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# Impact of aerobic exercise training and garlic consumption on fatigue and cardiovascular risk factors in women with rheumatoid arthritis

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This study aimed to investigate the effect of aerobic exercise and garlic supplementation on fatigue and cardiovascular risk factors in women with rheumatoid arthritis (RA). Twenty-eight patients who fulfilled the European League Against Rheumatism- American College of Rheumatology (EULAR-ACR) criteria for RA were assigned to three groups, exercise + placebo (E+P) (n = 6), exercise + garlic supplement 500 mg twice/day (E+G), (n = 11) and garlic supplement 500 mg twice/day (G), (n = 11) for 8 weeks. The training program consisted of working on an ergometer 3 sessions/week with a heart rate equal to 60% of VO2max and gradual overload. The outcomes of this study were a comparison of changes in the mean value of the fatigue assessment questionnaire score (FSI), cholesterol, and low-density lipoprotein (LDL) levels. For data analysis, paired t-tests and ANCOVA were used using SPSS software ($P \leq 0.05$). The results of the paired t-test showed that after the intervention, the levels of fatigue decreased in the E+G ($P = 0.025$) as well as in the G ($P = 0.002$), while it did not change in the E+P ($P = 0.151$). Additionally, the amount of cholesterol did not change in any of the study groups, and the amount of LDL decreased only in E+G ($p=0.028$). Furthermore, ANCOVA analysis showed that, there is no significant difference between the study groups in the levels of fatigue ($P = 0.962$), cholesterol ($P = 0.922$) and LDL ($P = 0.626$) after the intervention. According to the results, aerobic exercise and the consumption of garlic can be effective in reducing fatigue and the risk factors of cardiovascular.

***Keywords:*** aerobic exercise; garlic; fatigue; heart disease risk factors; rheumatoid arthritis

## Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease characterized by joint inflammation, destruction, deformity, and physical disability, including fatigue. It is also associated with high morbidity and mortality from cardiovascular diseases [1]. RA is more prevalent in individuals aged 40 and above, with women being up to five times more likely to develop RA compared to men [2]. Katz et al. (2006) conducted a study on 548 patients with RA and found that fatigue and psychological factors associated with the disease contribute to the inability to perform daily activities [3]. Fatigue in patients with RA is significant enough to impact other complications of the disease, making its elimination a top priority [4]. As a result, researchers have given special attention to this issue.

The risk of cardiovascular diseases is significantly higher in patients with RA. Common cardiovascular risk factors such as high blood pressure, diabetes, and physical inactivity are also prevalent among patients with RA [5]. Aerobic exercise (AE) is a type of physical activity to improve oxygen delivery to the body's


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active tissues [6]. AE is performed at a mild intensity and continuously [6]. It has been suggested that AE intervention can significantly reduce cardiovascular disease risk factors by alleviating fatigue in RA patients [4, 6]. Inactive RA patients have been shown to have a worse cardiovascular disease risk profile compared to physically active patients [1]. Santos et al. (2023) stated that physical activity, including exercise, is a safe and useful method for managing fatigue in individuals with RA [7].

Alongside exercise and physical activity, consuming food products with special therapeutic properties is recommended for many diseases. Garlic is a plant with medicinal properties known since around 3000 BC, and it has been used worldwide not only as a food but also as medicine since ancient times [8]. Among the functional benefits of garlic, we can mention antimicrobial, anticancer, antioxidant activity, the ability to reduce cardiovascular disease risk factors, improve immune system function, and have antidiabetic effects [8]. Garlic is found to be rich in allicin, S-allyl cysteine, and diallyl disulfide, which play a significant role in reducing cardiovascular complications [9]. Human studies have confirmed that garlic improves the symptoms of physical and systemic fatigue, although the mechanism of action is not completely clear [10]. Based on these findings and the hypothesis that AE and garlic consumption can effectively improve cardio-vascular risk factors and fatigue as non-pharmacological methods, this study aims to investigate the effects of AE and garlic supplement consumption on fatigue symptoms and cardiovascular disease risk factors in patients with RA. The study aims to provide new information in this field.

