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ORIGINAL ARTICLE

Effect of aerobic interval training on serum IL-10, TNFα, and adipokines levels in women with multiple sclerosis: possible relations with fatigue and quality of life

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Abstract

Purpose Multiple sclerosis is associated with immune system dysfunction and chronic inflammation; however, possible relations between immunologic and metabolic factors and some psychological indexes such as fatigue and quality of life, especially in relation to exercise training, have not yet been investigated. The present study was designed to investigate the effect of aerobic interval training on interleukin-10/tumor necrosis factor ratio and adipokine (leptin and adiponectin) concentrations in women with multiple sclerosis. Furthermore, the relationship between these factors with fatigue and quality of life were assessed.

Methods Forty women with multiple sclerosis (Expanded Disability Status Scale ≤3) were randomized into either a non-exercising control or training group. The training group performed 8-weeks of upper and lower limb aerobic interval training. Serum concentrations of tumor necrosis factorα, interleukin-10, leptin, and adiponectin were measured before and after the 8-week intervention. Moreover, antropometric measures and measures for fatigue and quality of life were determined at the onset of and after exercise training.

Results The results revealed that leptin and tumor necrosis factor*α* levels significantly decreased subsequent to the aerobic interval training. Although blood adiponectin levels considerably increased in the training group, interleukin-10 and interleukin-10/tumor necrosis factorα ratio underwent no substantial change after the exercise training. In addition, the aerobic interval training was associated with improvement in fatigue, quality of life, and maximal oxygen consumption.

Conclusions Our findings suggested that aerobic interval training can be an effective strategy for managing the immune system at least by its significant impact on inflammatory cytokines and adipokines levels in women with multiple sclerosis. Additionally, this positive impact improved fatigue and adipose tissue indicators.

Keywords Multiple sclerosis · Adipokines · Cytokines · Inflammation · Fatigue

Introduction

Multiple sclerosis (MS) is a neurological disease resulting from axonal damage to the central nervous system with multifactorial and unknown etiology [1]. It is estimated that approximately 2.5–3.5 million adults around the world suffer from MS [2, 3]. MS is found to be more common in women rather than men [2] that is might be caused by the immune system or nervous system differences between men and women, also the effects of gonadal hormones, different environmental exposures and as well as lifestyle change in women and men [4, 5]. People with MS differ in terms of clinical manifestations; nevertheless, the most prevalent

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symptoms include fatigue, a decline in quality of life [1, 6, 7], poor mobility and balance, gait disturbances, and an increasing risk of falling [6, 8]. Scientists and physicians agree that people with MS frequently experience fatigue as one of the most important clinical features of their disability [1, 6, 9].

Experimental evidence supports regular physical activity in improving quality of life, physical performance, and fatigue in people with MS [6, 9, 10]. Others have proposed that long duration exercise training can induce fatigue in some diseases [10, 11]. Using this evidence, we hypothesize that aerobic interval training can be an effective and safe intervention that can provide the benefits of physical activity without premature fatigue. It is generally known that aerobic interval training can improve anaerobic capacity, increase muscle function, and delay fatigue in healthy subjects and patients [12, 13]. Although a great number of studies have investigated the benefits of exercise training in people with MS who use aerobic training [12, 13], weight training [14], and combined exercise training [6, 15, 16], evidence on the benefits of aerobic interval training is sparse. Though most of these studies supported positive effects of sport training on some psychological factors such as quality of life, the results of biomarker analysis are contradictory and inconclusive in MS subjects.

On the other hand, we know that MS is associated with immune system dysfunction and chronic inflammation [15–17]. In addition, some studies have suggested that metabolic abnormalities such as changes in adipokines are one of the mechanisms affecting MS pathogenesis [18, 19]. Adipokines are cytokines secreted by adipose tissue [18] and are involved in the pathology and development of MS [18]. One of the first adipokines introduced is leptin [19, 20]. Previous studies reported that leptin has different between women and men [21] and proposed that leptin can regulate and stimulate the production of pro-inflammatory cytokines such as TNFα and promote inflammatory signaling leading to axonal degeneration and plague development [21, 22]. In contrast, adiponectin, adipocyte-derived hormone, is an anti-inflammatory factor that can mediate its effect by suppressing the production of pro-inflammatory cytokines such as TNFα, while increasing the synthesis of IL-10, a potent anti-inflammatory cytokine [19, 23]. Therefore, it can be theorized that evaluating the leptin to adiponectin ratio can be a more efficient assessment of inflammatory status.

The effect of exercise training on inflammatory status in people with MS remains inconclusive with mixed results [6, 9, 12–15]. Moreover, in recent studies, the effect of changes in leptin and adiponectin on MS patients and their pathogenesis have been described [18, 19], but changes related to exercise training in these patients are not understood. Therefore, the primary aim of this study was to investigate the effect of an 8-week aerobic interval training on adipokine mediated cytokine expression in women with MS. Further, it is generally understood that inflammatory state and adipokines levels influence fatigue and quality of life in patients suffering from diseases other than MS [24]; accordingly, in the current study, we endeavored to assess the possible relations between these factors and fatigue and quality of life in women with MS.

