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Effect of anti-tumor necrosis factor therapy on the efficacy of aerobic exercise in patients with ankylosing spondylitis

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Abstract

Background: This study aims to evaluate the effects of aerobic exercise on ankylosing spondylitis (AS) patients' clinical outcomes when combined with anti-tumor necrosis factor (TNF) treatments.

Methods: Fifty patients diagnosed with AS participate in the study, with 25 on anti-TNF treatment and 25 off anti-TNF treatment. Patients' age, education, body mass index, smoking habits, symptom duration, date of diagnosis, medication use, comorbidities, and surgical history were assessed. Patients receive instructions to walk for 30 minutes, three times per week for twelve weeks and receive evaluation at weeks 0, 6, and 12. Disease activity is evaluated using Visual Analog Scale (VAS) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), while sleep quality is assessed by the Pittsburgh Sleep Quality Index (PSQI). The Ankylosing Spondylitis Life Quality (ASQoL) is used to measure the quality of life and physical activity is measured by the International Physical Activity Questionnaire (IPAQ).

Results: During week 6, VAS, BASDAI, PSQI, and IPAQ scores were significantly lower in both groups, one taking anti-TNF and the other anti-TNF-free, in comparison to baseline and week 12 scores. After undergoing six weeks of aerobic exercise treatment, those taking anti-TNF displayed greater improvements in ASQoL scores in contrast to those who were not taking anti-TNF.

Conclusion: Aerobic exercise is an effective intervention for enhancing disease activity, quality of life, sleep quality, and physical activity in patients with AS. Additionally, anti-TNF treatment appears to amplify the clinical benefits associated with exercise and facilitate patients' physical activity.

Keywords: Ankylosing spondylitis; Anti-TNF; Exercise; Quality of life; Sleep

1. Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease that affects the spine and causes impairments in quality of life and disability [1]. It is accompanied by inflammation and pain in the spine and joints, resulting in decreased physical activity, fatigue, sleep disturbances, depression, anxiety, and stress [2]. Respiratory dysfunction of the restrictive type is common [3]. The objective of treatment is to prevent stiffness and bending and to maintain mental and physical fitness [4]. Pharmacological and non-pharmacological treatments are recommended for patients with AS. The non-pharmacological treatments consist of educational and regular exercise interventions that can be supervised medially or done at home. Implementing aerobic exercise programs increases an individual's walking distance and

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cardiopulmonary capacity, providing valuable benefits to their functional capacity, mobility, and disease activity [5]. Such aerobic exercises, including walking and swimming, are linked to the improvement of quality of life and respiratory function [6].

The purpose of this study is to evaluate the effects of aerobic exercise on clinical outcomes in patients with AS in combination with anti-Tumor necrosis factor (TNF) treatment.

2. Material and Methods

Fifty patients aged 18 to 65 years were diagnosed with AS based on modified New York criteria. Among them, 25 received anti-TNF treatment (adalimumab, infliximab, etanercept, golimumab) for a minimum of 3 months, while the other 25 did not receive non-steroidal anti-inflammatory drugs or disease-modifying anti-rheumatic drugs. Exclusion criteria for this study included patients with serious heart, lung, liver, or kidney diseases, any psychiatric or mental diseases, patients with serious arthritis, patients with prosthetics, patients who had been regularly exercising for the last 6 months, and pregnant patients. The ethics committee of University of Health Sciences, Hamidiye Etfal Training and Research Hospital granted ethical approval for this study. Informed consent was obtained from all participants.

At baseline, patients were asked about their age, Body mass index (BMI), smoking status, symptom duration, diagnosis dates, medications, comorbidities, and surgical history.

Patients undertook a 12-week intervention, consisting of 30-minute walking exercise 3 times per week. Walking took place outside on a flat surface, aiming to achieve a desired pulse range of 60% exercise density, with pulse recorded at 10, 20, and 30 minutes. Participants' walking speed was first assessed on a treadmill in the clinic. After a week, they were reassessed to ensure appropriate walking speed. Follow-up evaluations occurred at weeks 0, 6, and 12. Disease activity was evaluated using a visual analog scale (VAS) and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), while sleep quality was assessed through the Pittsburgh Sleep Quality Index (PSQI). The Ankylosing Spondylitis Quality of Life (ASQoL) was used to gauge their quality of life, and the International Physical Activity Questionnaire (IPAQ) was utilized to measure their physical activity.