## Materials and Methods

The current study is a semi-experimental clinical trial with a single-blind design and a pre-post-test design with a control group. The study has been registered in the Iranian Registry of Clinical Trials (clinical trial code: IRCT20180923041097N5). The study included 28 female RA patients who met Europe and America's international classification criteria in 2010. The participants were selected from patients referred to Imam Ali Hospital in Zahedan city during the summer of 2021, all in remission (disease activity score-28 < 2.6).

*Inclusion criteria:*

Female patients over 18 years old who were living in Zahedan and willing to participate in the study.

*Exclusion criteria:*

Having chronic physical diseases such as diabetes, kidney failure, liver failure, cardiovascular disease, lung disease, and cancer. Patients with known mental problems, including depression or those being treated with psycho-active drugs, were also excluded. Patients with joint injuries that would prevent them from engaging in exercise activities, such as arthritis, were excluded. Menopausal women were also excluded due to hormonal changes that could affect the study results. The subjects were required to have controlled disease activity, and the consumption of disease-regulating drugs remained unchanged during the study. They were monitored throughout the 8 weeks of the research. If any complications arose or they expressed unwillingness to continue, they were allowed to withdraw from the study.

*Randomization:*

Participants were divided into 3 groups by simple randomization method: exercise along with placebo (E+P) (n = 6), exercise along with garlic supplement (E+G) (n = 11), and garlic supplement (G) (n= 11). The subjects in the E+G and E+P groups were unaware of their group allocation.

*Training protocol:*

The AE protocol consisted of eight weeks, 3 sessions/week, and each session for 30-50 min. Each session included a 10 min warm-up (jogging and stretching), 15-35 min running on a treadmill (at 60-70% reserve heart rate), and a 5 min cooling down period at the end (Table 1).

*Supplementation:*

The E+G group received a garlic supplement (500 mg twice a day) during 8 weeks along with the exercise protocol, the E+P group received a placebo (capsules filled with corn starch) twice a day in addition to exercise, and the G group did not participate in any exercise, but received

garlic supplement (500 mg twice a day). The garlic supplement was a coated tablet containing 500 mg of garlic produced by Gol Daru Company, Isfahan-Iran.

**Table 1:** Exercise training program

| ***Weeks*** | ***Exercise Duration*** *(Min)* | ***Exercise Intensity*** *(% Reserve heart rate)* |
|---|---|---|
| *First* | *15* | *60* |
| *Second* | *15* | *69* |
| *Third* | *15* | *65* |
| *Fourth* | *15* | *65* |
| *Fifth* | *20* | *70* |
| *Sixth* | *25* | *70* |
| *Seventh* | *30* | *70* |
| *Eighth* | *35* | *70* |

*Fatigue measurement:*

The level of fatigue was determined using the Fatigue Severity Inventory (FSI) questionnaire this questionnaire has been confirmed in previous studies [11]. The subjects filled out the questionnaire before and after the eight-week exercise program. The final score obtained from the questionnaire was considered the fatigue score [12].

*Cardiovascular risk factors measurement:*

To measure cardiovascular risk factors, the subjects visited the laboratory 24 hours before the first exercise session and 24 hours after the last exercise session. They arrived at 8 am after a 12-hour fasting period. Venous blood samples (3 cc) were collected using a syringe.

The samples were centrifuged at 3000 rpm for 7 minutes at 4˚C after 30 minutes of exposure to ambient temperature and clot formation. If there was no hemolysis, the serum was isolated and transferred to cryo tubes. Each sample was assigned a code based on the patient's group, and they were stored at -70°C for later measurement of total cholesterol and LDL.

*Statistical analysis*

Within-group comparisons were performed using the paired t-test, while between-group comparisons were conducted using one-way ANOVA (pretest) and ANCOVA (posttest). The data are presented as means ± standard deviation (SD). All statistical analyses were carried out using SPSS software (version 26) with a significance level set at $P < 0.05$.