Material and methods

All procedures were performed in accordance with the principles approved by the human Ethics Committee of Shahid Chamran University, Ahvaz, Iran (reference no. SCU/102/1395). Forty-five women with relapsing-remitting MS (RRMS) participated in this randomized controlled trial (RCT). The risks and benefits of the study were explained to all subjects, and all participants signed their written informed consent. Forty-five subjects had the inclusion criteria (expanded disability status scale (EDSS) ≤ 3, age = 20–40 years, RRMS, no serious comorbidities, and willing to participate) and were randomized into two groups (Fig. 1): the control group that received no intervention ($n = 20$), and the training group that performed 8-week upper-limb and lower-limb aerobic interval training ($n = 25$). Baseline demographic and clinical characteristics of the subjects are presented in Table 1.

Exclusion criteria

The exclusion criteria were as following: (a) immune modulatory therapy within the last 4 months; (b) those engaged in regular moderate to heavy training within the past a year; (c) documented relapses within the last 6 months; (d) individuals with orthopedic limitations; (e) current smoker; (f) liver or kidney disorder; (g) those with chronic diseases such as cardiovascular diseases or diabetes; or (h) had severe medical, psychiatric and neurological disorders other than MS.

Anthropometric measurements

Anthropometric measurements including weight, body mass index (BMI) and body fat percent (BFP) were measured 3 days before and after the intervention period. BMI derived from the body mass (kg) divided by the square of height (cm^2) of an individual. Skinfold thickness was measured at triceps, thigh, and suprailium sites with Harpenden calipers. BFP and body density were calculated as s previously described [25, 26]. All measurements were made on the right side of the body.

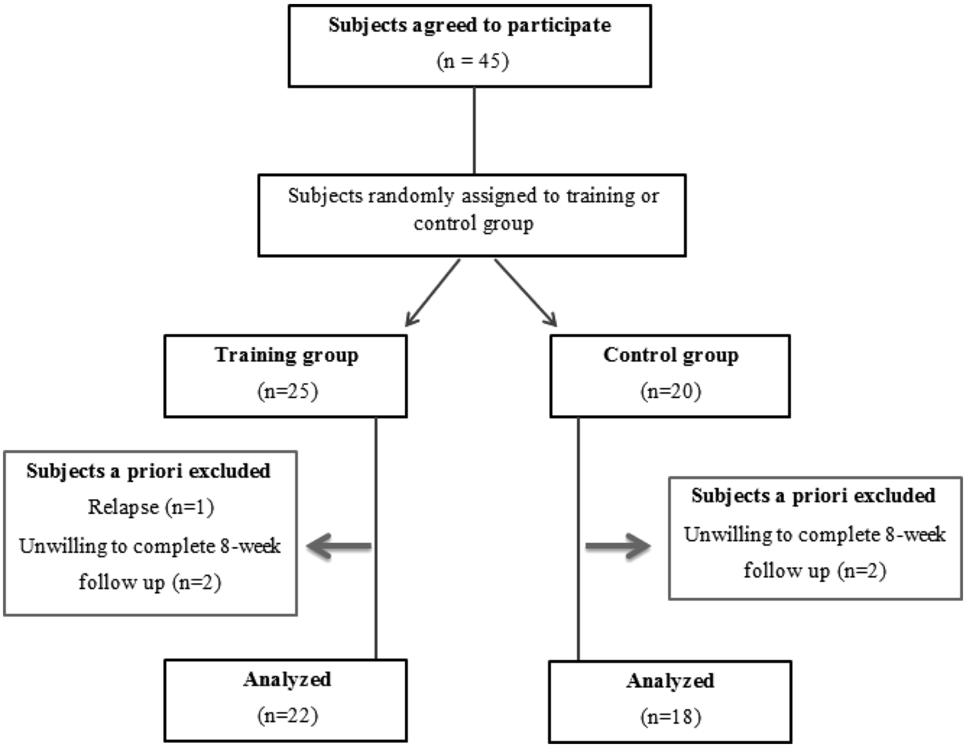

Fig. 1 Flowchart of experimental design and patients include. Forty-five women with RRMS participated in this study had the inclusion criteria EDSS ≤3, age = 20-40 years, RRMS, no serious comorbidities, and willing to participate. Participants were randomized into two groups: the control group that received no intervention (n = 20), and the training group that performed 8-week upper- and lower-limb aerobic interval training (n = 25). Finally, forty patients (the training group: 22 and the control group: 18) completed the 8-week follow-up

Questionnaires

BAECKE Activity Questionnaire: Baseline assessment of physical activity was assessed using the BAECKE Activity Questionnaire [24] The overall physical activity over the past year, including sports activities (four questions), household activities (four questions) and leisure time activities (eight questions) was assessed. Each index adopts values from 1 to 5, while the average of the three indexes was the overall activity score, with five indicating the highest possible physical activity [27].

