Arch Rheumatol 2025;40(1):98-111
doi: 10.46497/ArchRheumatol.2025.10924

ORIGINAL ARTICLE

Is there an anti-inflammatory effect of aerobic exercises on axial spondyloarthropathy patients? A prospective, randomized-controlled trial

Yeşim Özge Gündüz Gül[1], Ajda Bal[1], Ümmü Gül Erdem[2]

[1]*Department of Physical Medicine and Rehabilitation, Ankara Etlik City Hospital Physical Medicine and Rehabilitation Hospital, Ankara, Türkiye*
[2]*Department of Medical Microbiology, Ankara Etlik City Hospital, Ankara, Türkiye*

Correspondence: Yeşim Özge Gündüz Gül, MD.
E-mail: ozgeyesimgunduz@gmail.com

Received: August 23, 2024
Accepted: January 14, 2025
Published online: March 17, 2025

Citation: Gündüz Gül YÖ, Bal A, Erdem ÜG. Is there an anti-inflammatory effect of aerobic exercises on axial spondyloarthropathy patients? A prospective, randomized-controlled trial. Arch Rheumatol 2025;40(1):98-111. doi: 10.46497/ArchRheumatol.2025.10924.

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ABSTRACT

Objectives: This study aims to examine whether aerobic exercises, in addition to home-based exercise (HBE) program, had anti-inflammatory effects, evaluated by disease activity, acute phase reactants, and cytokine levels in axial spondyloarthropathy (axSpA).

Patients and methods: This two parallel-group, unblinded, 12-week, prospective, randomized-controlled trial (RCT) included a total of 54 participants who were followed for axSpa and the patients were equally allocated to the aerobic exercise group or HBE group. The aerobic exercise group included 27 patients (8 males, 19 females, mean age: 43.9±9.0 years; range, 27 to 58 years) and the HBE group included 27 patients (8 males, 19 females, mean age: 42.4±10.5 years; range, 23 to 63 years). The patients were evaluated using the Ankylosing Spondylitis Disease Activity Score (ASDAS), Visual Analog Scale (VAS), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Metrology Index (BASMI), chest expansion measurement, 6-Min Walk Test, and Ankylosing Spondylitis Quality of Life (ASQoL), Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α) and interleukin-17 (IL-17) levels at the beginning of the study and after treatment completion. The HBE group was provided conventional exercise program. The second group ran on the treadmill in addition to their HBE program. Exercise sessions were performed three times a week for a period of 12 weeks.

Results: After treatment, only the aerobic exercise group showed a significant improvement in disease activity ($p<0.001$). Both HBE and aerobic exercise groups showed a significant improvement in pain levels, functional statement, spinal mobility, chest expansion, functional exercise capacity, and life quality ($p<0.001$, $p<0.001$; $p<0.001$, $p<0.001$; $p=0.03$, $p<0.001$; $p=0.008$, $p<0.001$; $p=0.004$, $p<0.001$; $p<0.001$, and $p<0.001$, respectively). Only the HBE group showed a significant decrease in TNF-α levels and ESR ($p=0.015$, $p=0.014$). After treatment, the aerobic exercise group showed more improvement in disease activity, pain levels, functional exercise capacity, and quality of life compared to the HBE group ($p<0.001$, $p=0.005$, $p<0.001$, $p=0.038$). The change in post-treatment ESR, CRP, TNF-α, and IL-17 levels compared to pre-treatment did not show a statistically significant difference between the HBE and aerobic exercise groups ($p>0.05$).

Conclusion: Adding aerobic exercise to a conventional exercise program may have an anti-inflammatory effect by reducing disease activity and help to manage disease.

Keywords: Aerobic exercise, axial spondyloarthropathy, cytokines, acute phase reactants, non-pharmacological intervention.

Spondyloarthropathies (SpAs) are a group of chronic, inflammatory, and multisystemic diseases with common genetic, epidemiological, and clinical features. These diseases primarily involve the axial skeleton.[1] The pathogenesis of SpA is multiple factors. The disease-specific inflammatory response, with the contribution of environmental factors based on genetic predisposition, is responsible for the pathogenesis of the disease.[1] The main cytokines thought to be involved in the pathogenesis of axial SpA (axSpA) are tumor necrosis factor-alpha (TNF-α), interleukin-17 (IL-17), IL-23, IL-22, IL-6, IL-7, interferon-gamma (IFN-γ), IL-12, and IL-26.[1-3]

There is no definitive marker associated with disease activity. Studies on cytokine levels and disease activity have shown that TNF-α, IL-6, IL-17, IL-23, and IFN-γ levels may be associated

with disease activity in ankylosing spondylitis (AS) patients.[4-9] Non-pharmacological and pharmacological methods are used together for the treatment of SpA. Non-pharmacological methods include patient education, smoking cessation, regular exercise, and physiotherapy practices.[10]

