Effects of Aerobic Training in Patients with Ankylosing Spondylitis

Fábio Jennings, Hilda Alcântara Oliveira, Marcelo Cardoso de Souza, Vaneska da Graça Cruz, and Jamil Natour

ABSTRACT. ***Objective.*** To evaluate the effects of aerobic exercise in patients with ankylosing spondylitis (AS).

Methods. Seventy patients classified with AS by the modified New York criteria were included. The patients were randomly assigned into 2 groups. The intervention group (IG) performed 50 min of walking followed by stretching exercises 3 times a week for 12 weeks. The control group (CG) performed only stretching exercises. The outcome measurements were the Bath indexes [Bath AS Functional Index (BASFI), Bath AS Disease Activity Index (BASDAI), and Bath AS Metrology Index (BASMI)], Health Assessment Questionnaire for the Spondyloarthropathies (HAQ-S), AS Disease Activity Score (ASDAS), the 6-min walk test (6MWT), chest expansion, and the Medical Outcomes Study Short Form-36. Aerobic capacity was assessed by ergospirometry on a treadmill. Routine laboratory techniques were used in determining lipid levels. Assessments were performed immediately before randomization and after 6, 12, and 24 weeks.

Results. Thirty-five patients were randomized to the IG and 35 to the CG. There was significant improvement in the BASFI, HAQ-S, BASMI, BASDAI, and ASDAS in both groups ($p < 0.05$), but did not differ between groups. There was a significant increase in the walking distance in the 6MWT in the IG compared with CG ($p < 0.001$). The IG showed significant improvement in cardiopulmonary capacity compared with CG. Cholesterol and triglyceride levels did not change in either group.

Conclusion. In patients with AS, aerobic training improved walking distance and aerobic capacity. Aerobic training did not provide additional benefits in functional capacity, mobility, disease activity, quality of life, and lipid levels when compared with stretching exercises alone. (First Release November 1 2015; J Rheumatol 2015;42:2347–53; doi:10.3899/jrheum.150518)

Key Indexing Terms:

ANKYLOSING SPONDYLITIS | AEROBIC EXERCISE | PAIN
FUNCTIONAL CAPACITY | QUALITY OF LIFE | AEROBIC CAPACITY

Ankylosing spondylitis (AS) is an inflammatory disease that mainly affects the axial skeleton, causing inflammatory lumbar pain with structural and functional compromise[1]. The symptoms of AS such as pain, stiffness, and fatigue determine varying degrees of functional limitation[2,3].

Physical exercise is fundamental in evidence-based international recommendations for the management of AS[4,5]. However, the evidence supporting exercise as fundamental in the treatment of AS is weak[6,7].

In the literature, there is a paucity of studies that evaluate the specific effects of aerobic exercise as well as the biological responses to these exercises. Also, few studies have included details about the exercise programs used[8]. The identification of the frequency, duration, and type of exercise ideal for patients with AS represents a void in the current literature[7,9].

The primary aim of our study was to assess the effectiveness of aerobic training in the improvement of functional capacity, spinal mobility, disease activity, and quality of life of patients with AS, and with a secondary aim to assess the effect of aerobic training in the plasma lipid levels and cardiopulmonary fitness in those same patients.

MATERIAL AND METHODS

Study design. This was a 24-week randomized controlled study with a blinded evaluator. The participants were allocated to the intervention group (IG) or the control group (CG) according to a randomization by a computer-generated list. The envelopes containing the determination of the group were opaque, sealed, and kept in the possession of a person who was not involved in our study.

Population. We selected patients of both sexes, classified with AS, and aged 18 to 60 years from the outpatient clinics of the Federal University of São Paulo.

Our study was approved by the Ethics Committee of our institution. All patients read, understood, and signed the term of free and informed consent before the procedures of our study were performed. This trial is registered on ClinicalTrials.gov (NCT01586650) and this manuscript was prepared according to the Consolidated Standards of Reporting Trials statement.

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Patient criteria. The inclusion criteria were patients classified according to the modified New York criteria for AS and the Steinbroker functional class I–II[10]. The disease-modifying antirheumatic drugs, which included methotrexate, sulfasalazine, and anti-tumor necrosis factor (TNF) agents, were on stable dosages for at least 3 months prior to randomization. Nonsteroidal antiinflammatory drugs (NSAID) and/or corticosteroids were on stable doses for at least 4 weeks. A corticosteroid maximum dose of 10 mg/day of prednisone or equivalent was permitted.

The exclusion criteria were uncontrolled hypertension, history of heart failure and/or coronary revascularization, history of syncope or exercise-induced arrhythmias, decompensated Type 1 diabetes mellitus, severe psychiatric diseases, fibromyalgia, and other medical conditions more incapacitating than AS. Those conditions were excluded because they could influence the benefits of exercise. Also considered as an exclusion criterion was a history of regular physical exercise (at least 30 min 3 times/week) in the last 6 months. Patients with a history of hip arthroplasty in the last year and any other condition that prevented walking were excluded.