Multiple Sclerosis Quality of Life Questionnaire (MSQOL-54): This 54-item self-reported questionnaire elevates the generic and specific domains of quality of life in people with MS. MSQOL-54 contains 12 subscales in two fields, physical health and mental health, with score range from 0 to 100. Measurement of MSQOL was done as previously described [28].

Fatigue severity scale (FSS): This nine-item validated structured self-reported questionnaire assesses the level of fatigue on a seven-point scale [29].

Table 1 Baseline demographic and clinical characteristics

	Experimental group ($n = 22$)	Control group ($n = 18$)
Age (years)	32.04 ± 2.81	31.27 ± 3.28
Weight (kg)	71.38 ± 3.18	69.89 ± 3.27
BMI (kg/m^2)	27.08 ± 2.49	26.21 ± 1.67
EDSS score	1.84 ± 0.35	1.57 ± 0.64
Disease duration (years)	2.69 ± 1.84	3.47 ± 1.26
Physical activity	1.67 ± 0.34	1.50 ± 0.59

Data presented Mean ± SD

n number in each group, *BMI* body mass index, *EDSS* expanded disability status scale

Aerobic interval exercise training and aerobic exercise test

The subjects participated in upper and lower limb aerobic interval training program for 8 weeks (24 sessions, 3 days per week). The training program included a 10-min warm-up at the beginning and a 10-minute cool-down at the end of each session. Upper and lower ergometer cycles (Monark 891E and 894E Varberg, Sweden, respectively) were utilized. The aerobic interval training program consisted of three intervals with 60% loads of watts maximum ($W_{\max}$) in the first week for upper and lower limbs separately. The load increased by 5% of $W_{\max}$ every 2 weeks (the last week: 75% $W_{\max}$). Moreover, the number of intervals rose in the second, the fourth, and the sixth weeks of training (the eighth week: six intervals). The pedal rate was fixed at 50 rpm during the 8-week training. Passive rest periods between the intervals as well as the training periods lasted for 2 min. The first and the last sessions lasted for 42 and 66 min, respectively.

The $W_{\max}$ of lower and upper limbs was determined by Storer et al. [30] and Sawka et al. [31], respectively (4 days before and after the intervention period). To determine the $W_{\max}$ of lower limb, the subjects cycled for 4 min at 0 watt on an ergometer cycle. Thereafter, the work rate of the cycle ergometer increased by 15 W min^{-1} until the subjects were exhausted. The pedal rate was maintained at 60 rpm during the test and was confirmed by pedal revolution counter. The $W_{\max}$, weight (kg), and age (years) of the subjects were used to calculate the maximum rate of oxygen consumption ($VO_{2\max}$) based on the following formula:

$VO_{2\max}$ (ml/kg min) = 9.39 ($W_{\max}$) + 7.7 (Weight)−5.88 (Age) + 136.7 (Storer et al. [30]).

To determine the $W_{\max}$ of upper limb, the subjects cycled for 2 min at 25 watt on an ergometer cycle; subsequently, the cycle ergometer work rate increased by 25-W min^{-1} until the subjects reached their threshold of tolerance. The pedal rate was maintained at 60 rpm during the test and was confirmed by pedal revolution counter (Sawka et al. [31]). In both tests, the subjects were verbally encouraged by test administrators to provide a true maximal effort.

Blood sampling and analyze

Three days before training and 72 h follow final training session, a venous blood sample (5 cc) was collected after a 10-h overnight fast between 7:30 a.m. and 9:00 a.m. Serum concentrations of all markers were measured by enzyme linked immunoassay with ELISA kits based manufacturer's instructions of company. Leptin and adipenctin concentration were measured by using R&D Systems kit (Minneapolis, USA) and Biovendor kit (Brno, Czech Republic), respectively. Also cytokines levels (TNFα, IL-10) were measured by IBL International GMBH kit (Hamburg, Germany). Coefficients of variance were determined for all the variables and were less than 10%.

Data analysis

Descriptive statistics were quantified and data are presented as means and SD (Mean ± SD). Shapiro–Wilk and Levene tests were used to assess data normality and variance equality, respectively. A Paired *t*-test was used to investigate within group difference (pre-test to post-test), and an analysis of covariance was used to examine between group differences. A pre-test value was used as covariates to improve precision and to control for possible imbalances during the randomization process. Pearson correlation coefficient was used to determine relation between factors. Statistical analyses were performed with SPSS Statistics version 21 (IBM SPSS Statistics, version 21, Armonk, NY). The level of statistical significance was considered at $P < 0.05$.