The main goals of exercise therapy are to improve or preserve range of motion, flexibility, balance and to improve muscle strength and aerobic capacity. Posture, stretching, breathing, strengthening, and aerobic exercises are the most recommended in treating AS.[11] Exercise therapy is described as the cornerstone treatment of axSpA by the European Alliance of Associations for Rheumatology (EULAR). Although patient compliance with exercise therapy is not easy, the advantages of exercise are that it is cost-effective, low-risk, and easy to apply compared to pharmacological treatments.[10]

The anti-inflammatory effects of exercise have recently been discussed. Few studies have investigated the anti-inflammatory effects of exercise in patients with AS. While some of these studies have shown a significant improvement in disease activity, functional status, flexibility, and C-reactive protein (CRP) with aerobic exercise in patients with AS, some have not. Although a few studies have shown a significant decrease in TNF-α levels in AS patients with non-aerobic exercise programs, no study has examined the changes in TNF-α and IL-17 levels with aerobic exercise treatment yet.[6-15]

The primary objective of the present study was to examine whether aerobic exercise, in addition to the home-based exercise (HBE) program, had an anti-inflammatory effect in patients with axSpA, as evaluated by disease activity, acute phase reactants, and cytokine levels. Our secondary objective was to determine whether aerobic exercise, in addition to HBE, had a positive effect on functional status, functional exercise capacity, quality of life, non-steroidal anti-inflammatory drug (NSAID) consumption, chest expansion, and spinal mobility.

PATIENTS AND METHODS

This two parallel-group, unblinded, 12-week, prospective, randomized-controlled trial (RCT) was conducted at Ankara Etlik City Hospital Physical Medicine and Rehabilitation Hospital, Department of Rheumatology between November 2021 and July 2023. A written informed consent was obtained from each participant. The study protocol was approved by the Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Research Ethics Committee (date: 06.09.2021, no: 119/11). The study was conducted in accordance with the principles of the Declaration of Helsinki. The study is registered at ClinicalTrials.gov with the study No. NCT06699238. Inclusion criteria were as follows: a diagnosis of axSpA according to the Assessment of SpondyloArthritis International Society (ASAS) classification criteria, voluntary participation in the study, age between 20 and 65 ages, regular use of disease-modifying anti-rheumatic drugs (DMARDs) at a stable dosage for three months, regular use of NSAID at a stable dosage for at least four weeks, presence of low disease activity (1.3≤ Ankylosing Spondylitis Disease Activity Score [ASDAS-CRP] <2.1), having a phone number which can be used to communicate with oneself or a family member, and at least a primary school graduate. Exclusion criteria were as follows: presence of active peripheral joint involvement, having used a biological agent at any time before, exercising regularly for the previous six months, the presence of cardiovascular, orthopedic, and neurological problems that may prevent exercise (unstable angina, uncontrolled sinus tachycardia, presence of severe aortic stenosis, uncontrolled atrial or ventricular arrhythmia, third-degree atrioventricular block, fracture, prosthesis, neuropathy, myopathy), any other respiratory or neuromuscular disease that affects the respiratory muscles, presence of malignancy, presence of pregnancy, having undergone any surgery in the previous six months, presence of severe psychiatric illness, findings related to infection during interrogation, having an infection in the last three months, communication problems, having known diabetes mellitus, the presence of severe comorbidity that may affect the kidneys and livers, inability to participate in at least 75% of the exercises, having left study voluntarily, presence of any new symptoms or findings that develop during exercise or evaluations, and may interfere with exercise. A total of 302 patients

were diagnosed with axSpA and followed in our clinic. However, only 87 patients met the inclusion criteria. These patients were allocated to the aerobic group (n=44) and HBE group (n=43) according to randomization using the closed envelope drawing method chosen by the patient. After the randomization, the two groups were adjusted for age and sex. Sixteen patients in the HBE group and 17 patients in the aerobic exercise group were excluded from the study for various reasons during follow-up. Finally, 27 patients in the aerobic exercise group (8 males, 19 females, mean age: 43.9±9.0; range, 27 to 58 years) and 27 patients in the HBE group (8 males, 19 females, mean age: 42.4±10.5 years; range, 23 to 63 years) completed the study. The study flowchart is shown in Figure 1.

All patients included in the study received standard conventional exercise for 12 weeks, three days a week, once a day for 30 min, including cervical, thoracic, and lumbar spine flexibility, shoulder muscles, hip flexors, hamstring and quadriceps muscle stretching, spinal flexor stretching, and extensor strengthening and breathing exercises program was shown by the same physician. Patient compliance with the exercise program was monitored weekly using telemedicine.

The aerobic exercise group performed the following training: warm-up for 5 min, walking for 20 min at an intensity that would use 60 to 70% of the heart rate reserve, and cool down for 5 min. Additionally, they performed standard conventional exercises at home. The aerobic exercise group performed on a treadmill under the supervision of a physician. The pulse measurement feature of the treadmill was used to monitor pulse rate.

Non-steroidal anti-inflammatory drug consumption and compliance with conventional and aerobic exercises were recorded weekly. Blood samples were collected from all the patients before the start of the exercise program. At the end of the exercise program, it was obtained from the aerobic exercise group at 12 weeks, immediately after the last exercise program, and from the HBE group at the end of 12 weeks.