Sample size. The Bath AS Functional Index (BASFI) was considered as the primary outcome of our study. The sample size for each group was calculated based on the difference of the value of BASFI before and after intervention and using 2.0 as the value of SD, power of 80%, and 5% significance. The values of SD and significant differences of BASFI were based on the study by van Tubergen, *et al*[11].

Interventions. The IG performed aerobic exercise (walking) associated with stretching exercises. The sessions lasted about 80 min with a frequency of 3 times per week for 12 weeks. The CG performed only stretching exercises for about 30 min 3 times per week for 12 weeks.

Aerobic training. The IG performed the following training: (1) warmup for 5 min; (2) walking for 40 min at anaerobic threshold heartrate, previously determined by ergospirometric test; (3) cool down for 5 min; and (4) stretching exercises for 30 min.

Stretching exercises. Stretching exercises were directed to the segments and muscle groups for the trunk and upper and lower limbs. Stretching exercises were performed in 3 repetitions of 30 s each. A complete description of stretching exercises is in Appendix 1.

Assessments. Assessments were performed immediately before randomization (T0), 6 weeks after the start of the exercise program (T6), immediately after the end of the program (T12), and 12 weeks after the end of the program (T24). The evaluators applying the tests did not know to which group the patients were allocated.

Functional capacity was assessed by BASFI, Health Assessment Questionnaire for Spondyloarthritis (HAQ-S), and the 6-min walk test (6MWT). We used validated versions of the BASFI and HAQ-S for the Portuguese language[12,13]. The 6MWT was performed on a 22-m indoor track following the guidelines of the American Thoracic Society[14].

Spinal mobility was assessed by the Bath AS Metrology Index (BASMI) using a validated version for the Portuguese language[15]. Also, chest expansion was measured at the level of the fourth intercostal space[16].

Disease activity was assessed by the Bath AS Disease Activity Index (BASDAI) and the AS Disease Activity Score (ASDAS), and by measurement of the C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)[17].

Standardized laboratory techniques were used to measure ESR and ultrasensitive CRP, which were expressed in mm/h and mg/l, respectively. Normal reference values for CRP were up to 1 mg/l and for ESR, up to 8 mm/h.

The Assessment of Spondyloarthritis international Society (ASAS) 20 response criteria were applied to the results after 12 weeks of the program relative to baseline (T0)[18].

The general quality of life was assessed by the Medical Outcomes Study Short Form-36 questionnaire (SF-36) in the version adapted for the Brazilian population[19].

The amount of analgesic and NSAID used by patients were monitored during the 12 weeks of our study. Prescription-standardized use of acetaminophen 500 mg up to 4 times a day in case of mild pain or diclofenac 50 mg 3 times a day in case of moderate to intense pain were permitted. Patients wrote down the information in a standardized diary for our study.

Ergospirometry was performed on a Life Fitness HR9700 treadmill following an incremental protocol. Testing began with the patient at rest for 1 min, followed by walking on the treadmill for a period of 3 min of warmup at a speed of 3 km/h. Next, treadmill speed was increased 1 km/h every minute on a fixed incline of 1%. The test was interrupted at the patient's request because of dyspnea, pain, or muscle fatigue. Heartrate was measured every 20 s of the test. Expired gases were analyzed by a Quark PFT4 ergo (COSMED) computerized metabolic system. Peak oxygen uptake (VO_2 peak) was defined as the highest VO_2 value obtained during the test. The anaerobic threshold was obtained by the VO_2 value at the speed of ventilatory threshold 1[20].

Blood samples of patients were collected after 12 h of fasting for the measurement of plasma lipids. Measurements were made at baseline (T0), after 12 weeks (T12), and after 24 weeks (T24) from the start of the program. Patients were instructed to follow their regular diet routine. Routine laboratory techniques were used in determining plasma lipid levels.

Statistical analysis. The program used for statistical analysis was the Statistical Package for the Sciences (SPSS) version 17.0. Descriptive statistics (mean, SD, 95% CI) were used for the clinical characteristics of patients in both groups. Baseline continuous variables of the 2 groups were compared using the Student t test for normally distributed variables and the Mann-Whitney U test for variables with non-normal distribution. The categorical variables were tested through the chi-square test.

Intention-to-treat analysis was used to assess response to intervention. ANOVA with repeated measures was used to assess response to intergroup and intragroup treatment over time. The significance level adopted was 5%.

RESULTS

One hundred and thirty-six patients were contacted; however, 56 were not selected for the following reasons: unavailability because of work schedule (n = 20), no interest in the program (n = 18), living far from the rehabilitation center (n = 8), change of therapy for disease activity (n = 5), and regularly performed exercises (n = 5). Three patients were excluded during the ergometric testing phase because screening showed changes suggestive of myocardial ischemia and were referred to the cardiology sector. These patients had no symptoms of coronary heart disease in initial clinical assessment.

Seventy-seven patients completed the baseline assessment; however, 7 patients withdrew consent before being randomized for the following reasons: unavailability because of work schedule (n = 4), living far from the rehabilitation center (n = 1), worsening of disease activity (n = 1), and no interest in participating (n = 1).