Results

Baseline characteristics

Among the 45 RRMS patients (all women) who were enrolled in this study, 40 patients (the training group: 22 and the control group: 18) completed the 8-week follow-up.. Two subjects from both the training and the control groups were excluded from the study because they were unwilling to complete the follow-up. In addition, one subject from the training group was excluded due to clinical relapse. There was no significant difference between the groups in terms of age, weight, BMI, EDSS, physical activity, duration of disease, and BFP at the baseline (all values of $P > 0.05$, Table 1).

Maximal oxygen consumption and anthropometric characteristics

VO_2max and maximum power substantially increased from the baseline to the post-test in the training group ($P < 0.05$; Table 2). Furthermore, weight, BMI, and BFP changed significantly ($P < 0.05$; Table 3) following the 8-week aerobic exercise training. We observed a marked improvement in anthropometric characteristics in the trained subjects and no change in the control group.

Table 2 Effects of the 8-week of aerobic interval training on measures of FSS and MSQOL-54 in trained ($n = 22$) and control ($n = 18$) women with MS

Parameter	Group	Pre	Post	P*
FSS	Training	3.45 ± 0.87	2.67 ± 1.28$^{\#}$	0.029*
	Control	3.51 ± 1.11	3.56 ± 1.16	
MSQOL-54	Training	54.21 ± 14.63	63.78 ± 12.47$^{\#}$	0.008*
(total)	Control	52.20 ± 12.91	50.87 ± 11.20	
MSQOL-54	Training	58.45 ± 15.00	66.32 ± 11.87$^{\#}$	0.030*
Physical Health	Control	56.87 ± 14.09	57.94 ± 12.57	
MSQOL-54	Training	50.17 ± 21.81	67.18 ± 14.16$^{\#}$	0.038*
Mental Health	Control	51.92 ± 21.27	52.92 ± 18.28	

Data presented Mean ± SD

FSS fatigue severity scale, *MSQOL-54* multiple sclerosis quality of life-54

$^{\#}$ *P*-values ($P < 0.05$) refers to the level of significance in the paired *t*-test

* *P*-values ($P < 0.05$) refer to level of significance in the analysis of covariance (between-group differences). Pre: before 8-week; Post: after 8-week

Table 3 Effects of the 8-week of aerobic interval training on VO_{2max}, BMI, Weight, Max power and B.F.P in trained ($n = 22$) and control ($n = 18$) women with MS

Parameter	Group	Pre	Post	P*
VO_{2max} (ml/kg min)	Training	17.77 ± 1.57	19.98 ± 1.35$^{\#}$	0.001*
	Control	16.65 ± 1.39	17.02 ± 2.72	
Max power(watt)	Training	37.11 ± 8.84	57.65 ± 7.64$^{\#}$	0.001*
	Control	37.39 ± 8.65	37.57 ± 10.28	
BMI (kg/m^2)	Training	27.08 ± 2.49	26.65 ± 3.06$^{\#}$	0.030*
	Control	26.21 ± 1.67	27.01 ± 3.01	
Weight (kg)	Training	71.38 ± 3.18	70.30 ± 4.62$^{\#}$	0.034*
	Control	69.89 ± 3.27	70.25 ± 3.70	
B.F.P (%)	Training	34.66 ± 5.68	32.97 ± 5.70$^{\#}$	0.048*
	Control	35.41 ± 4.47	35.36 ± 4.38	

Data presented Mean ± SD

VO_{2max} maximum oxygen consumption, *BMI* body mass index, *BFP* body fat percentage

$^{\#}$ *P*-values ($P < 0.05$) refers to the level of significance in the *t*-test

* *P*-values ($P < 0.05$) refer to level of significance in the analysis of covariance (between-group differences). Pre: before 8-week; Post: after 8-week

Training significantly improves fatigue status

Fatigue and quality of life was measured as psychological parameters. Fatigue scores demonstrated a significant decrease after the 8-week aerobic interval training ($P <$ 0.05; Table 2). Moreover, the results indicated a considerable change in MSQOL-54 (total) and physical and mental quality of life subsequent to the exercise training ($P < 0.05$; Table 2).

Training significantly improves leptin/Adiponectin ratio and TNFα level

In the current study, leptin, adiponectin, TNF-*α*, and IL-10 were measured. Figure 2 indicates the changes in cytokines concentration in the subjects during pre-training and post-training. Leptin concentrations notably declined in the training group. Post-test concentrations were also significantly lower in the training group compared to the control group. On the other hand, adiponectin level considerably increased in the training group ($P < 0.05$; Fig. 2). Additionally, the level of TNFα significantly ($P < 0.05$) decreased after 8 weeks of exercise training ($P < 0.05$; Fig. 2). Contrary to our hypothesis, we did not observe any meaningful changes in IL-10 protein levels.