2.1. Statistical Analysis

The research data were digitally processed and assessed utilizing SPSS ver. 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Mean (±) standard deviation, frequency distributions, and percentiles were presented as descriptive statistics. Categorical variables were evaluated using the Pearson chi-square test, Fisher's exact test, and Yates corrected chi-square test. The study assessed the normality of the variables through both visual (histograms and probability plots) and analytical (Shapiro-Wilk tests) means. Two independent groups were assessed for significance using the Student *t*-test, while an analysis of variance was used to determine the statistical significance of three related groups for variables that conformed to a normal distribution. For the significant variables, the paired sample *t*-test was employed in pair-wise comparisons with Bonferroni correction to validate the source of significance. The Mann-Whitney U test was used to determine the statistical significance between the two independent groups for variables that were not normally distributed, while the Friedman test was used for the three related groups. In the paired comparisons using the Bonferroni hoc method to identify the source of statistical differences, a statistical significance level of $p<0.05$ was utilized.

3. Results

There were no statistically significant differences between the group receiving anti-TNF treatment and the group that did not receive it in relation to age, BMI, symptom duration, date of diagnosis, education level, smoking frequency and quantity, comorbidity status, or surgical history ($p<0.05$).

Patients who received anti-TNF had an average VAS score of 3.44±3.51 at baseline, 0.32±0.69 at week 6, and 2.44±2.84 at week 12, while those who did not had a mean VAS score of 7.04±2.76 at baseline, 1.40±2.16 at week 6, and 5.56±3.22 at week 12. The VAS scores at weeks 0, 6, and 12 showed a statistically significant difference between the anti-TNF group and anti-TNF-free group ($p<0.05$). The VAS scores of patients who did not receive anti-TNF treatment were significantly higher. Additionally, there was a statistical difference in VAS scores for assessment times between the anti-TNF and anti-TNF-free groups. Further analysis through post-hoc paired comparisons confirmed that the difference between the anti-TNF and anti-TNF-free groups was due to the evaluation at the 6th week. The mean VAS scores for the anti-TNF and anti-TNF-free groups in week 6 were significantly lower compared to baseline and week 12.

As displayed in Table 1, the average BASDAI scores for both the anti-TNF and anti-TNF-free groups exhibited a significant decrease in week 6 as compared to baseline and week 12.

There was a statistically significant difference observed between the anti-TNF and anti-TNF-free groups in relation to the baseline and 12-week ASQoL scores ($p<0.05$). Significantly higher baseline and 12-week ASQoL scores were found in the anti-TNF-free patients as compared to the anti-TNF patients. However, no such difference was found between the groups in terms of ASQoL at week 6 ($p>0.05$). There was a significant statistical divergence in ASQoL scores between the groups receiving anti-TNF drugs and those receiving no such treatment at the times of assessment ($p<0.05$). Furthermore, the ASQoL score dropped significantly in the anti-TNF group at week 6, as compared to baseline and week 12 scores (Table 1).

There were no statistically significant differences in PSQI scores between the anti-TNF and anti-TNF-free groups at baseline, week 6, and week 12 ($p>0.05$). In both groups, PSQI scores were significantly lower at week 6 than at weeks 1 and 12. Therefore, while patients experienced high sleep quality at week 6, they had poor sleep quality at weeks 1 and 12 (Table 1).

There was no significant statistical difference between the groups treated with anti-TNF and without anti-TNF in terms of IPAQ scores at baseline, week 6, and week 12 ($p>0.05$). However, the IPAQ scores at week 6 were significantly lower than those at week 1 and week 12 in both groups, indicating that while patients were physically active at week 6, their physical activity levels were average at weeks 1 and 12 (Table 1).