Seventy patients were randomized and included in our study: 35 in IG and 35 in CG. During the course of our study, there were 3 dropouts: 2 patients (1 from IG and 1 from CG) withdrew from the study because of a change in work scheduling, and 1 patient from the CG after experiencing a car accident. Two patients, 1 from IG and the other from CG, had poor adherence to the exercise program, but underwent evaluations at all periods.

Table 1 shows the demographic and clinical characteristics of the patients included in our study. The groups had similar characteristics in all variables.

Table 1. Baseline demographic and clinical characteristics of patients with AS included in the study (n = 70) according to randomized group. Values are mean (SD) unless otherwise specified.

Variables	Intervention Group, n = 35	Control Group, n = 35	p
Age, yrs	42.9 (9.9)	40.2 (9.3)	0.245*
Men:women, n	26:9	23:12	0.434#
Non-white:white, n	26:9	24:11	0.597#
Education level, yrs	8.6 (3.6)	8.8 (3.5)	0.840*
BMI	26.69 (4.58)	25.86 (4.00)	0.423*
Disease duration, yrs	16.0 (8.9)	13.4 (7.8)	0.208*
Time of diagnosis, yrs	7.4 (6.3)	7.5 (6.5)	0.934§
Smoking, n (%)	4 (11.4)	4 (11.4)	1.000†
SH, n (%)	8 (22.9)	13 (37.1)	0.192#
DM, n (%)	2 (5.7)	2 (5.7)	1.000†
Dyslipidemia, n (%)	5 (14.3)	4 (11.4)	1.000†
Use of statins	3 (8.6)	2 (5.7)	0.500†
Medications, n (%)			
No medication	5 (14.3)	5 (14.3)	1.000#
NSAID continuous	15 (42.9)	11 (31.4)	0.322#
Corticosteroid	0 (0)	4 (11.4)	0.114†
Methotrexate	7 (20)	8 (22.9)	0.771#
Sulfasalazine	4 (11.4)	6 (17.1)	0.734†
Anti-TNF therapy	14 (40)	17 (48.5)	0.868#
Infliximab	4 (11.4)	6 (17.1)	
Adalimumab	5 (14.3)	6 (17.1)	
Etanercept	5 (14.3)	5 (14.3)	

* Student t test. # Chi-square test. § Mann-Whitney U test. † Fisher's exact test. AS: ankylosing spondylitis; BMI: body mass index; SH: systemic hypertension; DM: diabetes mellitus; NSAID: nonsteroidal antiinflammatory drug; anti-TNF: anti-tumor necrosis factor.

Table 2 shows the assessment of functional capacity and mobility in different assessment times. There were improvements in the BASFI and HAQ-S in relation to baseline; however, there was no statistically significant difference between groups. As for 6MWT, the IG showed increase in distance traversed compared with the CG, with significant difference.

Mobility measured by BASMI showed improvement in T6 and T24 compared with T0 in both groups, with no significant intergroup difference.

The variables related to disease activity are shown in Table 3. Both groups had improved BASDAI and ASDAS scores in T6 and T12 compared with T0. However, there were no significant differences between groups. There was no change in the levels of ESR and CRP in either group over time.

Regarding treatment response assessed by the ASAS20 criteria, 31.4% (n = 11) of the IG achieved ASAS20 response, whereas in the CG, 34.3% (n = 12) achieved ASAS20 response. The results showed no statistically significant difference (p = 1.00 by Fisher's exact test).

Table 4 shows the general quality of life assessment by questionnaire SF-36. Only the domain functional capacity showed improvement in T12 in relation to the evaluation of T6 in both groups, and there was no difference between groups. The other domains remained unchanged over time.

In Table 5, we observed the variables of cardiopulmonary assessment in both groups at different times. The IG experienced significantly increased VO_2 levels after 12 weeks of training while the CG remained unchanged from the initial assessment. There was significant difference between groups (p = 0.049) in the absolute results in VO_2 peak. The IG showed an increase in anaerobic threshold after 12 weeks of training while the CG remained unchanged. However, the difference between groups was not statistically significant. Anaerobic threshold measured by percentage in relation to VO_2 peak was similar in both groups and did not change after 12 weeks.

The peak O_2 pulse behaved differently in the groups. The IG had increased peak O_2 pulse after 12 weeks of aerobic training while the CG showed a significant reduction of the variable.

Table 6 shows cholesterol levels [total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL)] and triglycerides of both groups at T0, T12, and T24. There was no significant difference between the groups at any time.

As for the consumption of NSAID (diclofenac sodium) and analgesic (acetaminophen) after 12 weeks of our study, there was no difference between the groups in medication consumption. The IG took an average of 6.1 (SD 16.7) tablets

Table 2. Evaluation of functional capacity and mobility of patients with AS in the 2 groups. Values are mean (SD) unless otherwise specified.

