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Original Article

Aerobic exercise improves oxidant-antioxidant balance in patients with rheumatoid arthritis

Zeynep Tuna, PT, MSc[1)*], Tulin Duger, PT, PhD[2)], Nevin Atalay-Guzel, PT, PhD[1)], Arzu Aral, MD, PhD[3)], Bilkay Basturk, MD[3)], Seminur Haznedaroglu, MD[4)], Berna Goker, MD[4)]

[1)] *Department of Physiotherapy and Rehabilitation, Faculty of Health Sciences, Gazi University: Ankara 06500, Turkey*
[2)] *Department of Physiotherapy and Rehabilitation, Faculty of Health Sciences, Hacettepe University, Turkey*
[3)] *Department of Immunology, Faculty of Medicine, Gazi University, Turkey*
[4)] *Department of Internal Medicine, Division of Rheumatology, Gazi University, Turkey*

Abstract. [Purpose] Although oxidative stress is known to be present in rheumatoid arthritis (RA), the effects of exercise on oxidative parameters are unknown. The aim of this study was to investigate the effects of acute aerobic exercise on serum oxidant and antioxidant levels in patients with RA. [Subjects and Methods] Sixteen patients with RA and 10 age-matched healthy volunteers participated in this study. All participants wore polar telemeters and walked on a treadmill for 30 minutes at a speed eliciting 60–75% of maximal heart rates. Blood samples were obtained before, immediately and 24 hours after exercise and malondialdehyde (MDA) and total sulfhydrile group (RSH) levels were measured. [Results] Both groups had similar heart rates during the test but the treadmill speed of the RA patients was significantly lower than that of the healthy volunteers. Serum MDA levels were lower than in both groups immediately after exercise, with greater decrements in the RA patients than controls. MDA levels returned to baseline 24 hours after the exercise only in the controls; they remained low in the RA patients. There was a slight increase in serum RSH levels after exercise compared to baseline in both groups. [Conclusion] Moderate intensity treadmill exercise did not have any adverse effect on the oxidant-antioxidant balance. The results suggest that such an exercise may be safely added to the rehabilitation program of RA for additional antioxidant effects. Morever, this antioxidant environment is maintained longer in RA patients.
Key words: Aerobic exercise, Oxidative status, Rheumatoid arthritis

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INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disorder which is characterized by chronic inflammation mainly affecting the joints and dysregulated oxidative metabolism is a significant mechanism playing a major role in the pathophysiology of the disease. Most RA studies focusing on oxidative metabolism have reported that the oxidant levels are increased in rheumatic patients indicating that RA patients are subjected to oxidative stress[1–3)]. Therefore, RA treatment strategies should aim to alter the inflammatory and oxidative pathways to recover as close as possible the normal physiological states.

A growing number of clinical studies have shown that exercise is beneficial for RA patients. It is well known that exercise has beneficial effects on the physical parameters of RA, including pain, fatigue, quality of life, aerobic capacity and muscle strength without inducing any structural damage[4–6)]. A wide range of types of exercise, including strengthening and aerobic exercises, are concluded to be safe without any adverse effects on RA[5, 7)].

Although aerobic exercise improves the functional parameters of RA, its effects on the pathophysiology of the disease remain to be elucidated. The aim of this study was to investigate the effects of an acute bout of moderate aerobic exercise on the plasma oxidant and antioxidant profiles of RA patients. The hypothesis of this study is that aerobic exercise alters the oxidative status and exerts beneficial effects on the pathophysiology of the disease.

SUBJECTS AND METHODS

The study design was approved by Gazi University Clinical Researches Ethics Committee and is registered with the number 275-13.07.2011.

Subjects

Sixteen RA patients diagnosed according to the Ameri-

*Corresponding author. Zeynep Tuna (E-mail: zeyneptuna6@yahoo.com)

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Table 1. Eligibility criteria for inclusion in the study

Age 18–60
Confirmed RA diagnosis according to ACR 1987 criteria (10)
Functional ACR Class I, II and III
In remission for the previous 3 months
No history of any other metabolic or cardiovascular diseases
No steroid treatment in the previous 3 months
No tobacco or excessive alcohol consumption in the previous 12 months