## Results

The baseline characteristics of the subjects are presented in Table 2. The participants' age, body weight, and body composition did not differ significantly between the three before or after the study, and no significant changes were observed during the study. ANOVA analysis revealed no significant differences between the groups for any variables at the start of the study.

The results of the paired t-test analysis

**Table2.** Compared the pre- and post-test of variables in three groups

| **Variable** | | **E + G** (n = 11) **Mean ± SD** | **P-value** | **E + P** (n = 6) **Mean ± SD** | ***P-value*** | **G** (n = 11) **Mean ± SD** | **P-value** |
|---|---|---|---|---|---|---|---|
| **Age** (year) | | 37.81 ± 7.61 | | 36.83 ± 9.94 | | 36.90 ±8.005 | |
| **Height** (cm) | | 164 ± 5.84 | | 160.3 ± 5.68 | | 163.18 ± 5.89 | |
| **Weight** (Kg) | **Pre** | 70.27 ± 8.78 | 0.012* | 61.66 ± 5.85 | 0.163 | 68.18 ± 5.79 | 0.104 |
| | **Post** | 70.02 ± 8.68 | | 61.54 ± 6.03 | | 68.29 ± 5.21 | |
| **BMI** ($Kg/m^2$) | **Pre** | 26.6 ± 2.28 | 0.062 | 24.00 ± 2.14 | 0.204 | 25.76 ± 3.44 | 0.126 |
| | **Post** | 26.53 ± 2.30 | | 23.94 ± 2.11 | | 25.79 ± 3.36 | |
| **Fatigue** (FSI Score) | **Pre** | 5.85 ± 1.86 | 0.025* | 4.26 ± 0.94 | 0.151 | 5.85 ± 1.86 | 0.002* |
| | **Post** | 3.75 ± 1.58 | | 2.85 ± 1.53 | | 3.75 ± 1.58 | |
| **Cholesterol** (mg/dl) | **Pre** | 181 ± 29.34 | 0.218 | 160.16 ± 19.77 | 0.298 | 181± 29.34 | 0.452 |
| | **Post** | 175.09 ± 24.31 | | 157.83 ± 18.88 | | 175.09 ± 24.31 | |
| **LDL** (mg/dl) | **Pre** | 114.36 ± 19.97 | 0.028* | 94.13 ± 17.64 | 0.929 | 114.36 ± 19.97 | 0.217 |
| | **Post** | 106.60 ± 20.91 | | 94.66 ± 20.65 | | 106.60 ± 20.91 | |

*P ≤ 0.05

E, exercise; G, garlic; P, placebo; SD, standard deviation; BMI, body mass index; FSI, fatigue symptom inventory; LDL, low-density lipoprotein

revealed that after the intervention, the level of fatigue decreased in the E+G group (P = 0.025) and in the G group (P = 0.002). However, the E+P group did not significantly change in fatigue score after the intervention (P = 0.151). Regarding the cardiovascular risk factors, the amount of cholesterol did not show any significant changes in any of the study groups. However, the E+G group showed a significant decrease in LDL levels (P = 0.028) Figures 1-3.

