ORIGINAL ARTICLE

# Effects of aerobic exercise on hematologic indices of women with rheumatoid arthritis: A randomized clinical trial

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**Background:** To investigate the effects of moderate aerobic exercise on the hemoglobin, hematocrit, and red blood cell (RBC) mass of women with rheumatoid arthritis (RA). **Materials and Methods:** This randomized clinical trial was conducted at the Specialized Clinic of Physical Medicine and Rehabilitation, Al-Zahra Hospital of Isfahan, during a 4-month period in 2014. We included patients with RA who did not have any malignancy and hematologic disorder. Two groups — one group receiving aerobic therapy along with medical therapy ($N$ = 16) and the other group receiving medical therapy alone ($N$ = 17) both for a period of 8 weeks. The levels of RBC mass, Hb, and HCT were measured before and after the intervention. The changes in these parameters were compared between the two study groups. **Results:** There was no significant difference between the two study groups regarding the baseline characteristics. The aerobic exercise resulted in increased RBC mass ($P < 0.001$), Hb ($P < 0.001$), and HCT ($P < 0.001$). However, those who received medical therapy alone did not experience any significant changes in these parameters. We found that the RBC mass ($P = 0.581$), Hb ($P = 0.882$), and HCT ($P = 0.471$) were comparable between the two study groups after 8 weeks of intervention. **Conclusion:** Although the aerobic exercise results in increased Hb, HCT, and RBC mass in patients with RA, the increase was not significant when compared to that in controls. Thus, the increase in the HB, HCT, and RBC could not be attributable to aerobic exercise.

**Key words:** Aerobic exercise, hematocrit (HCT), hemoglobin (Hb), red blood cell (RBC) count, rheumatoid arthritis (RA)

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## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disorder of the joints characterized by systemic inflammation of the joints leading to severe disability.[1] The dysregulated oxidative metabolism is a significant mechanism playing a major role in the pathophysiology of the disease. Several lines of evidence suggest that the patients with RA are subjected to oxidative stress based on the finding that these patients have increased levels of elevated oxidative metabolism.[2-5] Thus, many RA therapeutic strategies and protocols are based on minimizing the oxidative stress and reducing the inflammatory response in order to retain the normal physiological status.

In healthy individuals, physiologic exercise and relevant mechanical loading promotes specific response in systemic and local immune and hematologic parameters and muscle function.[1,6,7] Most of the patients with RA suffer from impaired muscle function such as (or including) imbalance and reduced muscle strength.[8] The symptoms of RA, such as joint swelling, pain, stiffness, and other complications, may hamper the physical training and reduce physical fitness.[9,10] Chronic inflammation and destruction of the joints result in deformities that also exacerbate the inactivity in the

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patients with RA.[2] This makes a vicious cycle in which the inactivity resulted in decreased muscular balance and joint deformity that in turn causes pain and disability. The pain prohibits the patient from exercise and moving the joints leading to the aggravation of the vicious cycle.[11] The inactivity and lack of exercise also result in decreased level of hemoglobin (Hb) and hematocrit (HCT) because of the decrease in intramedullary hematopoiesis. Chronic inflammation in the patients with RA also can cause anemia of chronic disease.[12]

The aerobic performance is enhanced by prolonged endurance training through improving oxidative capacity and increasing glycogen stores of the muscle cells.[13] Growing lines of evidence have demonstrated that exercise is beneficial for RA patients. 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.[14-18] A wide range of exercises, including strengthening and aerobic exercises, are concluded to be safe without any adverse effects on the patients with RA.[19,20] Although the aerobic exercise improves the functional parameters of RA, its effects on the pathophysiology of the disease remain to be elucidated. The exercise, especially the aerobic subgroup, in healthy individuals result in increased total Hb concentration, HCT, and red blood cell (RBC) mass.[21] The aim of the current study is to investigate the effects of moderate aerobic exercise on the Hb, HCT, and RBC mass of women with RA.

## MATERIALS AND METHODS

### Study population

This randomized clinical trial was conducted at the Specialized Clinic of Physical Medicine and Rehabilitation, Al-Zahra Hospital, which is a tertiary health-care center affiliated with the Isfahan University of Medical Sciences, located in central Iran. The study was conducted from September to December 2014. The study protocol was approved by the institutional review board (IRB) and medical ethics committee of the Shahrekord University of Medical Sciences. The study protocol of the current study is registered with the Iranian Registry of Clinical Trials (www.irct.ir; IRCT2015072923394N1). Informed written consents were obtained from all the patients before their inclusion in the study. We included women aged between 18 years and 70 years with diagnosis of RA according to the 2010 rheumatoid arthritis classification criteria.[22] The patients were excluded if they had thalassemia disorders, malignancies, sickle-cell anemia, megaloblastic anemia; were pregnant or breastfeeding; being treated with steroids, hypnotics, antidepressants, or antipsychotics; and were within the flare phase of the disease. None of the subjects participated in any activity at least in the last 3 years. We also excluded those who were smoker, opium addicted or alcoholic, and substance abusers.