All patients in the study groups were evaluated clinically and in the laboratory at the beginning (Week 0) and end (Week 12) in the present study. Disease activity, pain level, functional status, spinal mobility, functional

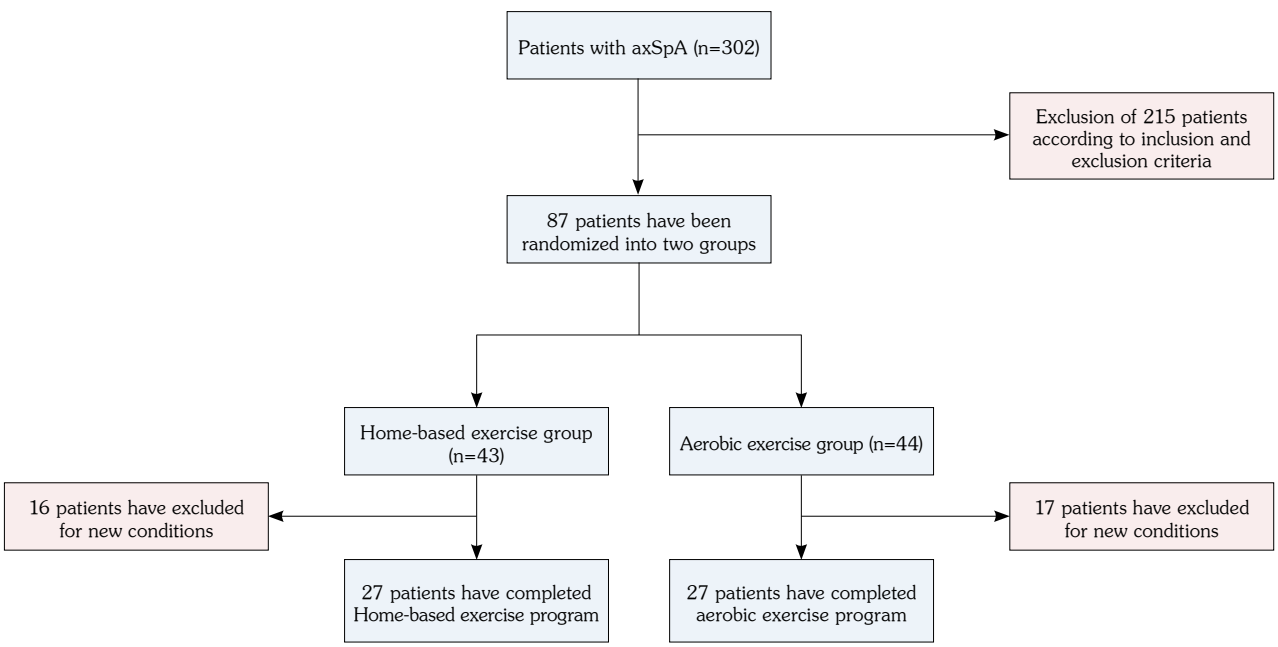

Figure 1. Home-based exercise.
axSpA: Axial spondyloarthritis.

exercise capacity, quality of life, and chest expansion were assessed using the ASDAS-CRP, Visual Analog Scale-pain (VAS-pain), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Metrology Index (BASMI), Six-Minute Walk Test (6MWT), Ankylosing Spondylitis Quality of Life (ASQoL), and chest expansion measurements. We used validated versions of BASFI and ASQoL for the local language.[16,17] The 6MWT was performed on a 30-m indoor track.[18] Also, chest expansion was measured at the level of the fourth intercostal space.[19] The amount of NSAID used by the patients was monitored during the 12 weeks of our study. The CRP value was determined using the turbidimetric method. Erythrocyte sedimentation rate (ESR) was measured using the modified Westergren method on a Vision C erythrocyte sedimentation analyzer (Nova Diagnostik Tıbbi Cihazlar A.Ş., Adana, Türkiye). To measure cytokine levels (IL-17 and TNF-α), 4 to 5 mL of blood samples were collected from the patients and kept at room temperature for 10 to 20 min. After centrifugation at 3,000 rpm for 20 min, 1 mL of the supernatant serum sample was placed into two Eppendorf tubes and stored at –80°C until the day of the study. Serum IL-17 and TNF-α levels were measured quantitatively by the enzyme-linked immunosorbent assay (ELISA) method using micro-ELISA kits commercially designed for research purposes, following the manufacturer's recommendations.