RA: Rheumatoid arthritis; ACR: American College of Rheumatology

Table 2. Characteristics of the RA patients and healthy controls

	Patients	Controls
Age	45.3±11.8	40.6±8.7
Height (cm)	164±9.6	163.8±8.1
Body weight (kg)	79±10	67.6±11.2*
IPAQ score (METs-min/wk)	1,825±1,719	2,056±1,533

Values are the mean ±SD. METs-min/wk: METs-minutes/week
* $p<0.05$

Table 3. Comparison of the physical activity of both groups

	Patients	Controls
Test speed (km/h)	5.1±1.4	6.2±1.1*
Test heart rate	130±14	129±6

km/h: kilometers/hours. *$p<0.05$

can College of Rheumatology (ACR) criteria[8] and 10 age-matched healthy volunteers participated in this study. All of the RA patients were on synthetic disease modifying anti-rheumatic drugs (DMARD) therapy, and they had been in remission for at least 3 months before entry into the study. Patients with metabolic or cardiovascular disorders were excluded. Patients who had received steroid therapy (any dose or any form) in the previous 3 months were also excluded. Those smoking tobacco or with excessive alcohol consumption in the previous 12 months were also excluded. The eligibility criteria are listed in Table 1.

All of the participants were assessed for eligibility after a detailed explanation about the study and all gave signed their informed consent. They were instructed not to exercise and not to take any drugs except their routine medications the day before the test.

Methods

On the test day, the participants were assessed for the descriptive parameters of age, sex, height, body weight, resting heart rate and blood pressure. Prior to the exercise, they completed the Turkish version of the International Physical Activity Questionnaire (IPAQ)[9] which assesses individual's weekly physical activity levels and allows evaluation of metabolic equivalents of tasks (METs).

The aerobic exercise protocol was carried out on a treadmill at a submaximal intensity for 30 minutes. Exercise intensity was determined individually for each participant, with the aim of eliciting 60–75% of the calculated maximal heart rate (220-age)[7] . Heart rate was monitored by a polar telemeter during the test. The testing included 3 minutes warm-up and 2 minutes cool-down and the treadmill speed was adjusted to elicit the target heart rate of each participant during the test. Venous blood samples were obtained from the antecubital vein prior to baseline, immediately after, and 24 hours after the exercise. All the participants performed the test in the afternoon and 24-hour blood samples were drawn the next day at about the same time in the afternoon. The blood samples were centrifuged at 3,500 rpm for 10 minutes and stored at −80 °C until the analyses.

Malondialdehyde (MDA) as an indicator of lipid peroxidation (an indicator of oxidant state) and total sulfhydrile groups (RSH), as an indicator of antioxidant state, were measured using Kurtel's spectrophotometric method[10].

Statistical analyses were performed using SPSS Version 15.0. Friedman's non-parametric test was used to analyze the plasma levels of oxidants and antioxidants. In the case of significant results, Wilcoxon's test was used for further analysis. The comparison of the groups were performed using the Mann-Whitney U test. The results are expressed as mean±SD, and statistical significance was accepted for values of $p<0.05$.

RESULTS

The baseline characteristics of the study patients and healthy controls are given in Table 2. The groups did not differ with age, height or physical activity levels (Table 3). However, patients had greater body weight than the healthy controls ($p<0.05$).

Although both groups performed the treadmill walking exercise at similar heart rates, the treadmill walking speed of the RA patients during the exercise was significantly lower than that of the controls ($p=0.047$). The baseline mean serum MDA level of the patients was higher than that of the control group ($p<0.05$). Serum MDA levels decreased significantly with exercise in both groups ($p<0.05$). Although a return toward baseline MDA levels were seen at 24-hour post-exercise in both groups, the increase in MDA was significant only in the control group ($p<0.05$); serum MDA levels of RA patients remained lower than the baseline even at 24 hours after the exercise (Table 4).

No difference in serum RSH levels was noted between the groups at any time point. Serum RSH levels increased

Table 4. Comparison of mean±SD plasma MDA levels (nmol/ml) in the patients and healthy controls

MDA (nmol/ml)	Pre-test	Post-test	Post-test	24 hours later
Patients	5.7±3	3.4±1.5*	3.4±1.5	4.5±3
Controls	3.1±1¥	1.8±0.5*,¥	1.8±0.5¥	2.6±1.2

*: Significant difference within groups; ¥: Significant difference between groups

Table 5. Comparison of plasma RSH levels in the RA patients and control groups ($p>0.05$)

RSH (nmol/ml)	Pre-test	Post-test	24 hours later
Patients	349.2±157.2	365.2±169.8	326.1±82.7
Controls	278.4±31.8	297.7±47.4	283.9±31.7

with exercise in both groups, but the change was not statistically significant (Table 5).

