4 T-cells counting, a small sample of blood (450μL) was obtained from a peripheral vein of the arm (EDTA vacutainer tubes, Becton-DickinsonTM, San Jose, CA, USA) and was immediately analyzed through flow citometry (BD FACSArrayTM, Franklin Lakes, NJ, USA), which is considered gold standard for CD4 T-cell counting¹³.

Cell counting was performed with a specific monoclonal antibodies (CD3+ CD4+ T-cells), fluorescein isothiocyanate (FITC) and fluorescein conjugated monoclonal antibodies (PE) (Becton DickinsonTM Immunocytometry Systems, San Jose, CA, USA). The antibodies were fixed, and the specific structures of CD4 T-cells surface were identified through fluorescence detection. All measures were performed in a hospital environment, at the same time of day. The blood samples were collected after, at least, 48h from the last training session, in order to avoid acute effects from the exercises. Patients were instructed not to ingest alcohol and caffeine 24 hours prior to the exams. The exams were performed according to the double-blind proceedings, in which the examiners were unaware of the treatment allocation (CG or EG).

Life satisfaction index

The level of life satisfaction was evaluated through the Life Satisfaction Index (LSI)^{14,15}, an instrument previously validated for this purpose. This is a self-report questionnaire to measure psychological well-being. The score ranges from 0 to 40, being higher scores representing better perception of life satisfaction. Both validity and reliability of the LSI type A (Life Satisfaction Index A – LSI-A) were tested in different situations and populations¹⁶⁻¹⁸. The questionnaire aim to identify five components (willingness, resolution, relationship between intended goals and achievements, positive self-concept and state of mind) of what is understood as factors that contribute to the subject's satisfaction with his/her present existence. Just as

flow cytometry, the measurement of LSI was also performed in double-blind design by examiners with experience in applying the questionnaire.

Statistical analysis

After verifying the assumptions of normality and homoscedasticity, a two-way analysis of variance (ANOVA) was used to test significant differences between groups for CD4 T-cells, followed by post-hoc Fisher test whenever necessary. Differences of LSI obtained by the questionnaire were assessed using the Friedman test with subsequent post-hoc verification using Wilcoxon test. In all situations, the level of significance was set at p<0.05. The software STATISTICA 6.0 was used for all analysis (Statsoft $^{\text{TM}}$, OK, USA).

Results:::.

The effect-sizes associated with the differences between the measurements pre and post exercise training, for CG and EG, ranged from 2.13 to 2.94 (95% CI: 1.2 to 3.25). A post-hoc sample size calculation analysis for both within and between groups repeated measures was performed (GPower 3.0.10, Kiel, Germany) considering a $P \le 0.05$ and the effect-sizes obtained revealed that the statistical power (1-beta) ranged between 0.80 and 0.85, which was considered as satisfactory.

Table 1 presents the descriptive analysis and the results of ANOVA for the CD4 T- cells and for the LSI. There was no significant differences for the levels of lymphocytes CD4 T-cells in both groups, although the clear trend of increase in cells count in the EG, with a positive percentage variation for absolute counting exceeding 12% (P=0.39). The counting decreased about 14% for the CG (P=0.49). With regards to the relative counting, the EG had an increase of 16% (P=0.19) compared to the CG that had an increase of only 2% (P=0.67). Considering the LSI, statistically significant improvements were observed in the EG (aproximately15%; P=0.002), while no differences

Table 1. T CD4 cell count (total and relative) and Life Satisfaction Index (LSI) pre and post exercise training in experimental and control groups.

Age, Years	Experimental Group			Control Group		
	46±3 (n=19)			43±5 (n=10)		
	Pre	Post	Δ%	Pre	Post	Δ%
T CD4. cells/mm ³	503.9±55.0	565.6±72.1	12.3	462.2±39.7	398.1±69.4	-13.9
T CD4. %	20.3±2.1	23.5±2.0	15.8	20.8±4.0	21.7±3.5	4.3
LSI	25±7	28±4¥	15.1	28±5*	28±5	1.8

 $[\]Psi$ significant difference in relation to baseline (p=0,002); * significant difference in relation to experimental group (P=0,03). CD4 T (total and relative) [Mean \pm SD]. LSI [Median \pm interquartile range].

were observed for the CG (P=0.39). In fact, the perception of life satisfaction in the EG, initially lower for the CG (P=0.03), improved in such a way that, at the end of the study, both groups presented similar scores (P=0.56).