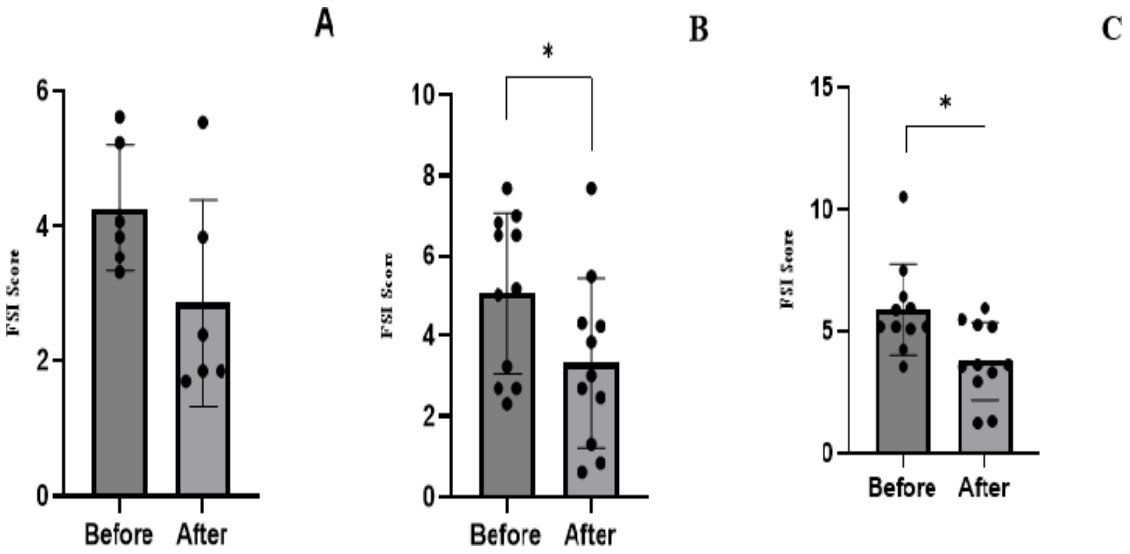


**Figure 1.** Fatigue levels before and after intervention, A: E+P group (P = 0.151), B: E+G group (P = 0.025) and C: G group (P = 0.002).

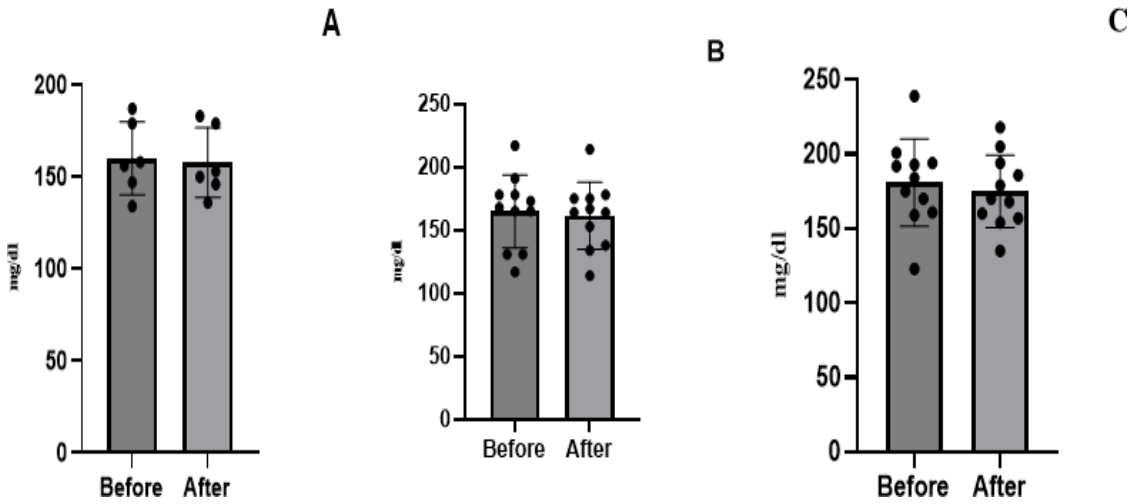


**Figure 2.** Cholesterol levels before and after intervention, A: E+P group (P = 0.298), B: E+G group (P = 0.218) and C: G group (P = 0.452).