### Randomization and Intervention

All the participants were randomly assigned to two study groups using a computer-based random digit generator using the admission numbers. Those who were assigned to the training group were placed in a training program including aerobic cycling that was done on the stationary bike (E828 Monark, Sweden)—three sessions per week in addition to medical treatment for 8 weeks. Those who were assigned to the control group received only medication for 8 weeks. The pharmacological treatment included methotrexate (7.5 mg per week) and prednisolone (5 mg per day) to modulate their disease. The training program lasted for 12 min during the first session and gradually it increased to 35 min during the 8 weeks of the study. The entire training program was conducted under the supervision of a physiatrist. Due to the special type of exercise, the risk of serious injury or illness was very low. The exercise was conducted at a submaximal intensity (60-70% of reserve heart rate). A gradual increase in exercise load was applied during the training period. The training program was designed according to Domsic *et al*.[23]

### Study protocol

All the eligible patients were invited for a coordination meeting being held at the rehabilitation department of our center in two separate sessions. The study protocol and the exercise protocol were thoroughly explained to the patients. All the patients underwent a complete physical examination and history determination by a physical medicine resident. The demographic information as well as examinations findings were recorded in a data-gathering form. The ability of the patients' performance in aerobic exercises was evaluated by a physiatrist before the study. The disease activity, pharmacological treatments, and previous surgeries for RA were also recorded in the forms. The patients' weights were assessed by laboratory scale with an accuracy of less than 100 g (Seca, Sweden) in a status without shoes and with minimal clothes. Their heights were assessed by height gauges with an accuracy of less than 0.5 cm (Seca, Sweden), and the body mass index (BMI) was calculated according to the weight and height of the patients.

### Outcome and Follow-up

The exercise was held for 8 weeks. During the exercise, the intensity was measured by Karvonen formula:

Reserve heart rate = maximum heart rate – rest
Targeted heart rate = rest + (60% of reserved heart rate)
Targeted heart rate = rest + (70% of reserved heart rate)

Venous blood samples were withdrawn from all the patients 2 days before and after the training period in a fasting status. The complete blood count (CBC), including the Hb, HCT, and RBC count, was measured before and after the intervention in all the subjects. The follow-up period of 8 weeks was chosen according to Cooper *et al*.[24] who demonstrated that 6 weeks of aerobic exercise will result in favorable changes in hemodynamic of patients with RA.

### Statistical analysis

In order to have 80% power to detect significant differences among mean Hb, HCT, and RBC count with effect size of 20% with $\alpha$ equal to 0.05, a number of 15 patients were required in each study group ($P < 0.05$, two-sided). In order to compensate for nonevaluable patients we screened 51 patients for eligibility. All the statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, USA) version 17.0. The data were presented as mean ± standard deviation (SD) and proportions as appropriate. The parametric data were compared using independent sample *t*-test for comparison between training and control groups and paired *t*-test within each groups. A two-sided *P*-value less than 0.05 was considered statistically significant.

## RESULTS

We screened 51 patients for eligibility out of whom 36 fulfilled the study criteria and were randomized to two study groups each including 18 patients. During the study, two patients from the training group and one from the control group were excluded and thus the final number of patient included in the final analyses were 16 in the training group and 17 in the control group [Figure 1]. The demographic characteristics of the patients are summarized in Table 1. There was no significant difference between two study groups regarding the baseline characteristics.

The baseline levels of RBC count, Hb, and HCT were comparable between two study groups. The aerobic exercise resulted in increased RBC mass ($P < 0.001$), Hb ($P < 0.001$), and HCT ($P < 0.001$). However, those who received medical therapy alone did not experience any significant changes in these parameters [Table 2]. We found that the RBC mass ($P = 0.581$), Hb ($P = 0.882$), and HCT ($P = 0.471$) were comparable between the two study groups after 8 weeks of intervention. The results were summarized in Table 3.