The ratio of leptin to adiponectin was applied as an index reflecting inflammation related to fat tissue [32].This ratio was employed widely as a predictor of comorbidities such as metabolic syndrome and insulin resistance [32]. This ratio indicated an improvement in the training group at the end of the training period ($P < 0.05$). Also, the ratio of IL-10 to TNFα was utilized as an index reflecting the anti-inflammatory status [33]. We observed no significant changes in both groups (Fig.3).

Correlations between changes in concentrations of blood factors and FSS, MSQOL-54, VO_{2max}, and anthropometric characteristics

Significant positive correlations between leptin and FSS, BMI, and BFP were observed (Table 4). Adiponectin changes indicated a modest significant negative correlation with BMI, BFP, and weight. TNF-*α* and IL-10 changes only demonstrated a significant positive correlation with FSS and VO_{2max}, respectively (Table 4).

Discussion

The purpose of this study was to investigate the effect of aerobic interval training on adipokines and inflammation in women with MS. Furthermore, changes in physical and psychological parameters were examined. Moreover, the possible relations between changes in blood markers and psychological and anthropometric factors were assessed. Our findings demonstrated the beneficial effect of aerobic interval training on lowering the levels of leptin and TNF-*α* as pro-inflammatory factors and increasing adiponectin. In this regard, aerobic interval training was associated with improvement in the physical and psychological parameters such as fatigue, quality of life, and VO_{2max}. A significant correlation was observed between adipokines levels and fat mass indicators BMI and BFP. In addition, notable negative correlations were noticed between fatigue and leptin and TNF-*α* levels in serum.

Our results revealed that aerobic interval training improved VO_{2max}, fatigue, and quality of life in women with MS. Currently, the evidence has clearly indicated that people with MS are less physically active than healthy individuals and even those suffering from other chronic diseases such as diabetes and asthma [7, 8]. To date, people with MS are known to adopt inactive lifestyle that leads to concurrent comorbidities and a decrease in physical performance more than healthy people with inactive lifestyles [8]. Previous evidence supports the benefits of exercise training in people with MS [6, 8, 34]. To support the effect of exercise training, Rietberg et al. [34], in a review of the impact of regular physical activity on people with MS, reported a positive effect on VO_{2max}, fatigue, balance, and quality of life. These findings highlighted the key role of regular physical activity as a non-pharmacological adjuvant