DISCUSSION

This study demonstrated that a bout of moderate intensity aerobic exercise created an antioxidant environment in patients with RA. Moreover, the exercise had no significant adverse effects on the oxidant-antioxidant balance. Hence, it appears that moderate intensity aerobic exercise is beneficial for general health and is safe with respect to inflammatory status in RA. The results also showed that the patients had lower cardiovascular fitness levels than the healthy controls as indicated by their lower walking speeds at the target heart rates.

The beneficial effects of different exercise types for RA have previously been described[4–7]. Although several previous studies have reported a link between exercise and RA, they have generally aimed to assess functional and physical parameters such as aerobic capacity, bone mineral density, pain, fatigue, and quality of life[5–7, 11]. Furthermore, exercise has recently been suggested to alter the pathophysiological pathways; therefore it may improve the symptoms of chronic inflammatory diseases[12]. However, the effects of acute exercise on the dysregulated oxidative processes and their mechanisms in RA are still unclear.

There are many studies in the medical literature suggesting that a mechanism impaired in RA, and that oxidative metabolism plays a role in its pathophysiology. Oxidant levels were shown to be increased in RA patients exhibiting oxidative stress, indicating their link with the chronic inflammation[1, 2]. Studies have revealed that the levels of oxidative molecules are increased[2, 3]; however, antioxidant defenses are insufficient in RA patients. Although a great number of studies of the beneficial effects of exercise in RA are present in the literature, its effects on disease pathophysiology are still unclear. The results of the present study support the view that aerobic exercise can affect the pathophysiology of the disease, as evidenced by the serum MDA analyses.

Current data on the oxidative response to exercise show that it varies with exercise intensity[13, 14]. It is thought that exhaustive exercise at maximal intensity increases serum oxidant levels causing oxidative stress; however, submaximal exercise generally does not affect the oxidant levels. In our present study, plasma MDA levels decreased in response to acute aerobic exercise at submaximal intensity in both groups. This result is consistent with some other studies[15, 16]. The small increase observed in the RSH levels is possibly a manifestation of other antioxidant defenses. The most exciting result of our study is that the MDA levels did not return to the baseline levels the next day in the RA patients, as opposed to the healthy individuals. This suggests that aerobic exercise exerts an acute antioxidant effect which is maintained longer in RA patients.

Increased risk of cardiovascular diseases has significant effects on disease morbidity and mortality, and RA patients have 60% increased risk of cardiovascular death compared to the general population[17]. In this study, the lower treadmill walking speeds of the RA patients at the target heart rate indicate the poor cardiovascular status of these patients and this result is in agreement with the literature. Oxidative stress and overproduction of reactive oxygen species play a major role in atherosclerosis and cardiovascular diseases[18]. Oxidative stress resulting from chronic inflammation in RA seems to enhance cardiovascular risks, and an integrated therapeutic approach combining anti-inflammatory treatment and aerobic exercise may have beneficial effects on the cardiovascular morbidity and mortality of RA. Hence, aerobic exercise could be a powerful physiotherapy intervention in the non-pharmaceutical management of both the disease and its co-morbidities. Walking, which was chosen as the exercise for our study, is the most popular aerobic exercise as it needs no special equipment and has proven effects on blood markers[19].

Our study had several limitations. First, we were able to study only a limited number of patients. However, the number is comparable to similar previous exercise intervention studies[20, 21]. Second, we measured serum levels; thus, systemic, rather than local effects of acute aerobic exercise were investigated. Further studies to examine synovial samples are also needed to investigate local changes. Finally, we measured only the serum levels of MDA as an oxidative marker, which is the most commonly used indicator of lipid peroxidation. However, MDA has been the most commonly measured parameter of the oxidative state in the most recent exercise metabolism studies[13–16].

In conclusion, moderate aerobic exercise exerts an antioxidant effect lasting over 24 hours, providing additional evidence in support of the importance of exercise in the rehabilitation of RA.

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