**Table 1: Baseline characteristics of the 33 patients with RA receiving 8 weeks of aerobic exercise along with medical therapy (*N* = 16) and medical therapy alone (*N* = 17)**

| Hematologic indices | Training group (*N* = 16) | Control group (*N* = 17) | *P*-value |
|---|---|---|---|
| Age (years) | 51.18±8.01 | 52.67±7.74 | 0.656 |
| Height (cm) | 159.18±4.98 | 159.25±5.77 | 0.976 |
| Weight (kg) | 73.18±9.47 | 71.62±10.83 | 0.718 |
| BMI ($m^2$/kg) | 28.87±4.3 | 28.12±5.4 | 0.501 |
| Disease duration (years) | 4.91±1.47 | 4.59±1.24 | 0.567 |
| Therapy duration (years) | 3.82±1.10 | 3.62±0.96 | 0.657 |

BMI = Body mass index

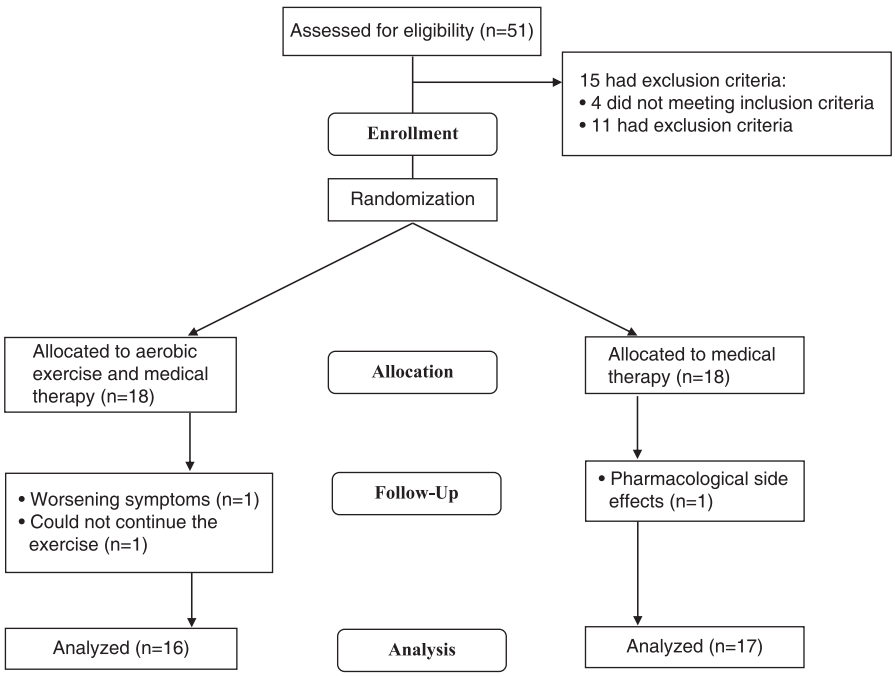


**Figure 1:** CONSORT flow diagram of the study

**Table 2: The changes in RBC count, hemoglobin, and hematocrit in 33 patients with RA receiving 8 weeks of aerobic exercise and medical therapy (*N* = 16) and medical therapy alone (*N* = 17)**

| Hematologic indices | Training group (*N* = 16) | | | Control group (*N* = 17) | | |
|---|---|---|---|---|---|---|
| | Before | After | *P*-value | Before | After | *P*-value* |
| RBC (×10⁶/μL) | 4.86±0.71 | 4.62±0.75 | <0.001 | 4.47±0.7 | 4.48±0.7 | 0.351 |
| Hb (mg/dL) | 10.57±1.02 | 11.56±1.32 | <0.001 | 11.74±1.34 | 11.71±1.40 | 0.451 |
| HCT (%) | 34.83±3.36 | 36.83±3.36 | <0.001 | 36.83±3.36 | 36.40±4.07 | 0.398 |

Hb = hemoglobin, RBC = red blood cell, HCT = hematocrit; *A two-sided *P*-value of less than 0.05 is considered statistically significant

**Table 3: Comparing the hematological indices of 33 patients with RA receiving 8 weeks of aerobic exercise and medical therapy (*N* = 16) or medical therapy alone (*N* = 17)**

| Hematologic indices | Training group (*N* = 16) | Control group (*N* = 17) | *P*-value* |
|---|---|---|---|
| RBC (×10⁶/μL) | 4.62±0.75 | 4.48±0.7 | 0.581 |
| Hb (mg/dL) | 11.56±1.32 | 11.71±1.40 | 0.882 |
| HCT (%) | 36.83±3.36 | 36.40±4.07 | 0.471 |

Hb = hemoglobin, RBC = red blood cell, HCT = hematocrit; *A two-sided *P*-value of less than 0.05 is considered statistically significant