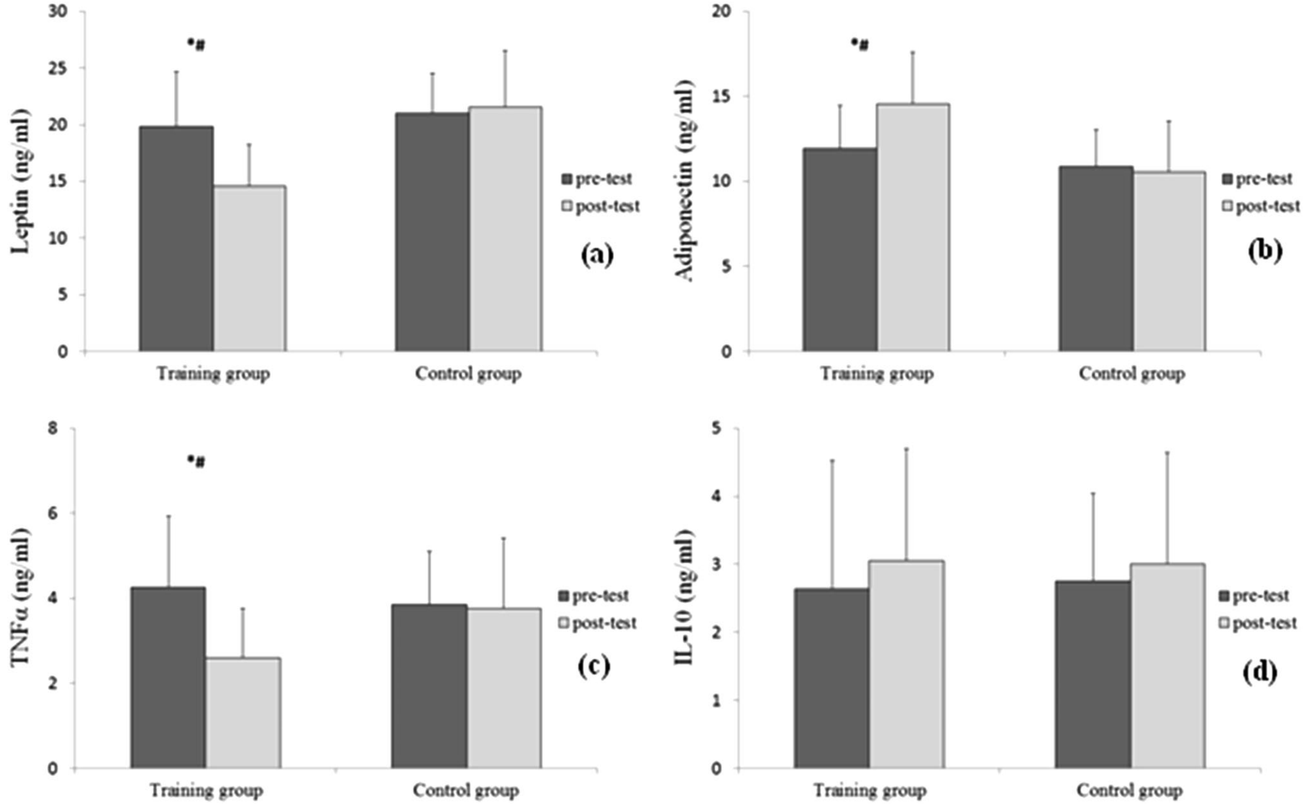

Fig. 2 Effects of the 8-week aerobic interval training on measures of leptin (**a**), adiponectin (**b**), TNF-α (**c**), and IL10 (**d**). Data are given as Mean ± SD. # *P*-values ($P < 0.05$) refers to the level of significance in the *t*-test. * *P*-values ($P < 0.05$) refer to level of significance in the analysis of covariance (between-group differences). Pre-test: before 8-week; Post-test: after 8-week; TNF-α: tumor necrosis factor alpha, IL10: Interleukine-10

treatment, not agreeing with the previous belief that exercise training had a high risk or could be harmful to people with MS [34, 35].

Previous work has suggested that quality of life declines by more than 80% in people with MS compared to healthy people [3, 4, 10]. We found beneficial effects of aerobic interval training on quality of life and fatigue. These positive outcomes from our study can lead to positive impact on the daily activities of people with MS. It is well established that fatigue is a common symptom of MS disorder that can interact with other aspects of MS, especially the quality of life. However, in this study we used FSS that is the most widely used toll to indicate severity of fatigue [29], but one limitation of the study was the lack of experimentally test the time to fatigue.

It is also known that interventions improving mental and physical health and affecting energy balance in MS can influence fatigue and, therefore, quality of life [6, 34]. On the other hand, improving muscle and cardiovascular function is known as a key factor that influences quality of life and fatigue. In this regard, VO_{2max} is an important index of function that is closely associated with various aspects of health [36]. Our findings demonstrated that the lower-limb and upper-limb aerobic interval training in women with MS is feasible, safe and can improve their VO_{2max}. Hence, we can conclude that exercise training contributes to improving fatigue through enhancing VO_{2max}. To support this hypothesis, Ponichtera Mulcare et al. [37] reported a 5–20% improvement in VO_{2max} after training period. In our study, the subjects performed upper-limb and lower-limb aerobic interval training with 60–75% maximal work rate (in watts) leading to significant increases in VO_{2max} (~17%) in the trained subjects. Although VO_{2max} is closely associated with fatigue in people with MS, fatigue pathophysiology in MS disorder is not entirely clear. It is a speculated that fatigue in MS patients has multifactorial causes. In this regard, some studies have focused on the immune system and neuromuscular mechanisms.

Our findings supported the hypothesis that inflammatory cytokines play a role in the etiology and progression of MS-related fatigue. We found that TNF-α expression [17, 38] is positively correlated with fatigue in people with MS. TNF-α is substantially increased in the acute relapse phase of MS [39]. Undoubtedly, during acute relapses of MS, fatigue worsens or, in some cases, is the sole clinical presentation [39, 40].