Variables	Intervention Group, n = 35				Control Group, n = 35				p Intergroup#
	T0	T6	T12	T24	T0	T6	T12	T24	
BASFI	4.28 (2.78)	3.49 (2.57)*	3.37 (2.49)*	3.47 (2.48)*	4.27 (2.32)	3.96 (2.06)*	3.34 (2.07)*	3.73 (2.19)*	0.743
HAQ-S	1.04 (0.59)	0.90 (0.51)	0.84 (0.52)*	0.92 (0.57)	1.01 (0.55)	0.98 (0.57)	0.92 (0.62)*	0.97 (0.59)	0.722
6MWT, m	443.14 (51.50)	479.13 (53.63)*	479.97 (54.56)*	473.53 (54.68)*	423.81 (64.17)	429.33 (64.17)	434.48 (52.56)	432.14 (45.87)	0.001**
BASMI	5.15 (1.95)	4.93 (1.98)*	4.93 (1.94)	4.95 (2.03)*	4.79 (2.22)	4.60 (2.22)*	4.65 (2.14)	4.61 (2.24)*	0.512
Chest expansion, cm	2.95 (1.72)	3.17 (1.81)	3.33 (1.97)	2.91 (1.53)	3.35 (1.71)	3.47 (1.91)	3.50 (1.90)	3.32 (1.61)	0.425

* $p < 0.05$ compared to T0. # ANOVA test. ** Comparing both groups in all assessments, and between the groups in T6, T12, and T24 by Student t test. AS: ankylosing spondylitis; T0: baseline assessment before randomization; T6: assessment 6 weeks after the start of the program; T12: assessment 12 weeks after the start of the program; T24: assessment 24 weeks after the start of the program; BASFI: Bath AS Functional Index; HAQ-S: Health Assessment Questionnaire for Spondyloarthritis; 6MWT: 6-min walk test; BASMI: Bath AS Metrology Index.

Table 3. Evaluation of disease activity of patients with AS in the 2 groups at different assessment times. Values are mean (SD) unless otherwise specified.

Variables	Intervention Group, n = 35				Control Group, n = 35				p Intergroup**
	T0	T6	T12	T24	T0	T6	T12	T24	
BASDAI	3.46 (2.39)	2.85 (2.20)*	2.75 (2.12)*	2.87 (1.97)	3.62 (2.06)	3.10 (2.00)*	2.79 (1.99)*	3.27 (2.07)	0.645
ASDAS, CRP	2.44 (1.07)	2.00 (0.95)*	1.98 (0.93)*	2.10 (0.92)	2.24 (0.91)	2.13 (0.88)*	2.00 (0.94)*	2.24 (0.89)	0.928
ASDAS, ESR	2.35 (0.93)	2.09 (0.89)*	2.05 (0.92)*	2.24 (0.95)	2.31 (0.83)	2.18 (0.82)*	2.00 (0.87)*	2.24 (0.84)	0.991
CRP, mg/l	10.49 (11.90)	7.04 (7.64)	7.14 (8.21)	6.53 (6.01)	6.01 (7.33)	5.50 (6.19)	4.95 (4.86)	7.84 (11.59)	0.290
ESR, mm/h	18.5 (12.5)	17.0 (10.0)	17.5 (12.8)	20.5 (15.2)	17.1 (13.6)	16.23 (13.7)	14.1 (12.5)	14.7 (9.7)	0.264

* $p < 0.05$ compared to T0. ** ANOVA test. AS: ankylosing spondylitis; T0: baseline assessment before randomization; T6: assessment 6 weeks after the start of the program; T12: assessment 12 weeks after the start of the program; T24: assessment 24 weeks after the start of the program; BASDAI: Bath AS Disease Activity Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ASDAS: AS Disease Activity Score.

Table 4. Evaluation of general quality of life using the SF-36 of the 2 groups at different times. Values are mean (SD) unless otherwise specified.

Domains of SF-36	Intervention Group, n = 35				Control Group, n = 35				p Intergroup**
	T0	T6	T12	T24	T0	T6	T12	T24	
Bodily pain	58.5 (26.3)	62.7 (21.0)	65.0 (22.6)	60.8 (19.2)	54.4 (23.2)	61.5 (22.6)	60.3 (22.5)	57.9 (23.1)	0.479
General health	56.4 (23.7)	54.0 (24.2)	56.6 (23.1)	54.3 (24.1)	42.3 (21.4)	6.9 (21.3)	46.9 (22.9)	47.2 (23.2)	0.056
Mental health	64.2 (25.5)	68.1 (24.0)	71.1 (21.6)	69.5 (22.7)	65.9 (22.0)	67.2 (25.0)	66.3 (22.0)	69.7 (21.1)	0.843
Physical functioning	60.7 (20.8)	61.0 (24.5)	66.3 (19.8)*	66.4 (20.9)	57.9 (20.4)	58.0 (18.4)	62.4 (20.8)*	58.7 (24.3)	0.340
Role emotional	57.0 (42.5)	59.9 (42.6)	58.0 (46.0)	58.0 (44.6)	54.2 (46.5)	51.3 (43.8)	54.1 (40.5)	52.3 (45.9)	0.541
Role physical	53.6 (42.5)	54.3 (40.4)	57.9 (42.8)	56.4 (43.4)	45.0 (44.5)	41.4 (38.8)	47.9 (40.8)	43.6 (44.7)	0.177
Social aspects	72.3 (28.2)	73.0 (24.0)	74.1 (24.4)	71.9 (28.3)	60.9 (25.9)	69.4 (25.8)	66.6 (26.8)	67.3 (24.0)	0.199
Vitality	60.6 (23.8)	61.3 (23.0)	62.7 (24.1)	63.3 (24.0)	56.0 (20.8)	57.6 (18.4)	59.6 (21.7)	57.7 (22.1)	0.364