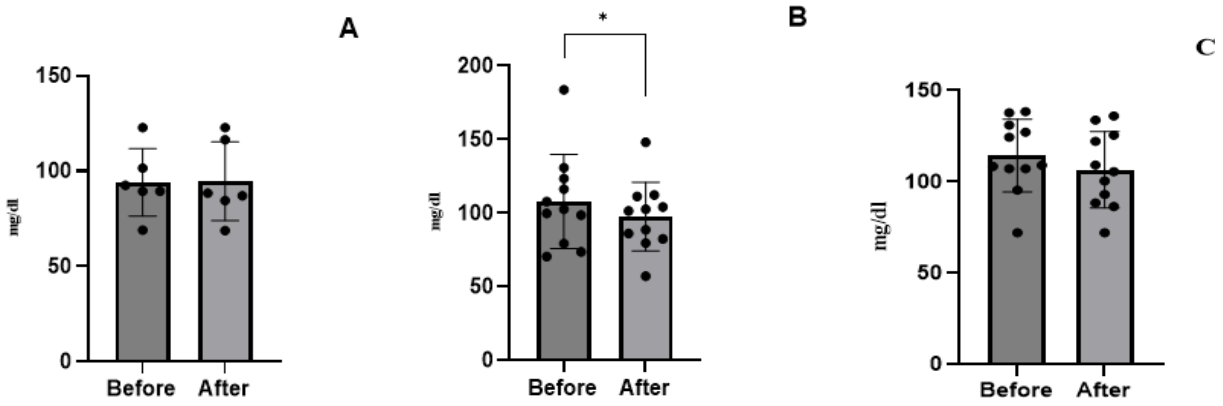


**Figure 3.** LDL levels before and after intervention, A: E+P group (P = 0.929), B: E+G group (P = 0.028) and C: G group (P = 0.217).

**Discussion**

The findings of the present study suggest that eight weeks of AE positively reduced fatigue in female patients with RA. However, the reduction was not statistically significant. Interestingly, the combination of AE with garlic consumption significantly reduced fatigue levels among women with RA.

Several studies have also reported the beneficial effects of AE on fatigue reduction in individuals with RA. Kelley et al. (2018) and Yentur et al. (2021) found significant reductions in fatigue following AE interventions [13, 14]. Santos et al. (2023) also highlighted the usefulness and safety of exercise and physical activity in managing fatigue in RA patients [7]. These findings support the notion that exercise and physical activity are effective non-pharmacological approaches for managing fatigue in RA. However, in contrast to these findings, our study did not find a significant difference in fatigue levels after the AE intervention. One possible explanation for this discrepancy is the lack of a standardized tool for measuring fatigue in RA patients. Fatigue experienced by these patients can vary depending on the stage of the disease, the type of activities performed, and individual differences in energy levels [13]. Previous studies have reported a wide range of fatigue levels in RA patients, ranging from 41% to 80% [15-18]. In line with our findings, a meta-analysis conducted by Rongen et al. (2015) reported a non-significant reduction in fatigue levels after twelve weeks of aerobic exercise training in RA patients [4]. This suggests that while AE may have positive effects on fatigue reduction, the lack of statistical significance in some studies may be attributed to the complexity and variability of fatigue experiences in RA patients. Overall, our study adds to the existing literature by highlighting the potential benefits of AE and garlic consumption in reducing fatigue levels in women with RA. Nevertheless, further research using standardized tools and larger sample sizes is needed to validate these findings and determine the optimal exercise interventions for managing fatigue in RA patients.

The findings of our study indicate that the combination of AE and garlic consumption reduced fatigue in patients with RA. Previous studies have also suggested that certain foods, such as garlic and fish, can alleviate symptoms of RA [19]. Morihara et al. (2007) reviewed the use of garlic in the treatment of fatigue and found positive effects [10]. In a separate study, Morihara et al. (2006) investigated the mechanism of garlic's therapeutic effect on fatigue induced by repeated endurance exercises in rats. They measured markers of physical fatigue, including succinate dehydro-genase activity (a marker of aerobic glucose metabolism), nitric oxide metabolite concentration, and lactic acid concentration. The results showed that repeated endurance exercises increased succinate dehydrogenase activity by 2-4 times, while aged garlic increased it by 40%. Nitric oxide metabolite concentration slightly decreased during endurance exercise, but aged garlic increased it by up t o 2 times. Lactic acid

concentration did not change significantly in the groups [20]. These findings suggest that garlic may enhance aerobic glucose metabolism and improve oxygen supply by dilating blood vessels, thereby improving fatigue-related disorders. In our study, the reduction in fatigue observed after AE and garlic supplement consumption could be attributed to the potential effects of garlic on improving oxygen supply and metabolism. However, further research is needed to understand the underlying mechanisms of garlic's anti-fatigue effects fully. Additional studies exploring the dimensions of garlic's impact on fatigue in RA patients will contribute to a better understanding of its potential benefits and mechanisms of action.