## DISCUSSION

Physical activity is a major modifiable determinant of chronic disease.[25] The Australian National Physical Activity Guidelines for Adults recommend that for good health, "adults should put together at least 30 min of moderate-intensity physical activity on most, preferably all, days." The aerobic exercise has been shown to be associated with increased RBC mass, Hb, and HCT in healthy individuals.[21] During the current study we tried to determine the effects of aerobic exercise on hematologic indices of women with RA. We found that although 8 weeks of aerobic exercise resulted in increased HB, HCT, and RBC mass in women with RA, the difference was not significant when compared with that in controls. In other words, the increase in RBC count, Hb, and HCT could not be attributed to aerobic exercise in women with RA. Further research is required to elucidate the effects of aerobic exercise on hematologic indices of the women with RA.

During the exercise, oxygen, which is carried by RBCs, is transferred through the network of arteries and capillaries in the circulatory system. The oxygen demand and production of carbon dioxide increase and the demands for more RBCs and then oxygen consumption with generating of superoxide anion increases. The body responds by increasing the number of RBCs and also in other ways to increase the oxygen-carrying capacity of blood.[26,27]

The results of the current study is consistent with previous reports.[26,28] Various surveys have shown changes in cytokines and natural killer cell activity (effects of three different types of exercise on blood leukocyte count during and following exercise). HB, HCT, and RBC have basic duty of transferring oxygen to active tissues. Body capacity and $VO_2$ max depend on transferring of active oxygen to active tissues. Therefore, the importance of hematological indexes in body efficiency is obvious.[27] It has been shown that the hematological indices decrease after aerobic exercise due to increase in plasma volume. The increase in plasma volume results in a decrease in Hb concentration.[6,10] Tocopherols and ubiquinones are intrinsic lipid components, which are involved in antioxidant protection, and also glutathione is an important water soluble antioxidant.[29] Metsios *et al*.[30] demonstrated that 12 weeks of aerobic exercise was associated with improved endothelial function in patients with RA. They also showed that an exercise program designed to meet individual needs and physical abilities significantly improves microvascular and macrovascular function in parallel with disease-related characteristics in RA patients.

There is a significant increase in estimated maximum oxygen uptake ($VO_{2max}$) in those who receive aerobic exercise and medical therapy.[31] Greater cardiorespiratory fitness has long been associated with the decreased risk of disease and death.[32] Obese individuals with higher fitness levels generally have lower mortality rates compared to sedentary normal-weight counterparts.[33] Previous studies have shown increases in $VO_{2max}$ from baseline levels after resistance exercise training[34] and combined aerobic and resistance exercise training.[33] All these investigations are in support of aerobic exercise in those with RA. However, the current study failed to show a significant increase in hematologic indices of the patients with RA.

Animal and human studies have shown increases in HCT and in Hb concentration during exercise. One factor that contributes to the increase in HCT during exercise, at least in dogs, is an increase in the number of circulating erythrocytes due to splenic contraction.[35] The effect of exercise on splenic erythrocyte storage may in part be mediated by circulating catecholamine.[36] However, exercise training might be a promising, additional, safe, and economical method to help alleviate anemia and improve body capacity and $VO_{2max}$.

The present study had a number of limitations. Due to its limited sample size, our study may have been

underpowered to detect significant changes in some variables. Another limitation is that we did not measure inflammatory parameters as well as dynamic ones. We just measured the hematologic indices, thus we cannot comment on the pathophysiology of the changes. In other words, measuring the hemodynamic changes as well as anthropometric changes of the subjects could help us in discussing the results. Other shortcoming of the study was that we did not match the patients regarding the disease severity and the involved joints that could affect the results. The follow-up period of the study was 8 weeks that seems to be inadequate for a chronic disease such as RA. However, we have chosen this period according to the previous report by Cooper *et al*.[24] demonstrating the favorable outcome of RA after 6 weeks of aerobic exercise. Further studies with longer follow-up periods are suggested.

## CONCLUSION

The aerobic exercise results in increased Hb, HCT, and RBC mass, yet the increase in RA patients was not significant when compared to that in controls. Thus, increase in the HB, HCT, and RBC could not be attributable to aerobic exercise. Further investigations are required to shed light on the effects of aerobic exercise on hematologic indices of women with RA.

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### Conflicts of interest
There isn't any conflict of interest to be declared regarding the manuscript.

## AUTHOR'S CONTRIBUTION

YJ contributed in the conception of the work. YJ, BV, and MS contributed in conducting the study. YJ, BV, and HR contributed in revising the draft. BV and HR contributed in the approval of the final version of the manuscript. BV agreed in all aspects of the work.

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