* $p < 0.05$ compared with T6. ** ANOVA test. SF-36: Medical Outcomes Study Short Form-36; T0: baseline assessment before randomization; T6: assessment 6 weeks after the start of the program; T12: assessment 12 weeks after the start of the program; T24: assessment 24 weeks after the start of the program.

Table 5. Evaluation of aerobic capacity in the 2 groups of patients with AS at different times. Values are mean (SD) unless otherwise specified.

Variables	Intervention Group, n = 35			Control Group, n = 35			p Intra-group	p Intra-group
	T0	T12	p Intragroup	T0	T12	p Intragroup		
VO_2 peak absolute, l/min	2.18 (0.65)	2.34 (0.66)	**0.002**	2.10 (0.60)	2.03 (0.63)	0.143	**0.001**	**0.049****
VO_2 peak relative, ml/kg/min	30.08 (6.99)	32.32 (7.20)	**0.005**	30.89 (6.08)	29.83 (6.63)	0.127	**0.002**	0.137**
Anaerobic threshold, absolute, l/min	1.36 (0.35)	1.52 (0.43)	**0.003**	1.38 (0.41)	1.39 (0.50)	0.879	**0.045**	0.261**
Anaerobic threshold, relative, ml/kg/min	19.08 (4.01)	21.29 (5.08)	**0.003**	20.59 (4.73)	20.51 (5.93)	0.917	**0.033**	0.558**
Anaerobic threshold, % of VO_2 peak	63.9 (9.3)	66.3 (10.9)	0.238	66.8 (11.9)	68.6 (12.8)	0.238	0.238	0.208*
Maximum speed, km/h	9.1 (1.8)	9.7 (2.1)	**< 0.001**	9.0 (1.8)	9.1 (1.6)	0.768	**0.025**	0.139**
Anaerobic threshold speed, km/h	5.5 (1.1)	6.0 (1.2)	**0.043**	5.5 (1.2)	5.6 (1.2)	**0.043**	0.236	0.532*
HR maximum, bpm	167.4 (19.1)	170.3 (17.6)	0.142	170.9 (19.9)	172.2 (20.9)	0.142	0.576	0.554*
HR, anaerobic threshold, bpm	125.5 (14.9)	133.1 (19.9)	**0.028**	133.2 (19.3)	135.1 (20.5)	**0.028**	0.182	0.226*
Peak O_2 pulse, ml/bpm	12.9 (3.3)	13.7 (3.8)	**0.028**	12.4 (3.4)	11.9 (3.4)	**0.024**	**0.002**	**0.038**

* ANOVA test. ** Student t test comparing the groups in T12. Bold face indicates a difference between the behavior patterns of variables of the 2 groups. AS: ankylosing spondylitis; T0: baseline assessment before randomization; T12: assessment 12 weeks after the start of the program; HR: heart rate.

of 50 mg diclofenac and 7.4 (SD 13.1) tablets of 500 mg paracetamol while the CG took 7.6 (SD 19.8) and 8.7 (SD 22.9) tablets, respectively ($p > 0.05$).

Adherence to the exercise program was similar in both groups, with the IG having 82.5% and the CG having 81.4% frequency in the 12-week training program ($p = 0.759$).

After completion of 12 weeks of the program, the participants were encouraged to perform the exercises at home and return after 12 weeks (T24) for final evaluation. All patients reported that drug therapy had not changed to T24 and that they continued to perform exercises shown. Nonetheless, no patient claimed to have performed the exercises for the same duration and frequency as the time they were under supervision.

DISCUSSION

The treatment of AS is based on the use of drugs that control the inflammatory activity of the disease and on the prescription of physical exercise at all stages of the disease[5].

Table 6. Assessment of lipid levels of patients with AS in the 2 groups at different assessment times. Values are mean (SD) unless otherwise specified.

Plasma Levels, mg/dl	Intervention Group, n = 35			Control Group, n = 35			p**
	T0	T12	T24	T0	T12	T24	
Total cholesterol	176.09 (34.64)	178.71 (40.21)	185.66 (43.02)	182.54 (29.25)	185.77 (31.43)	186.57 (28.90)	0.533
LDL	108.47 (25.80)	110.81 (38.78)	118.22 (39.81)*	112.38 (25.80)	117.42 (27.15)	18.37 (23.84)*	0.614
HDL	45.34 (11.12)	46.40 (12.26)	47.37 (10.72)	47.11 (11.94)	47.71 (12.19)	48.20 (11.74)	0.611
Triglycerides	111.29 (44.62)	107.60 (59.89)	100.17 (35.05)*	115.14 (40.29)	103.14 (40.29)	99.83 (32.20)*	0.970

* $p < 0.05$. ** ANOVA test. AS: ankylosing spondylitis; T0: baseline assessment before randomization; T12: assessment 12 weeks after the start of the program; T24: assessment 24 weeks after the start of the program; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

The results of our study suggest that physical exercise improves functional capacity, mobility, and disease activity in patients with AS. Aerobic exercise added benefits in cardiopulmonary variables and the 6MWT.