Our study showed that LDL levels did not significantly decrease in patients with RA after AE with/without garlic consumption. However, the cholesterol levels did decrease after AE with/ without garlic consumption, and the reduction was statistically significant only in the AE and garlic group. Previous studies have reported inconsistent results regarding the effects of AE and garlic consumption on LDL and cholesterol levels. Some studies have shown that AE and garlic consumption can improve these lipid profiles [21- 23]. However, consistent with our findings, Bashiri et al. (2015) did not find significant differences in LDL and cholesterol levels between exercise and garlic consumption groups compared to a control group [24]. One possible explanation for our study's lack of significant changes in LDL and cholesterol levels is the initial levels of these indicators. It has been suggested that the effects of AE on lipid profiles may be more pronounced in individuals with higher initial levels of cholesterol and LDL [23]. In other words, AE may have a greater impact on individuals with elevated levels, helping to bring them closer to desired levels. In our study, the subjects had normal initial levels of cholesterol and LDL, which may explain the lack of significant changes. Regarding garlic consumption, previous research has shown that it can significantly reduce blood pressure, prevent atherosclerosis, lower serum cholesterol and triglycerides, inhibit platelet aggregation, and increase fibrinolytic activity [25]. Animal studies have demonstrated that garlic administration can significantly reduce serum cholesterol, triglycerides, and LDL in hyper-cholesterolemic mice but does not affect HDL levels [26]. Human studies have also reported significant reductions in serum cholesterol and triglycerides with garlic consumption [27]. A meta-analysis of 39 preliminary trials on the effects of garlic products found that a 2-month administration of garlic can reduce total cholesterol by 17±6 mg/dl and LDL by 9±6 mg/dl, particularly in individuals with high cholesterol levels (over 200 mg/dl) [28]. In our study, although LDL values were reduced after AE and garlic consumption, the reduction was insignificant compared to the exercise and placebo or the garlic supplement group alone. This difference in results may be attributed to the fact that previous studies included subjects with high cholesterol levels (above 200 mg/dl). In comparison, our study focused on individuals with normal blood cholesterol levels (less than 200 mg/dl). Nonetheless, it is evident that garlic consumption, when combined with an AE program, can be effective in reducing cardiovascular risk factors in patients with RA. To the best of our knowledge, our study represents the initial report comparing the impact of aerobic exercise in conjunction with garlic consumption on cardiovascular risk factors and fatigue in RA patients. Nevertheless, we did not investigate the correlation among multiple variables. Nonetheless, we thoroughly examined the impact of the specified variables.

**Conclusion**

The findings of this study suggest that an AE program combined with garlic consumption may have beneficial effects in reducing fatigue and cardiovascular risk factors in patients with RA. While the reduction in fatigue was not statistically significant, it indicates a potential positive impact of AE and garlic on managing fatigue in RA. Furthermore, although the reduction in LDL levels after AE and garlic consumption was not significant compared to other groups, the overall combination of exercise and garlic appears to contribute to improving cardiovascular risk factors in RA patients.

These findings highlight the potential benefits of incorporating an AE program and garlic consumption as non-pharmacological approaches in managing RA symptoms. However, further research with larger sample sizes and standardized measurement tools is necessary to validate these findings and better understand the underlying mechanisms of action. Future studies should also

consider the optimal duration, intensity, and frequency of AE and the dosage and duration of garlic consumption to maximize the benefits for patients with RA.

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**Conflict of interest**
No conflict of interest was declared between the authors.

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