Table 1 Distribution of BASDAI, ASQoL, PSQI, and IPAQ scores in terms of anti-TNF status and evaluation times

	0	**6th Week**	**12th Week**	**p**
BASDAI				
Anti-TNF	2.34±2.28	0.38±0.88[ac]	1.96±2.35	<0.001
Anti-TNF Free	5.86±2.50	1.12±1.82[ac]	4.90±2.93	<0.001
P	<0.001	0.004	0.001	
ASQoL				
Anti-TNF	6.72±4.65	1.84±2.34[ac]	5.60±4.21	<0.001
Anti-TNF Free	11.32±4.48[bc]	2.52±3.47[c]	8.80±5.66	<0.001
P	0.001	0.197	0.015	
PSQI				
Anti-TNF	8.16±4.08	1.96±1.34[ac]	6.36±3.17	<0.001
Anti-TNF Free	9.20±4.18[bc]	2.96±3.35[c]	6.72±4.00	<0.001
P	0.378	0.087	0.726	
IPAQ (MET-min/wk)				
Anti-TNF	2046.7±6301.2	4866.6±2242.1[ac]	2148.7±6290.1	<0.001
Anti-TNF Free	1191.8±3953.8	5134.2±4548.1[ac]	1342.7±4314.0	<0.001
P	0.064	0.648	0.607	

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, TNF: Tumor Necrosis Factor; ASQoL: Ankylosing Spondylitis Quality of Life Scale; PSQI: Pittsburgh Sleep Quality Index; IPAQ: International Physical Activity Questionnaire; Values are presented as mean±standard deviation. [a]: A statistically significant difference was found with post-hoc comparison in group "0". [b]: A statistically significant difference was found with post-hoc comparison in group"6th Week". [c]: A statistically significant difference was found with post-hoc comparison in group"12th Week".

4. Discussion

AS is a chronic inflammatory disease that significantly impacts the sacroiliac and spinal joints, potentially leading to spinal fusion [7]. The aim of AS treatment is to manage inflammation and prevent deformities and disability caused by new bone growth, while also safeguarding the patient's quality of life by reducing or halting any negative impact on

their community activity or function [8]. According to Assessment of Spondyloarthritis international Society/European Alliance of Associations for Rheumatology, regular exercise and patient education are considered to be the fundamental aspects of non-pharmacological AS treatment [8]. Currently, updated guidelines suggest that home exercise is generally effective, while supervised individual and group exercise is even more effective and desirable as it promotes adherence to treatment [9]. In this study, we aim to assess the impact of aerobic exercise in combination with anti-TNF treatment on the clinical outcomes of patients with AS. In some studies, on aerobic exercise, including our own, the exercise's intensity remains constant, while in other studies, it progressively increases. We maintained the exercise's intensity level to remain consistent, considering the limitation of not being able to continually monitor our patients at the clinic.

Numerous studies have confirmed that rehabilitation programs combined with TNF inhibitors, particularly supervised or group exercise, result in improved pain, function, and disability. This, in turn, demonstrates the synergistic effects of combination treatments on AS patients [8, 10, 11].

In a cross-sectional study assessing exercise outcomes before and after TNF inhibitor treatment, 32 patients with AS participated in a program consisting of walking and swimming. It was discovered that after treatment, patients were able to exercise for a longer period. Specifically, patients exercised for 133.61 minutes per week after treatment, compared to 67.97 minutes per week before treatment. Patients reported improvements in stiffness, function, fitness, postural healing, pain, breast expansion, and spinal mobility of low to moderate degree with exercise and anti-TNF treatment. Furthermore, anti-TNF treatment significantly increased motivation to exercise on a scale of 10 with ratings of 6.32 and 3.78 after and before anti-TNF treatment, respectively [12].

No significant differences were found in pain levels between the treatment and control groups after a 4-month home exercise program in a separate study [13]. In a separate study, the group that completed home exercises exhibited a minor but meaningful reduction in pain levels [14]. Lim et al conducted a study that found a significant improvement in VAS scores among the treatment group that performed home exercises [15]. In our study, we examined the impact of walking exercises on two groups: one receiving anti-TNF treatment and another not. We discovered a significant decrease in VAS scores in both groups that underwent aerobic exercise therapy after treatment. However, we observed that this effect had not persisted by the 12th week. These results suggest that the aerobic exercise program is efficacious in both groups as long as it is continued, but its effect diminishes over time. The exercise treatment was successfully applied by all our patients, resulting in decreased pain until the end of the treatment period in both patient groups. No hindrance was encountered during the treatment.