Discussion :::.

This study aimed to investigate the effect of a physical training program on immunological function and psychological well-being of seropositive individuals. The results indicated that, at least, the exercise program did not cause harm with regards to the immunological function. On the other hand, a significant improvement in perception of life satisfaction was observed for the participants allocated to the experimental group (physical exercises).

Two limitations of the methods used should be pointed out. Firstly, it must be recognized that the allocation of the participants into the EG and CG was not random. Therefore, the baseline values were not similar in relation to the observed variables, mainly the results of the questionnaire for LSI. However, there was no reason, at an ethical level, to exclude of the exercise's program the patients who were interested and able to follow it, thus benefiting from its effects.

There was no previous sample calculation according to the characteristics of the HIV-infected patients. It is known that it is difficult to compose large groups with this type of patient, because of the likelihood of dropouts due to clinical problems. Moreover, these patients do not always want to have disclosed their condition. For this reason, most of the available studies on the relationship between AIDS and exercise were performed with small samples, such as de Souza et al.5 (14 patients in the experimental group, without CG), Dolan et al.¹⁹ (40 patients in the experimental group, homebased program, without GC), Driscoll et al.20 (11 patients in the experimental group and 14 controls), and Roubenoff and Wilson²¹ (6 patients in the experimental group and 19 controls), MacArthur, Levine and Birk²² (3 patients in the experimental group and 3 controls), Rigsby et al.²³ (19 patients in the experimental group, without GC) or Spence et al.²⁴ (24 patients in the experimental group and 12 controls). This study, therefore, has a sample consistent with those other similar studies in which the CG has a smaller number of participants in relation to the EG, and many did not even have a CG. Moreover, this difference did not affect the assumptions of homoscedasticity and sphericity required for the application of ANOVA. Note that, even with this limitation, the confirmatory sample size calculation showed a satisfactory statistical power (>0.80).

The second limitation concerns the establishment of the intensity of aerobic workload on the basis of the absolute load corresponding to the heart rate of 150 bpm (PWC150) instead of using percentages of maximum heart rate as a reference. Furthermore, it should be noted that the training program should be performed at an intensity that could not acutely compromise the immunological function. The establishment of the intensity based on Karvonen's formula would be problematic in this population because of the level of sarcopenia and predisposition for peripheral fatigue in some patients. Due to the impossibility to observe the actual maximal heart rate or maximal oxygen consumption (for operational reasons and the desire to avoid exercises of that intensity), the commonly approach of PWC was chosen. Classically, there are two options for this method, the PWC150 and the PWC170. At the age range of our patients, the PWC150 would probably lead them to a intensity below the point of respiratory compensation, which was consistent with the goals of this study. Moreover, this method greatly facilitated the control of the intensity during the sessions since the patients could themselves contribute, keeping in mind that they could not exceed the limit of 150 bpm²⁵. This approach was used in the same perspective by previous studies with different sedentary, obese children, pregnant women or elderly populations²⁶⁻²⁸.

Depression and anxiety seem to be the main psychological symptoms assessed in seropositive subjects undergoing an exercise program. It was impossible to find studies that had examined the psychological condition from a more positive view, such as the evaluation of well-being instead of negative psychological traits. To determine the individual quality of life is complex and always subjective, since this is a concept that refers to a huge amount of constructs such as psychological well-being, social adjustment, personal fulfillment, physical independence or social support. However, life satisfaction seems to have an evident relationship with general well-being, and with quality of life, whatever the construct chosen.

Some studies have been conducted to verify the effects of exercise on psychological parameters of several special populations, demonstrating positive results and improvement in the levels of depression and anxiety. Singh et al. 16 demonstrated that high intensity strength training, 3 times a week over eight weeks would be a safe, feasible and effective treatment method of treatment for depressive older adults. Brochu et al. 29 studied elderly women with coronary disease, observing that those enrolled in strength training for six months presented lower levels of depression compared to the inactive group. In general, it is accepted that the preservation of physical and functional fitness contributes to a better perception of quality of life 30.

The improvement of life satisfaction of seropositive individuals observed in this study, is consistent with previous researches and confirm their results. The study of LaPerriere et al.³¹ may have been the first to examine this relationship. However, the objective of this group was different since the participants were still unaware of their infection. Those who performed aerobic exercises and were seropositive for HIV had lower levels of depression in relation to individuals with the same results but that did not exercise.