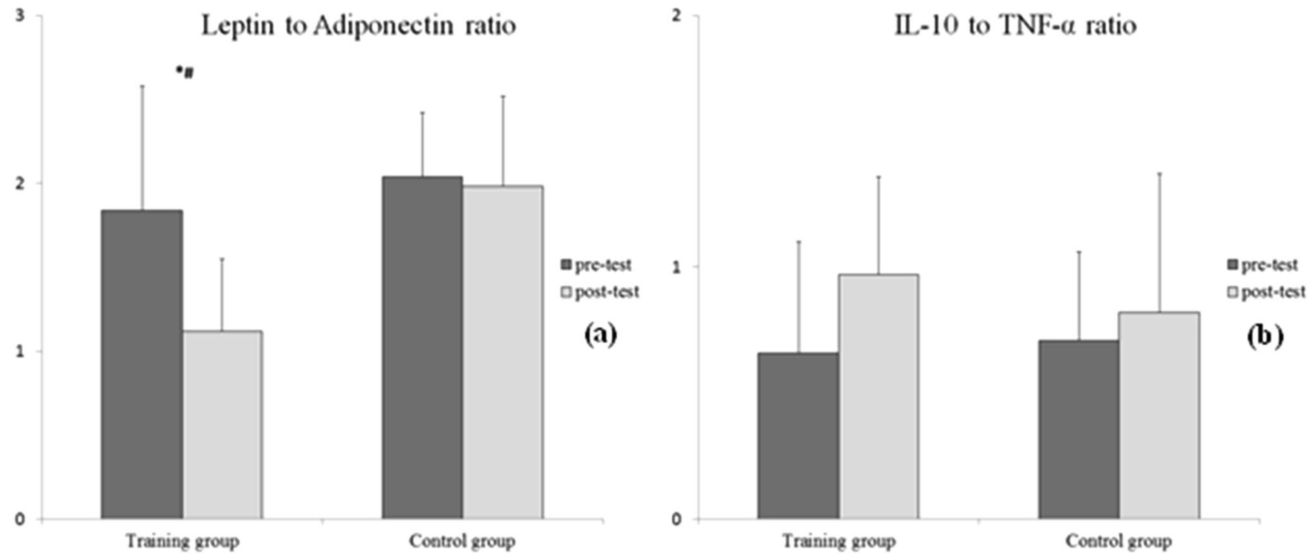

Fig. 3 The effects of 8 weeks of aerobic interval training on leptin to adiponectin ratio (**a**) and IL-10 to TNF-α ratio (**b**). Data are given as Mean ± SD. $^{\#}$ *P*-values ($P < 0.05$) refers to the level of significance in the *t*-test. * *P*-values ($P < 0.05$) refer to level of significance in the analysis of covariance (between-group differences)

In our study, 8 weeks of aerobic interval training resulted in a significant decrease in TNF-α and no significant change in IL-10. Previous studies have indicated inconsistent results about the effect of exercise intervention on TNF-α in MS subjects. For instance, Castellano et al. [12] and Deckx et al. [13] reported an increase and a decrease in the TNF-α concentration, respectively. In contrast, Alvarenga-Filho et al. [6] and Kjølhede et al. [14] reported no change after training period. These inconsistent results could point to the pleiotropic function of TNF-α. Although recent studies have reported the destructive effect of TNF-α on blood-brain barrier and myelin sheath [41], TNF-α is associated with remittion in RMMS patients and stimulates axonal remyelination [42]. One possible explanation for this event is the divergent roles of TNF-receptors: p75 with neuroprotection role or p55 with apoptotic role [43]. Similarly, IL-10 adaption to exercise training is inconsistent in MS patients. White et al. [16] reported a decline in level of IL-10 after the resistance training period, inconsistent with our findings and other previous reports [9, 12, 13]. However, our results are consistent with those of the majority of previous findings. Among all cytokines, IL-10 is considered as a protecting marker for immune system and metabolism [6, 13]. It appears that IL-10 levels change depending on the body mass [44] and fitness levels [45]. The results of the present study showed no change in IL-10 that can be accounted for by the subjects' low level of physical fitness at the baseline and the short term of the training period. The trained subjects had an increase in VO_{2max} by approximately 17%, being positively correlated with the change in the IL-10 level. Nevertheless, VO_{2max} in the trained MS patients is still less than that of the healthy subjects [36].

In recent years, some studies have investigated obesity as a risk factor during childhood and late adolescence [46, 47]. These findings indicate that the risk of MS is increased twofold among individuals with a BMI $\geq 30\,\mathrm{kg/m^2}$. I Munger et al. [48] revealed a relationship between high BMI in girls age 7–13 years and the risk of MS. Applied investigations proved that one of the most effective strategies to control body weight is exercise training [49]. Accordingly our study suggests that 8 weeks of aerobic interval training improves indicators of obesity (BMI, BFP). A significant moderate relationship was observed between changes in BMI and those in adipocyte-derived hormone. Matsubara et al. reported a significant negative relation between the BMI, and circulating adiponectin [50]. Likewise, we observed a significant positive relation between BMI and leptin and a negative relationship between BMI and adiponectin, respectively. Moreover, Eftekhari et al. [51] indicated in another study that leptin in women with MS had a positive correlation with weight and BMI. Indeed, previous studies on obesity reported an increasing clinical inflammatory process during obesity, which is responsible for pro-inflammatory/anti-inflammatory cytokine imbalance and up-regulated pro-inflammatory pathways [21, 22].