In assessing disease activity in AS, the commonly used tool is BASDAI [16]. In a study, after undergoing a 50-minute aerobic exercise treatment three times a week for 12 weeks, both the treatment and control groups demonstrated significant enhancements in BASDAI. Nevertheless, there were no substantial variations between the two groups [5]. In another study, researchers compared a group that received both home exercise and aerobic exercise with a group that only received home exercise. Patients in the combined exercise group participated in 20 to 30 minutes aerobic exercise sessions with 50% exercise density. However, no significant difference in BASDAI was observed between the two groups [17]. Aerobic exercise was administered in our study to two groups, one receiving anti-TNF treatment and the other not. Both groups showed significant improvement by the 6th week. The initial BASDAI scores of the anti-TNF group were lower than the other group, and their diseases were not active. The group that did not receive anti-TNF treatment had high BASDAI scores at the beginning of the study. Despite being in the active phase of the disease at week 12, they adhered to the exercise program without any difficulty, resulting in a significant reduction in their BASDAI scores by week 6. In other words, the aerobic exercise program was effective for both groups in the short term, but its long-term effectiveness diminished.

It is widely understood that AS substantially reduces a patient's quality of life due to resulting disabilities that negatively impact social relationships. To address this, the ASQoL scale was created to measure quality of life for AS patients. The ASQoL scale has been shown to be both a valid and reliable tool for use in clinical and research settings [18]. Nineteen patients were evaluated in a study performed by Lubrano et al.[19], in which the AS patients who only take rehabilitation treatment and the ones who take rehabilitation treatment combined with anti-TNF are being compared. At first, 3 weeks of intense inpatient rehabilitation treatment was applied to patients. Exercises were performed by a physiotherapist twice a day. The patients in the rehabilitation program completed strengthening exercises subsequent to warm-up exercises and then participated in endurance exercises involving 15 minutes of spinning, 10 minutes on the treadmill, 10 minutes of walking, and 15 minutes of breathing exercises. The patients' workout intensity began at 60% and gradually increased to 80%. The patients' treatment concluded after three weeks, with final evaluations of Bath Ankylosing Spondylitis Functional Index, Leeds Disability Questionnaire, European Quality of Life Questionnaire, BASDAI, tragus wall distance, chest expansion, modified Schober and 6-minute walking test. Following a six-week post-treatment period, the same patients underwent a regimen of 25 mg subcutaneous etanercept twice per week alongside

a concurrent three-week rehabilitation program. Patient reassessments occurred 3 weeks after the treatment. At the conclusion of the study, the treatment regimen in conjunction with etanercept proved to be more effective in enhancing functionality, reducing disability, and improving overall quality of life [19]. In our study, the group treated with anti-TNF demonstrated a noteworthy enhancement in ASQoL by the 6th week. ASQoL scores of anti-TNF patients at the start and conclusion of the study were considerably less than those who did not receive anti-TNF. Thus, our findings reveal that an aerobic exercise program improves the quality of life of the anti-TNF group. Patients who received anti-TNF had lower disease activity and better functional status compared to those who did not receive anti-TNF. Consequently, they were able to perform aerobic exercises with greater ease and motivation. The combination of reduced disease activity and increased motivation during exercise may have contributed to these positive results.

The PSQI is a questionnaire designed to assess sleep quality across seven main domains, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction [20]. We assessed our patients' sleep quality using PSQI and found that both groups had poor sleep quality at the beginning of our study. A literature search returned no studies investigating the impact of aerobic exercise on sleep quality among AS patients. In a study conducted by Li et al., PSQI values were significantly higher in AS patients than in the control group [21]. Kashefi et al. investigated the impact of an 8-week aerobic exercise program on PSQI in over 50 middle-aged, non-athlete women. The results revealed a significant improvement in sleep quality [22]. Both groups demonstrated improved sleep quality six weeks after aerobic exercise in our study. These findings suggest that the aerobic exercise program is effective in improving sleep quality in both anti-TNF taking and non-taking AS patients in the short term. However, the long-term efficacy of this program decreases.