Other studies presented similar results with subjects already aware of their seropositivity. MacArthur, Levine e Birk²² administered the General Health Questionnaire to patients infected by HIV, before and after 12 weeks of general physical training. The score of the 28 items of this questionnaire is related to symptoms of anxiety and depression. The patients whom participated in more that 80% of the training sessions presented a non-significant trend to improve their scores, while the group with lower participation deteriorated significant. Neidig, Smith and Brashers¹¹0 also demonstrated that seropositive subjects enrolled in a 12-week aerobic training (60-80% of VO_2 max) presented significantly less depressive symptoms than subjects allocated in CG.

The majority of studies that evaluated the influence of physical training in psychological aspects focused exclusively in aerobic modalities. It differs from our training protocol that involved aerobic, strengthening and flexibility exercises performed together. Lox, McAuley and Tucker9 had also administered strengthening exercises for training, but worked with different groups (strengthening, aerobic, and control). As in our study, positive results were obtained with the groups that trained, improving the subjective well-being sensation. Finally, Roubenoff and Wilson²¹ reported that seropositive subjects benefited from strength training, showing improvement on self-reported physical function, which is also related to psychological function. Some factors could be cited as responsible by the improvement observed on EG. LaPerriere et al.⁶ proposed a theoretical model to describe the relations between exercises and the psychological, endocrine and immunological aspects. According to this model, physical training might contribute to the improvement of emotional status, increase the release of endogenous opioids and reduce the activity of the adrenocortical, pituitary and hypothalamic systems (ACPH). Considering this model, physical activity could moderate the psychological and physiological sequels from chronic diseases, including HIV/AIDS. It is relevant to mention yet, that the performance of these exercises in group, gathering people with same problems and anxieties, may have been a contribution to the results obtained. Additional studies should be developed to confirm this hypothesis.

The immunological function is a central concern of the exercises programs developed for HIV-infected patients. Thus, the CD4 T-cells counting is often used as a marker^{19,32}. The absolute count measures the number of cells in each mm³ of blood. The normal count in non-infected subjects ranges from 500 to 1500 cells/mm³. The relative count (%) is related to the rate of CD4 T-cells in comparison to all the lymphocytes, being normally around 40% and may decrease below 20% in HIV-infected patients, reflecting a high risk of opportunistic infections³³.

Despite a possible relationship of exercises with a general clinical improvement³⁴, the available researches do not allow us to say with certainty that there is a significant direct impact on indicators of immunological function (eg, CD4 Tcells count or viral load). A systematic review, including ten randomized studies with aerobic training three times a week for at least four weeks35 showed small improvements, but not significant in CD4 T-cells count weighted average difference: 14 cells mm⁻³; 95% CI: -26 to 54 and viral load (weighted mean difference: 0.40 log10 copies, 95% CI: -0.28 to 1.07). More recently, a meta-analysis of the same group³⁶ assessed the impact of resistance exercises (alone or combined with aerobic exercises) in patients with HIV or AIDS. They observed a non-significant increase in CD4 T-cell count [95% CI: -6.60 to 103.23, n=68] compared with CGs who did not exercise. The confidence intervals reported, however, suggest a possible trend toward higher cell counts in the EGs, which may be clinically relevant.

In this study, no significant differences between experimental and control groups were observed for both the absolute and the relative counts in response to the training program. However, the absolute values in EG rose 62 cells / mm 3 [\sim 12%], and has declined to 55 cells /mm 3 in CG [\sim 14%]. The relative count was critically low in both groups at baseline (approximately 20%), indicating risk for opportunistic infections. After the intervention, there was an increase of almost 16% in the EG and of only 2% in CG. Thus, although the differences did not have statistical significance, these changes represent a clinically important outcome, supporting the idea that physical exercise can positively affect the CD4 T-cell count. Additional investigative effort should be performed for a better understanding of the relationship between exercise and CD4 T-cells, and other immunological markers.

In conclusion, a physical training program of moderate intensity, combining aerobic, strengthening and flexibility exercises was able to significantly improve the perception of life satisfaction of seropositive subjects without causing immunological impairment, at least in the characteristics observed in the present study. Therefore, supervised physical activity

programs can be effective tools for improving psychological well-being of patients with HIV infection and may, potentially, have a positive influence on CD4 T-cells. This information is relevant in the context of interventions conducted by health professionals, such as physical therapists and physical trainers.

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