Table 1. Demographic and clinical characteristics of the participants according to groups

	Home-based exercise group (n=27)					Aerobic exercise group (n=27)					
	n	%	Mean±SD	Median	25th-75th percentile	n	%	Mean±SD	Median	25th-75th percentile	*p*
Age (year)			42.4±10.5					43.9±9.0			0.588†
Sex											NA
Female	19	70.4				19	70.4				
Male	8	29.6				8	29.6				
Marital status											0.669‡
Married	25	92.6				23	85.2				
Single	2	7.4				4	14.8				
Place of residence											0.577¶
Town center	15	55.6				18	66.7				
District or village	12	44.4				9	33.3				
Working status											0.913¥
Unemployed	14	51.9				12	44.4				
Retired	2	7.4				2	7.4				
Still working	11	40.7				13	48.2				
Education level											0.284§
Primary education	11	40.8				10	37.0				
High school	6	22.2				11	40.8				
University	10	37.0				6	22.2				
Body mass index (kg/m^2)				27.7	24.5-33.1				27.5	25.0-29.8	0.659#
Co-morbidity	6	22.2				8	29.6				0.756¶
DMARD receive	7	25.9				12	44.4				0.254¶
Smoking consumption	10	37.0				9	33.3				>0.999¶
Alcohol consumption	0	0.0				2	7.4				0.491‡
HLA-B27											0.510§
Positive	10	37.0				12	44.4				
Negative	14	51.9				10	37.0				
Unknown	3	11.1				5	18.5				
Disease duration (month)				96.0	36.0-168.0				108.0	48.0-168.0	0.505#

SD: Standard deviation; † Student t-test; ‡ Fisher exact probability test; ¶ χ^2 test with continuity correction; ¥ Fisher-Freeman-Halton test; § Pearson χ^2 test; # Mann-Whitney U test; NA: Not available; DMARD: Disease-modifying antirheumatic drug; HLA: Human leukocyte antigen.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Whether the distribution of continuous numerical variables was close to normal was investigated using the Shapiro-Wilk test, and whether the assumption of homogeneity of variances was met was investigated using the Levene test. Continuous data were expressed in mean ± standard deviation (SD) or median (25^{th}-75^{th} percentile), while categorical data were expressed in number and frequency. As a result of the goodness-of-fit tests, the significance of the differences between the groups in terms of continuous numerical variables for which parametric test statistics assumptions were met was evaluated using the Student t-test, while the significance of the differences for continuous numerical variables for which parametric test statistics assumptions were not met was examined using the Mann-Whitney U test. The Pearson chi-square test was used to analyze

Table 2. ASDAS-CRP, pain-VAS, BASFI, BASMI, chest expansion, 6MWT, ASQoL, weekly NSAID receive values of the participation in both groups at baseline and after treatment and comparisons between groups

	Week 0			Week 12			
	Mean±SD	Median	25^{th}-75^{th} percentile	Mean±SD	Median	25^{th}-75^{th} percentile	*p*¶
ASDAS							
Home-based exercise group		2.0	1.8-2.0		1.8	1.3-2.1	0.040†
Aerobic exercise group		2.0	1.8-2.0		1.3	1.2-1.5	<0.001†
Pain-VAS							
Home-based exercise group		3.0	2.0-4.0		2.0	1.0-4.0	<0.001†
Aerobic exercise group		4.0	3.0-5.0		2.0	1.0-3.0	<0.001†
BASFI							
Home-based exercise group		2.2	1.2-3.8		1.5	1.0-2.5	<0.001†
Aerobic exercise group		2.3	1.5-4.0		1.1	0.0-2.9	<0.001†
BASMI							
Home-based exercise group		1.0	0.0-2.0		0.0	0.0-1.0	0.003†
Aerobic exercise group		1.0	0.0-2.0		0.0	0.0-1.0	<0.001†
Chest expansion (cm)							
Home-based exercise group	5.29±1.21			5.57±1.08			0.008‡
Aerobic exercise group	4.98±1.08			5.50±1.13			<0.001‡
Six-Minute Walk Test (m)							
Home-based exercise group		515.0	459.0-550.0		520.0	460.0-560.0	0.004†
Aerobic exercise group		506.0	487.0-534.0		561.0	544.0-605.0	<0.001†
ASQoL							
Home-based exercise group		6.0	3.0-9.0		4.0	1.0-7.0	<0.001†
Aerobic exercise group		7.0	3.0-10.0		1.0	0.0-5.0	<0.001†
Weekly NSAID receive							
Home-based exercise group		7	3-8		4	0-10	0.245†
Aerobic exercise group		7	6-14		14	4-14	0.894†

ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein; VAS: Visual Analog Scale; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; 6MWT: Six-Minute Walk Test; ASQoL: Ankylosing Spondylitis Quality of Life; NSAID: Non-steroidal anti-inflammatory drug; SD: Standard deviation; † Wilcoxon signed-rank test; ‡ Dependent t-test; ¶ Results were considered statistically significant for p<0.025 according to Bonferroni correction.

categorical data, Fisher exact probability test, and Fisher-Freeman-Halton test. According to the follow-up times within the groups, the Wilcoxon signed-rank test was used to determine whether there was a statistically significant change in all parameters except for chest expansion. The significance of the change in chest expansion was investigated using the dependent t-test. Multivariate linear regression analyses were employed to ascertain whether aerobic exercise exerted a notable influence on the alteration in ASDAS, VAS, and inflammatory markers, respectively, following the adjustment for other confounding factors. Coefficients of regression, 95% confidence intervals (CIs) and t-statistics were also calculated for each variable. Given that the dependent variables exhibited a non-normal distribution, logarithmic transformation was applied in the regression analyses. Bonferroni correction was applied to control type 1 errors in all possible multiple comparisons. A *p* value of <0.05 was considered statistically significant.