The IPAQ is constructed with three forms: long, short, and very short, aimed at assessing physical activity and sedentary behavior patterns of adults. A study regarding its validity and reliability was conducted in Turkey [23]. Few studies have investigated the relationship between AS and IPAQ in the literature search. One such study evaluated the relation between IPAQ and the Short Questionnaire to Assess Health-enhancing Physical Activity (SQUASH), which is another physical activity survey, using daily physical activity and clinical assessments. It has been determined that both surveys were moderately reliable for assessing AS, but SQUASH is superior to IPAQ [24]. Gaunaurd et al. used the IPAQ to assess the physical activity levels of patients with idiopathic pulmonary fibrosis participating in a pulmonary rehabilitation program. They found that 3 months of a pulmonary rehabilitation program had significant improvements in IPAQ values [25]. Borland et al. administered group aerobic exercises twice a week for 60 minutes over three months to patients with chronic heart failure, but they did not observe any improvements in these patients [26]. The physical activity levels of individuals with AS were evaluated in our study using the IPAQ tool. Results indicated that the aerobic exercise program significantly improved physical activity levels by the 6th week, regardless of whether the individuals were taking anti-TNF treatment or not. Therefore, the findings suggest that the short-term effects of the aerobic exercise treatment were effective in increasing physical activity. However, these effects were not long-lasting once the exercise program was completed.

Several studies have compared exercise programs for patients with AS or investigated the effects of exercise. The findings indicate that group-based, supervised, or one-on-one physiotherapy sessions and in-patient treatments are more effective than home exercises and conventional exercises [27-30]. It remains undetermined which modality of exercise is optimal despite numerous studies. However, data suggest that effective rehabilitation programs must comprise supervised exercise programs while serving as an educational component. In addition, during the first week of treatment, we introduced our patients, who were initially given walking exercises, to our clinic and had them walk on a treadmill with supervision. We also checked in on them once a week to monitor their progress. We believe that we have increased their motivation and adaptation because every one of our patients told us that they have done their exercise program as suggested.

In this study, we analyzed the short-term and long-term effects of the exercise intervention. Based on our findings from existing research, the exercise intervention enhanced disease activity, sleep quality, quality of life, and physical activity during the 6-week short-term period when the exercises were carried out. Nonetheless, we observed a reduction of these effects during the 12-week long-term period.

The study has limitations due to the small number of patients included and the absence of additional follow-up beyond 12 weeks.

5. Conclusion

The outcomes show significant enhancements in disease activity, quality of life, sleep quality, and physical activity. Additionally, anti-TNF treatment amplifies the impact of exercise treatment and accelerates clinical improvements in

AS patients, as well as their adaptation to exercise. To conclude, it is recommended that AS treatment plans encompass aerobic exercise programs.

Compliance with ethical standards

Disclosure of conflict of interest

No conflicts of interest/competing interests have been reported by the authors or by any individuals in control of the content of this article.

Statement of ethical approval

Ethical approval was obtained from the Ethics Committee of University of Health Sciences, Hamidiye Etfal Training and Research Hospital for the study.

Statement of informed consent

The patients were informed about the content, purpose, and application of the study and their informed consent was obtained.

Availability of data and material

The data that support the findings of this study are available from the corresponding author, [author initials], upon reasonable request.

Authors' contributions

- Concept – Neşe Aksu Çoban, Banu Kuran;
- Design – Banu Kuran;
- Supervision – Banu Kuran;
- Materials – Aylin Ayyıldız, Selda Çiftci İnceoğlu;
- Data collection &/or processing – Neşe Aksu Çoban, Aylin Ayyıldız, Selda Çiftci İnceoğlu;
- Analysis and/or interpretation – Neşe Aksu Çoban, Aylin Ayyıldız;
- Literature search – Figen Yılmaz, Aylin Ayyıldız;
- Writing – Aylin Ayyıldız;
- Critical review – Aylin Ayyıldız, Banu Kuran, Figen Yılmaz

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