Our present study showed benefits both with aerobic exercise associated with stretching and stretching alone in improved functional capacity. Similar results were found by Analay, *et al*[21] and Lim, *et al*[22] despite having participants accompanied for a shorter time than in our present study. Different from our results, few studies did not show benefits of exercise on functional capacity[23,24,25]. However, in the study by Hidding, *et al*[23], the participants performed exercises for 30 min only twice weekly and the functional assessment instrument was only the HAQ-S.

The BASFI and HAQ-S are validated instruments to measure functional capacity and use questions about daily living activities in patients with AS[26,27]. Most questions are about simple activities such as dressing, getting up from a chair, and climbing steps. Thus, the instruments do not assess more intense physical activities and only detect changes in lighter physical tasks. This may explain the improved functional capacity of the group that performed only stretching exercises.

The IG showed significant improvement in the 6MWT over time and in comparison with the CG. The result was expected because of the specificity of training, because the IG performed walking. Similar results were found in the study of Karapolat, *et al* in which the groups who performed aerobic exercises (swimming and walking) improved the distance walked during the 6MWT[25].

The slight improvement in mobility (measured by BASMI) in both groups was likely because of the patients in our sample having prior moderate impairment in mobility and more advanced time of disease. In addition, patients with complete ankylosis of the spine were not excluded.

At baseline, the individuals in our study presented with disease by the BASDAI and high activity by ASDAS, and levels of CRP and ESR above normal benchmark values, although all were receiving stable drug therapy at study inclusion. After 12 weeks, both groups showed benefits in disease activity from supervised physical exercise, but aerobic training did not add further improvement to the IG when compared with the CG. We believe that the superiority of aerobic training in improving disease activity could be seen if the period of followup were longer.

The proof of the effectiveness of new anti-TNF therapies to control disease activity raised the question of the involvement of exercise in the treatment of AS. In our study, over 40% of patients were receiving anti-TNF agents, and still had improvement in disease activity after the exercise program. Likewise, Masiero, *et al* selected only patients receiving anti-TNF therapy and having high disease activity (BASDAI > 4), and were able to demonstrate improvement in disease activity with an exercise program[28]. In our study, patients returned to disease activity scores similar to baseline 12 weeks after completing their supervised program (T24), demonstrating the importance of supervision of the exercises in obtaining beneficial results.

The improvement in the BASFI and BASMI remained even after 12 weeks from the end of the exercise program in both groups, likely because of patients continuing to exercise despite having reported a lower frequency than when they were under supervision. The IG also showed an improvement in the distance traversed in walking maintained at T24, suggesting the benefits of the training specificity and that patients had continued to perform exercises even without supervision. We believe that by breaking the cycle of inactivity and promoting the practice of exercise in groups and under supervision, patients acquire the habit of exercising and obtain results in functional capacity and mobility in the long term.

The prescription of aerobic training in our study followed American College of Sports Medicine (ACSM) recommendations because the patients performed walking at an average intensity of 64% of VO_2 peak for 40 min 3 times a week[8]. The determination of maximal oxygen consumption and anaerobic threshold was performed in a straightforward manner by ergospirometry. Ventilatory threshold 1 (or anaerobic threshold) was used as the variable for prescription because it is the most reliable and easily obtained variable through testing. According to the ACSM position, direct measurements of oxygen uptake are recommended for individualized exercise prescription because of greater accuracy.

Cardiopulmonary testing on a treadmill showed improvement in the performance of participants in the IG, as expected. Improvement in VO_2 peak was about 7% in the IG. Differently, the CG showed maintenance of these variables over time. In intergroup analysis, the IG showed a statistically significant increase in the variables' absolute VO_2 peak and peak O_2 pulse compared with the CG. Additionally, the CG showed reduction of peak O_2 pulse after 12 weeks. The studies of Analay, *et al* and Hidding, *et al* also demonstrated an improvement in aerobic capacity after programs of exercise of 4% and 10%, respectively[21,23]. However, the authors used indirect measures of cycloergometer and the prescription of exercise was not described in those studies. The study of Karapolat, *et al* performed cardiopulmonary assessment by ergospirometric test, and similarly to our present study, demonstrated an improvement in VO_2 peak of about 12% and 13% in groups that performed swimming and walking, respectively[25].

In our present study, cholesterol levels (total, LDL, and HDL) of patients were normal at baseline according to the references of the Brazilian Society of Cardiology[29]. This fact cannot be explained by the use of statins because only a minority of patients (< 10%) received these medications. Aerobic exercises did not alter lipid levels after 12 weeks. The lack of beneficial effect can be explained by the short length of the program, baseline levels that already were normal, and the lack of an adjuvant nutritional intervention.