RESULTS

A total of 54 patients were included in the study. There were no statistically significant differences between the groups. The demographic data and clinical characteristics of the participants are presented in Table 1.

After treatment, a significant improvement was observed in disease activity determined by the ASDAS-CRP only in the aerobic exercise group (p<0.001). In both groups, improvements in pain level, functional status, spinal mobility, chest expansion, functional exercise capacity, and quality of life were observed after treatment compared to the beginning (p<0.001, p<0.001; p<0.001, p<0.001; p=0.03, p<0.001; p=0.008, p<0.001; p=0.004, p<0.001; p<0.001, and p<0.001, respectively) (Table 2). After treatment, ESR and TNF-α levels decreased only in the HBE group (p=0.015 and p=0.014, respectively) (Table 3). After the treatment, more improvements in disease activity, pain level, functional exercise capacity, and quality of life were found in the aerobic exercise group than in the HBE group (p<0.001, p=0.004, p<0.001, and p=0.038, respectively) (Table 4). After treatment, only the decrease in TNF-α level was greater in the HBE group (p=0.050) (Table 5).

After adjustment for other confounding factors, ASDAS levels continued to decrease statistically significantly more in the aerobic exercise group than in the HBE group (β=–0.252, 95% CI: –0.367 to –0.136, p<0.001). Similarly,

Table 3. Comparisons between pre- and post-treatment in terms of biochemical measurements within groups

	Week 0		Week 12		
	Median	25th-75th percentile	Median	25th-75th percentile	*p*†
ESR					
Home-based exercise group	11.0	4.0-8.0	7.5	5.0-13.0	**0.015**
Aerobic exercise group	10.0	4.0-22.0	10.0	5.0-17.0	0.294
CRP					
Home-based exercise group	3.78	2.16-8.27	5.47	1.72-12.15	0.355
Aerobic exercise group	5.00	1.44-9.86	4.89	1.68-6.88	0.072
TNF-α					
Home-based exercise group	117.0	54.9-155.9	65.0	44.9-131.4	**0.014**
Aerobic exercise group	103.1	57.8-147.8	78.9	50.8-179.5	0.981
IL-17					
Home-based exercise group	84.7	70.7-140.7	76.6	62.4-121.0	0.220
Aerobic exercise group	80.8	65.9-194.0	70.4	61.0-226.4	0.790

† Results were considered statistically significant for p<0.025 according to Wilcoxon signed-rank test and Bonferroni correction. ESR: Erythrocyte sedimentation rate; CRP: C reactive protein; TNF-α: Tumor necrosis factor-alpha; IL: Interleukin.

Table 4. Comparisons made between groups in terms of changes in clinical evaluations after treatment compared to the baseline

	Home-based exercise group (n=27)					Aerobic exercise group (n=27)					
	n	%	Mean±SD	Median	25th-75th percentile	n	%	Mean±SD	Median	25th-75th percentile	*p*
ASDAS				–0.2	–0.5 to 0.1				–0.6	–0.7 to –0.4	**<0.001**†
Pain-VAS (0-10 cm)				–1.0	–2.0 to 0.0				–2.0	–3.0 to –1.0	**0.004**†
BASFI				–0.4	–1.2 to 0.0				–0.9	–1.6 to –0.3	0.094†
BASMI				0.0	–1.0 to 0.0				–1.0	–1.0 to 0.0	0.241†
Chest expansion (cm)			0.28±0.51					0.52±0.61			0.121‡
6MWT (m)				1.0	0.0 to 10.0				46.0	35.0 to 75.0	**<0.001**†
ASQoL				–2.0	–4.0 to –1.0				–4.0	–6.0 to –2.0	**0.038**†
Weekly NSAID receive											0.756¶
Decreased	9	33.3				7	25.9				
Unchanged	13	48.2				16	59.3				
Increased	5	18.5				4	14.8				

SD: Standard deviation; ASDAS: Ankylosing Spondylitis Disease Activity Score; VAS: Visual Analog Scale; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; 6MWT: Six-Minute Walk Test; ASQoL: Ankylosing Spondylitis Quality of Life; NSAID: Non-steroidal anti-inflammatory drug; † Mann-Whitney U test; ‡ Student t-test; ¶ Fisher-Freeman-Halton test.

Table 5. Comparisons between groups in terms of changes in acute phase reactants and cytokine levels after treatment compared to baseline

	Home-based exercise group (n=27)		Aerobic exercise group (n=27)		
	Median	25th-75th percentile	Median	25th-75th percentile	*p*†
Erythrocyte sedimentation rate	–2.0	–3.0 to 1.0	–1.0	–4.0 to 2.0	0.554
C reactive protein	0.09	–1.07 to 3.92	–0.64	–3.27 to 0.34	0.072
Tumor necrosis factor-alpha	–20.4	–52.7 to 3.9	–1.3	–19.0 to 20.5	**0.050**
IL-17	–10.1	–28.2 to 13.7	0.0	–16.4 to 32.4	0.264

† Mann-Whitney U test; IL: Interleukin.

the decrease in VAS levels was statistically significantly greater in the aerobic group (β=–0.313, 95% CI: –0.527 to –0.099, p=0.005) (Table 6).