Our findings suggest that lower-limb and upper-limb aerobic interval training has anti-inflammatory effects on cytokine levels. This is based on the observation of reduced levels of leptin and TNF-α is accompanied by an improvement in the level of adiponectin. Autoimmune disorders such as MS are associated with increased secretion of leptin and increased levels of pro-inflammatory cytokines (i.e., TNF-α). Leptin is a sexually dimorphic hormone (higher in females) [21, 51] and is mainly released

Table 4 Correlation between changes blood factors and fatigue, quality of life, BMI and weight after 8-week of aerobic interval training

	Δ FSS	Δ MSQOL-54	Δ VO_{2max}	Δ BMI	Δ BFP	Δ Weight
Δ Leptin	0.51*	−0.15	0.22	0.63*	0.59*	0.41*
Δ Adiponectin	−0.21	0.27	0.16	−0.60*	−0.37*	−0.45*
Δ TNF-*α*	0.56*	−0.19	0.18	0.26	0.24	0.22
Δ IL10	−0.18	−0.07	0.44*	−0.25	−0.19	−0.23

TNF-α tumor necrosis factor alpha, *IL10* Interleukine-10, *FSS* fatigue severity scale, *MSQOL-54* multiple sclerosis quality of life-54, VO_{2max}: maximum oxygen consumption, *BMI* body mass index, *BFP* body fat percent

* Significant correlations ($P < 0.05$), obtained using Pearson correlation test

by the adipose tissue. Interestingly, leptin secretion is higher in the cerebrospinal fluid (CSF) than serum with a positive correlation between CSF and serum [18, 22]. The overall actions of leptin in the central nervous system and immune system are activating pro-inflammatory cells, promoting T helper 1 (Th1) responses, and mediating the production of pro-inflammatory cytokines TNFα, IL-6, and IL-2 s. Therefore, both innate and adaptive immune responses can be modulated by leptin [21, 52]. Moreover, recent studies have highlighted the possible central role of leptin in some autoimmune disorders and metabolic diseases [19, 52]. It appears that leptin modulator strategies in autoimmune disease of MS can be helpful in management and treatment of MS. The difference in adipocytokine level in MS patients, in comparison with the healthy control subjects, cannot be fully attributed to the adipose tissue amount. Instead, this difference could be attributed to the ongoing illness with an active and intense inflammatory background [19]. Based on the above-mentioned facts, the decrease in leptin level leads to reduction in body fat or other unknown mechanisms influenced by exercise. This fact was observed in our study, supporting the beneficial effect of physical training on MS patients. The first researchers who examined the effect of exercise intervention on leptin in MS subject was Ebrahimi et al. [53] who reported no marked change in rest level of leptin, inconsistent with our findings. The weakness with the Ebrahimi et al. [53] study was the use of whole body vibration which has found to have no significant effects on fatigue in MS patients.

Little research has been done into the relationship between MS and adiponectin level. In obesity and its related comorbidities such as insulin resistance and diabetes, adiponectin levels decline [24]. In addition, adiponectin is involved in various immunomodulatory processes. It is well accepted that adiponectin induces the production of anti-inflammatory cytokines such as IL-10 and IL-1 receptor antagonist [19, 20]. Moreover, by stimulating prostaglandin synthesis, adiponectin is responsible for suppression of IL-2 and subsequent inhabitation of B cell lymphopoiesis [20]. Interestingly, adiponectin expression and secretion are inhibited through some pro-inflammatory cytokines such as IL-6 and TNFα [19]. Similar to leptin, the secretion of adiponectin is related to the amount of adipose tissue [20, 23]. An improvement in the rest level of adiponectin after the training period can be attributed to the positive effect of exercise, rather than weight loss or change in energy metabolism. Finally, the ratio of leptin to adiponectin as pro-inflammatory index reduced, probably displaying an improved situation.

Although it appears that the consequences of a sedentary lifestyle can be reversed by exercise training [36, 37], to date studies have suggested that exercise training has an important potential to affect the pathogenesis of MS or, at least, the quality of life [37]. Yet, it is not crystal clear how physical exercise influences the underlying disease mechanisms. For several years, people with MS were advised to avoid exercising because it was speculated that exercise leads to worsening MS symptoms. Nevertheless, in recent years, performing exercise training and physical activity by MS patients has been found to be the most important intervention aimed for improving physical symptoms. Studies in the last decade have indicated substantial benefits obtained from physical training by MS individuals. In agreement with our findings, studies noticed that exercise training is safe for and well tolerated by MS individuals [12, 54].

In the present study, we endeavored to address some of the scientific uncertainties of previous studies on MS patients doing exercises. Accordingly, in a RCT, we investigated the impact of aerobic exercise training on inflammation and adipokines in women with MS; furthermore, we examined the possible relations between fatigue and quality of life and immunological changes. We demonstrated that an 8-week aerobic interval training improved the psychological and physiological characteristics, including quality of life, fatigue, and aerobic capacity, increased the level of adiponectin, and decreased the level of inflammatory cytokines (leptin and TNF-α) in women with MS. Furthermore, exercise has a beneficial effect on quality of life and fatigue in people with MS at least by influencing functional capacity, body composition, adipose tissue, or cytokine. Moreover, to the association between circulating cytokine and adipokine concentrations with performance and psychological parameters, we can more decisively prove the effect of exercise training on people with MS.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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