Adherence to the exercise program is one aspect that should be observed in studies with exercise because it is an important determinant of beneficial responses to intervention. In our study, adherence was high, i.e., greater than 80% of frequency to training. Most studies with exercises in AS did not describe patients' adherence. Hidding, *et al* reported adherence of 73.5% of patients who participated in supervised groups[23]. In our present study, the effect of group treatment and ongoing supervision by physiotherapists can be pointed to as factors that have led to high patient adherence.

Our study demonstrates the benefits of aerobic exercises prescribed on a regular basis and monitored on the distance traversed while walking, and in the aerobic capacity in patients with AS. In spite of not having a group of individuals without performing exercises for comparison, the results suggest that aerobic exercises and stretching are beneficial in improving functional capacity, mobility, and disease activity in patients with AS.

Aerobic training determined the improvement in the distance traversed while walking and aerobic capacity in patients with AS when compared with stretching exercises alone. Aerobic training did not determine additional benefits in functional capacity, mobility, disease activity, and quality of life. Cholesterol levels (total, LDL, and HDL) and triglycerides were not altered by 12 weeks of aerobic exercise. Moderate- to high-intensity aerobic training resulted in similar adherence to the program of stretching and did not determine a higher consumption of analgesics and antiinflammatory drugs.

REFERENCES

1. Braun J, Sieper J. Ankylosing spondylitis. Lancet 2007;369:1379-90.
2. Ward MM, Weisman MH, Davis JC Jr, Reveille JD. Risk factors for functional limitations in patients with long-standing ankylosing spondylitis. Arthritis Rheum 2005;53:710-27.
3. Carter R, Riantawan P, Banham SW, Sturrock RD. An investigation of factors limiting aerobic capacity in patients with ankylosing spondylitis. Respir Med 1999;93:700-8.
4. Braun J, van den Berg R, Baraliakos X, Boehm H, Burgos-Vargas R, Collantes-Estevez E, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis 2011;70:896-904.
5. Zochling J, van der Heijde D, Dougados M, Braun J. Current evidence for the management of ankylosing spondylitis: a systematic literature review for the ASAS/EULAR management recommendations in ankylosing spondylitis. Ann Rheum Dis 2006;65:423-32.
6. Dagfinrud H, Kvien TK, Hagen KB. Physiotherapy interventions for ankylosing spondylitis. Cochrane Database Syst Rev 2008:CD002822.
7. Passalent LA. Physiotherapy for ankylosing spondylitis: evidence and application. Curr Opin Rheumatol 2011;23:142-7.
8. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al; American College of Sports Medicine. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. Med Sci Sports Exerc 2011;43:1334-59.
9. Alonso-Blanco C, Fernández-de-las-Peñas C, Cleland JA. Preliminary clinical prediction rule for identifying patients with ankylosing spondylitis who are likely to respond to an exercise program: a pilot study. Am J Phys Med Rehabil 2009;88:445-54.
10. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361-8.
11. Van Tubergen A, Debats I, Ryser L, Londoño J, Burgos-Vargas R, Cardiel MH, et al. Use of a numerical rating scale as an answer modality in ankylosing spondylitis-specific questionnaires. Arthritis Rheum 2002;47:242-8.
12. Cusmanich KG, Kowalski SC, Gallinaro AL, Goldenstein-Schainberg C, Souza LA, Gonçalves CR. Cross-cultural adaptation and validation of the Brazilian-Portuguese version of the Bath Ankylosing Spondylitis Functional Index (BASFI). Rev Bras Reumatol 2012;52:737-41.
13. Shinjo SK, Gonçalves R, Kowalski S, Gonçalves CR. Brazilian-Portuguese version of the Health Assessment Questionnaire for Spondyloarthropathies (HAQ-S) in patients with ankylosing spondylitis: a translation, cross-cultural adaptation, and validation. Clin Rheumatol 2007;26:1254-8.
14. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111-7.
15. Shinjo SK, Gonçalves R, Kowalski S, Gonçalves CR. Brazilian-Portuguese version and applicability questionnaire of the mobility index for ankylosing spondylitis. Clinics 2007;62:139-44.
16. Sieper J, Rudwaleit M, Baraliakos X, Brandt J, Braun J, Burgos-Vargas R, et al. The Assessment of SpondyloArthritis international Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis 2009;68 Suppl 2:ii1-44.