On the other hand, after adjustment for other confounding factors, the change in post-treatment inflammatory marker levels compared to pretreatment did not show a statistically significant difference between the HBE and aerobic exercise groups (p>0.05) (Table 7).

DISCUSSION

Controlling the inflammation underlying axSpA is of utmost importance in preventing the devastating consequences of the disease. In this study, we detected a greater improvement in disease activity evaluated by ASDAS-CRP in the aerobic exercise group compared to the HBE group. However, in laboratory evaluations, we could not detect any significant improvement in ESR, CRP, TNF-α, or IL-17 levels in the aerobic exercise group. It is recommended that

Table 6. Multivariate linear regression analysis of the impact of aerobic exercise on the change in ASDAS, VAS scores after treatment, adjusted for other confounding factors

		95% CI for B			
	Coefficient of regression (B)	Lower bound	Upper bound	t	*p*
Delta ASDAS					
Age	-0.001	-0.009	0.006	–0.335	0.739
Male factor	–0.005	–0.145	0.135	–0.069	0.945
Body mass index	0.007	–0.006	0.021	1.071	0.290
Smoking exposure	–0.076	–0.196	0.043	–1.287	0.205
DMARD receive	0.081	–0.042	0.204	1.322	0.193
Duration of disease	0.000	0.000	0.001	1.021	0.313
Aerobic exercise	–0.252	–0.367	–0.136	–4.371	**<0.001**
Delta VAS					
Age	0.002	–0.012	0.016	0.256	0.799
Male factor	0.131	–0.127	0.390	1.021	0.312
Body mass index	0.004	–0.021	0.029	0.345	0.732
Smoking exposure	0.038	–0.183	0.259	0.342	0.734
DMARD receive	–0.035	–0.263	0.193	–0.309	0.759
Duration of disease	0.000	–0.001	0.002	0.472	0.639
Aerobic exercise	–0.313	–0.527	–0.099	–2.944	**0.005**

CI: Confidence interval; ASDAS: Ankylosing Spondylitis Disease Activity Score; VAS: Visual Analog Scale; DMARD: Disease-modifying anti-rheumatic drug.

ASDAS-CRP should be used in the evaluation of disease activity in patients with axSpA.[10] Although acute phase reactants such as ESR and CRP are used in follow-up and TNF-α and IL-17 inhibition have been shown to be effective in treatment, there is no definitive laboratory parameter which shows relationship with disease activity.[4-9] In addition, measurements of acute phase reactants and cytokine levels can be affected by many factors.[20,21]

Disease activity, as assessed by the ASDAS-CRP, decreased compared to baseline only in the aerobic exercise group. Similar to our results, Basakci Calik et al.[22] and Günendi et al.[23] also showed in their studies the effectiveness of aerobic exercise in reducing disease activity in axSpA patients. Additionally, in a meta-analysis conducted by Harpham et al.,[24] the decrease in disease activity was greater in aerobic exercise than in non-aerobic exercise. Jennings et al.[25] also showed the effect of aerobic exercises in reducing disease activity. However, unlike our results, this effect was not greater than that in the non-aerobic group. Our results are consistent with most previous studies. Evaluating disease activity with ASDAS, which also uses CRP values, can make the results more reliable.

A significant improvement in pain-VAS score was observed after exercise compared to the beginning in both the HBE and aerobic exercise groups. This improvement was greater in the aerobic exercise group than in the HBE group. Hu et al.[26] and Niedermann et al.[27] also showed the effect of various types of exercises on pain control in patients with axSpA. These results may suggest that many exercises reduce pain levels in patients with SpA.

In our study, a significant improvement in the BASFI value was observed in both groups. No significant difference was detected between the recovery rates in both groups. In their studies, Jennings et al.[25] also showed significant improvement in the BASFI with various types of exercise in axSpA patients. Additionally, in the meta-analysis conducted by Boudjani et al.,[28] exercise, regardless of exercise type, had a moderate effect on functionality and adding aerobic exercise to stretching and strengthening

Table 7. Multivariate linear regression analysis of the impact of aerobic exercise on the change in the levels of inflammatory markers after treatment, adjusted for other confounding factors