17. Machado P, Landewé R, Lie E, Kvien TK, Braun J, Baker D, et al; Assessment of SpondyloArthritis international Society. Ankylosing Spondylitis Disease Activity Score (ASDAS): defining cut-off values for disease activity states and improvement scores. Ann Rheum Dis 2011;70:47-53.
18. Anderson JJ, Baron G, van der Heijde D, Felson DT, Dougados M. Ankylosing spondylitis assessment group preliminary definition of short-term improvement in ankylosing spondylitis. Arthritis Rheum 2001;44:1876-86.
19. Ciconelli RM, Ferraz MB, Santos W, Meinão I, Quaresma MR. [Brazilian-Portuguese version of the SF-36. A reliable and valid quality of life outcome measure]. [Article in Portuguese] Rev Bras Reumatol 1999;39:143-50.
20. Serra S. [Ergospirometry]. [Article in Portuguese] Arq Bras Cardiol 1997;68:301-4.
21. Analay Y, Ozcan E, Karan A, Diracoglu D, Aydin R. The effectiveness of intensive group exercise on patients with ankylosing spondylitis. Clin Rehabil 2003;17:631-6.
22. Lim HJ, Moon YI, Lee MS. Effects of home-based daily exercise therapy on joint mobility, daily activity, pain, and depression in patients with ankylosing spondylitis. Rheumatol Int 2005;25:225-9.
23. Hidding A, van der Linden S, Boers M, Gielen X, de Witte L, Kester A, et al. Is group physical therapy superior to individualized therapy in ankylosing spondylitis? A randomized controlled trial. Arthritis Care Res 1993;6:117-25.
24. Karapolat H, Akkoc Y, Sari I, Eyigor S, Akar S, Kirazli Y, et al. Comparison of group-based exercise versus home-based exercise in patients with ankylosing spondylitis: effects on Bath Ankylosing Spondylitis Indices, quality of life and depression. Clin Rheumatol 2008;27:695-700.
25. Karapolat H, Eyigor S, Zoghi M, Akkoc Y, Kirazli Y, Keser G. Are swimming or aerobic exercise better than conventional exercise in ankylosing spondylitis patients? A randomized controlled study. Eur J Phys Rehabil Med 2009;45:449-57.
26. Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 1994;21:2281-5.
27. Daltroy LH, Larson MG, Roberts NW, Liang MH. A modification of the Health Assessment Questionnaire for the spondyloarthropathies. J Rheumatol 1990;17:946-50.
28. Masiero S, Bonaldo L, Pigatto M, Lo Nigro A, Ramonda R, Punzi L. Rehabilitation treatment in patients with ankylosing spondylitis stabilized with tumor necrosis factor inhibitor therapy: a randomized controlled trial. J Rheumatol 2011;38:1335-42.
29. Sposito AC, Caramelli B, Fonseca FA, Bertolami MC, Afiune Neto A, Souza AD, et al; Sociedade Brasileira de Cardiologia. [IV Brazilian Guideline for Dyslipidemia and Atherosclerosis prevention: Department of Atherosclerosis of Brazilian Society of Cardiology]. [Article in Portuguese] Arq Bras Cardiol 2007;88 Suppl 1:2-19.

APPENDIX 1. Stretching exercises.

1. Stretching exercises for trunk

1.1. Cervical spine extensors: Standing, interlace fingers and support the base of the head, pull the base of the head and chin toward the chest, hold for 30 s and relax (3 repetitions).

1.2. Lumbar spine extensors: Lying down with both knees bent, pull the legs toward the trunk, hold for 30 s and relax (3 repetitions).

1.3. Cervical spine rotators: Standing, looking to the right, hold for 30 s, relax, and then repeat on the other side (3 repetitions for each side).

1.4. Cervical spine lateral flexors: Standing, tilt the head to the right, hold for 30 s, relax, and then repeat on the other side (3 repetitions for each side).

1.5. Medial rotators and adductors of the humerus: Standing, extend the right arm behind the body and hold on a support surface, hold for 30 s, relax, and then repeat on the other side (3 repetitions for each side).

2. Stretching exercises for upper limbs

2.1. Elbow flexors: Standing, extend the right arm forward, forearm on top, and with the left hand pull the palm flexing the wrist, hold for 30 s, relax, and then repeat on the other side (3 repetitions for each side).

2.2. Elbow extensors: Standing with legs apart and knees slightly bent, bring the right hand to the neck and slide the hand behind the back. With the left hand, pull the right elbow, bringing the arm toward the ear, without misaligning the shoulders, hold for 30 s, relax, and then repeat on the other side (3 repetitions for each side).

3. Stretching exercises for lower limbs

3.1. Hip flexors: Standing, supporting the body with 1 arm on a support surface, flex the knee and provide contralateral force by hand on the same side toward the buttock, hold for 30 s, relax, and then repeat on the other side (3 repetitions for each side).

3.2. Hip extensors: Lying with knees bent, make a "4" with the right leg to support the ankle of the left knee, pull the left leg towards the chest, hold for 30 s, relax, and then repeat on the other side (3 repetitions for each side).

3.3. Hip adductors: Standing with legs shoulder-width apart, bend the right knee keeping the left knee in extension and lean torso upright to the right side, hold this position for 30 s, relax, and then repeat for the other side (3 repetitions per side).

3.4. Hip abductors: Lying with the right knee bent to make a "4" on the left leg extended. With your left hand pull your right leg in, hold for 30 s, relax, and then repeat on the other side (3 repetitions for each side).

3.5. Plantar and knee flexors: Lying with knees bent, stretch the right leg and, with the aid of an elastic band placed on the right foot, perform straight leg raise, hold for 30 s, relax, and then repeat on the other side (3 repetitions for each side).