		95% CI for B			
	Coefficient of regression (B)	Lower bound	Upper bound	t	*p*
Delta ESR					
Age	–0.005	–0.023	0.014	–0.501	0.619
Male factor	–0.146	–0.490	0.197	–0.857	0.396
Body mass index	–0.010	–0.044	0.023	–0.636	0.528
Smoking exposure	0.127	–0.167	0.421	0.871	0.388
DMARD receive	0.221	–0.082	0.524	1.469	0.149
Duration of disease	0.000	–0.002	0.003	0.431	0.668
Aerobic exercise	–0.160	–0.445	0.124	–1.134	0.263
Delta CRP					
Age	–0.001	–0.019	0.017	–0.125	0.901
Male factor	–0.153	–0.493	0.188	–0.904	0.371
Body mass index	–0.029	–0.062	0.004	–1.771	0.083
Smoking exposure	–0.269	–0.560	0.022	–1.858	0.070
DMARD receive	0.030	–0.270	0.330	0.199	0.843
Duration of disease	0.001	–0.001	0.003	1.135	0.262
Aerobic exercise	–0.178	–0.460	0.104	–1.273	0.209
Delta TNF-α					
Age	0.010	–0.021	0.041	0.663	0.511
Male factor	0.131	–0.441	0.703	0.460	0.648
Body mass index	0.005	–0.050	0.060	0.171	0.865
Smoking exposure	0.078	–0.411	0.567	0.322	0.749
DMARD receive	–0.051	–0.556	0.453	–0.205	0.838
Duration of disease	0.001	–0.003	0.004	0.380	0.706
Aerobic exercise	0.272	–0.201	0.746	1.157	0.253
Delta IL-17					
Age	–0.017	–0.044	0.010	–1.291	0.203
Male factor	0.094	–0.407	0.596	0.379	0.706
Body mass index	–0.036	–0.084	0.013	–1.482	0.145
Smoking exposure	0.132	–0.297	0.561	0.620	0.538
DMARD receive	–0.274	–0.716	0.168	–1.247	0.219
Duration of disease	0.003	–0.001	0.006	1.532	0.132
Aerobic exercise	–0.002	–0.417	0.413	–0.010	0.992

CI: Confidence interval; ESR: Erythrocyte sedimentation rate; DMARD: disease-modifying anti-rheumatic drug; CRP: C-reactive protein; TNF-α: Tumor necrosis factor-alpha; IL: Interleukin.

exercises increased functionality. All these data may indicate that many types of exercise increase functionality in patients with SpA.

Although we observed an improvement in the BASMI scale after exercise in both groups, we did not detect a significant difference between the two groups. Similar to our study, in the study conducted by Jennings et al.,[25] an improvement in BASMI value was observed in both the aerobic exercise and stretching exercise groups, but no difference was found between the groups. Differently, in the study conducted by Basakci Calik et al.,[22] an improvement in BASMI value could be shown only in the aerobic exercise group. Our data may suggest that the improvement in spinal mobility is mainly affected by flexibility and stretching exercises.

At the end of our study, a significant increase in chest expansion was detected in both groups. No significant differences were detected between the groups. Studies by Ortancil et al.[29] showed the effectiveness of breathing exercises in increasing chest expansion in axSpA patients. In the review conducted by Saracoglu et al.,[30] specific exercises, including breathing exercises and aerobic exercise, were more effective in increasing chest expansion in patients with axSpA and AS compared to conventional exercise. These findings suggest that breathing exercises are basic exercises to increase chest expansion.

In the current study, we observed a significant improvement in the 6MWT in both groups, and a greater increase in the 6MWT was detected in the aerobic exercise group than in the HBE group. In a study conducted by Karapolat et al.[31] and Jennings et al.,[25] a significant improvement in the 6MWT was observed only in the group that performed aerobic exercise in addition to conventional exercise. The increase in functional exercise capacity in the HBE group in our study may be related to the improvement in spinal mobility, functional status, and pain scores. Based on these data, a significant increase in the 6MWT in the aerobic exercise group compared to the HBE group may indicate the importance of aerobic exercise in increasing functional exercise capacity.

Furthermore, our study found an improvement in the quality of life evaluated using the ASQoL scale in both the HBE and aerobic exercise groups. The improvement in ASQoL score in the aerobic exercise group was greater than that in the HBE group. Studies by Bodur et al.[32] and Durmuş et al.[33] also showed that exercise was associated with increased quality of life in patients with AS. All these data indicate the importance of aerobic exercise in improving the quality of life of patients with SpA.

In the present study, we observed no significant changes in NSAID usage at the end of the study compared to the beginning in either group. In a cross-sectional study conducted by Ma et al.,[34] in patients with AS, individuals with low exercise compliance had higher NSAID use. In our study, the improvement in disease activity and functional status without making any changes in drug treatment showed exercise's positive effect in treating SpA.

We found no decrease in CRP levels from baseline in either the aerobic exercise or HBE group. There are studies in the literature in which aerobic exercise can and cannot be shown to reduce CRP levels in patients with axSpA.[24,35] Our results may be related to the fact that CRP levels do not increase in all AS patients and do not always correlate with the patients' symptoms.[20] We included individuals with low disease activity according to ASDAS-CRP in our study. The fact that the initial median CRP value was within the normal range may have contributed to our failure to show a decrease. There is a need for studies with larger patient numbers and groups with higher CRP levels.

In our study, a significant decrease in ESR level compared to baseline was observed in the HBE group, whereas no significant change in ESR level was observed in the aerobic exercise group. However, this decrease was not significantly different between the groups. To the best of our knowledge, there is no study showing a significant decrease in ESR levels with aerobic exercise in patients with axSpA.[24,35] However, there are studies showing a decrease in ESR or not in individuals with AS due to non-aerobic exercise.[20,36,37] Our data indicating that aerobic exercise does not significantly affect ESR levels in axSpA patients are compatible with the literature. Although we observed a decrease in disease activity in the aerobic exercise group, the reason why we could not show a decrease in ESR may be that the ESR level did not increase in all patients or the blood samples taken immediately after the last exercise mimicked the trauma model.[20,38,39] However, the number of studies on this subject is limited and more studies are needed.

Moreover, we observed a significant improvement in the TNF-α levels after treatment in the HBE group. However, the change in after-treatment TNF-α levels compared to before treatment did not show a difference between groups. Similar to our data, no study has investigated the effect of regular aerobic exercise on TNF-α levels in patients with axSpA. There is a limited number of studies showing a decrease in

TNF alpha levels with non-aerobic exercises.[36,40] The use of TNF-α inhibitors in patients with axSpA has been shown to reduce disease activity.[10] Although we showed a decrease in disease activity in the aerobic exercise group, the reason why we could not show a decrease in the TNF-α level may be that the blood samples taken immediately after the last exercise were affected by the mechanical stress factor.[21,41] It has been shown that regular exercise reduces the cytokine response by inhibiting Toll-like receptor-4 receptor expression.[42] However, acute moderate-intensity exercise increases the T-helper 1 (Th1)-dependent cytokine response.[38] Also, there was no clear relationship between the TNF-α level and disease activity. In addition, preclinical studies have shown that stress and microdamage applied to the enthesis area of subjects with axSpA activates the IL-23/17 pathway and TNF-α released.[21]

Our study showed no significant change in IL-17 levels after exercise in either group. To the best of our knowledge, no study has examined the effects of aerobic exercise on IL-17 levels in patients with axSpA or AS yet. However, some studies have investigated the effect of aerobic exercise on IL-17 levels in different patient groups.[43-46] In a study by Levitova et al.,[47] patients with AS and nr-axSpA followed a six-month exercise program that included cardiorespiratory fitness and multiple types of non-aerobic exercise. They took blood samples from those patients at the beginning of exercise and within seven days after its completion. Similar to our results they didn't observe any significant change in IL-17 nonetheless they observed decrease in disease activity. There are extremely few studies examining the relationship between IL-17 level and disease activity.[5,48] Also, similarly TNF-α, stress and microdamage applied to the enthesis area of subjects with axSpA activates the IL-23/17 pathway and IL-17 released.[21] The release of IL-17 caused by microtraumas during treadmill running may have masked the demonstration of a long-term decrease in IL-17 levels in blood samples taken immediately after the last exercise session.

It has been reported that, during regular exercise, blood samples taken within 1 h after the end of the last exercise program can reflect the acute effect of the exercise rather than its cumulative effect.[41] There are also studies reporting that the effect of acute exercise on the immune system ends in 3 to 72 h.[49] Therefore, the laboratory parameters we obtained in the aerobic exercise group may reflect the effect of acute exercise rather than regular exercise. Considering this issue, future studies may help clarify the effect of regular exercise on cytokines and acute-phase reactants.

The intensity of exercise, as well as the time elapsed after exercise, affects the immune response which develops after exercise.[49] In our study, patients in the aerobic exercise group performed moderate exercise at 60 to 70% of their heart rate reserve.[50] Investigating the effects of aerobic exercise at different intensities on inflammation in axSpA patients may also contribute to the literature.

Additionally, our study includes a 12-week exercise follow-up period. Monitoring long-term exercise results may also be important to better understand the effectiveness of exercise. Telemedicine should also be considered for long-term follow-up.

The main strengths of our study are that it is the first study to investigate the effect of regular aerobic exercise on TNF-α and IL-17 in patients with axSpA in the literature; compliance with HBE program and NSAID use was monitored by telemedicine method; and ASDAS-CRP was used to evaluate disease activity. The main limitations, on the other hand, are that blood samples were taken immediately after the completion of the last walking program in the aerobic exercise group, and since the participants consisted of individuals with low disease activity, the median ESR and CRP values were found to be within the normal range.

In conclusion, while aerobic exercise, in addition to a conventional exercise program, does not cause any changes in the cytokines and acute-phase reactants as evidenced by laboratory evaluations, it may have an anti-inflammatory effect by reducing the disease activity as determined by clinical assessment. Both aerobic and conventional exercises improve pain level, functional exercise capacity, quality of life, functional status, and spinal mobility in patients diagnosed

with axSpA. Aerobic exercise also provides additional benefits in reducing disease activity, pain control, increasing functional exercise capacity, and improving the quality of life. Adding an aerobic exercise program to the conventional exercise program for patients diagnosed with axSpA may further contribute to the control of disease activity and treatment management.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Author contributions: Idea/concept/design: A.B., Y.O.G.G.; Control/supervision, critical review: A.B.; Data collection and/or processing, writing the article: Y.O.G.G., U.G.E.; Analysis and/or interpretation: Y.O.G.G., U.G.E., A.B.; Literatüre review, materials: Y.O.G.G.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The study protocol was funded by Scientific Research Projects.

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