Effect of Home-Based Aerobic Training and Vitamin D Supplementation on Fatigue and Quality of Life in Patients with Multiple Sclerosis During COVID-19 Outbreak

Elahe Bahmani

Razi University

Rastegar Hoseini (✉ R.hoseini@razi.ac.ir)

Razi University <https://orcid.org/0000-0001-8685-2471>

Ehsan Amiri

Razi University

Research

Keywords: Exercise, vitamin D, fatigue, quality of Life, MS

Posted Date: June 28th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-655827/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: Multiple sclerosis (MS) is the most common neurological disease that causes disability in the nervous system which reduces the quality of life (QoL). Studies have shown positive effects of therapeutic exercise with supplementation on motor- and cognitive function and fatigue as well as on QoL in persons with MS. The purpose of this study was to the effect of home-based aerobic training (AT) and vitamin D (Vit D) supplementation on fatigue and QoL in patients with MS during the covid-19 outbreak.

Methods: We recruited 40 females (20 - 40 years) with MS (EDSS: 3-5). Then, using simple randomization, the subjects were assigned to four groups including aerobic training (AT; n=9; 50%-75%, 20-40 min/day, 3 days/wk aerobic training), vitamin D supplementation (Vit D; n=9; 50,000 IU one day/week), aerobic training plus vitamin D supplementation (AT + Vit D; n=10), and sedentary control (C; n=10 placebo). The data were analyzed using paired *t*-test and one-way analysis of variance and Tukey's post hoc test with SPSS21 at a significance level of $P < 0.05$.

Results: After eight weeks of intervention, fatigue grade markedly reduced in the AT + Vit D, AT, and Vit D groups; However, fatigue increased in the control group. QoL increased significantly in AT+Vit D, AT, and Vit D compared to C. Also, the results show that the AT+Vit D had significantly higher QoL compared to AT and Vit D.

Conclusion: These findings suggest that therapeutic AT and VitD supplementation is very effective in reducing fatigue and consequently improves the QoL in female MS patients.

Introduction

Multiple sclerosis (MS) is one of the most common immune-mediated chronic disorders of the central nervous system in which the immune system attacks the myelin covering nerve fiber that causes involvement [1] and destruction of the myelin sheath in the brain and spinal cord and eventually MS [2]. While the incidence of MS was reported significantly different in various parts of the world, it is likely between 2 and 2.5 million patients worldwide [3]. According to a Cameron study, the number of MS patients was 250 per 100,000 in northern Europe, compared with 6 per 100,000 in Japan [4]. In 2011, the prevalence of MS in Canada was estimated at 290 per 100,000 [5]. In the Middle East, Iran was reported to be one of the most highly MS prevalent countries [6] with 88 cases per 100,000 [7]. In October 2016, the Iranian MS Society reported approximately 70,000 MS cases [8]. Although environmental and genetic factors play a role in increasing the risk of MS, the exact etiology of the MS is unknown [9]. With a three-fold prevalence in women compared to men, approximately 70% of patients were female, which occurs mainly between the ages of 20 and 40 [10]. The incidence of MS at young ages has several consequences on the quality of life and functional capacity, including fatigue, weakness of limbs, and movement disorders that threaten the independence and ability of the individual, increases depression, and reduces the quality of life [11]. About 75 to 95% of patients with MS have experienced fatigue and as

the most important factor in reducing personal independence and quality of life in MS patients, it is also the most important reason for patients not participating in physical activity programs [12]. Regarding the important impacts of fatigue on other symptoms of MS, it has not been adequately studied [13].

Fatigue is more than a simple symptom and can negatively impact various aspects of life (i.e., employment, socialization, and coping with illness) and affect daily life activities [14]. Using inefficient coping approaches causes increased stress and disease severity in MS patients with low quality of life [15]. To reduce the symptoms (fatigue, pain, spasms, etc.) and increase the quality of life of MS patients, non-pharmacological approaches (e.g., exercise, meditation, nutrition therapy, herbal and medicinal supplements, energy therapy, and relaxation) could be used as a complementary, not alternative, therapy [16]. Some studies have considered exercise and physical activity as some of the important methods to help control MS symptoms and complications [17]. Due to the possible effects of physical activity on increasing body temperature, patients were advised to refrain from exercising in the past (17). Recently, studies have shown that therapeutic exercise (aerobics, stretching, and stretching exercises) with moderate intensity or other rehabilitation techniques can be effective in improving fatigue and physical function in MS patients [18, 19]. Several studies have shown the positive effects of regular aerobic exercise on reducing symptoms including muscle spasms, fatigue, back pain, increased quality of life, and improved mood [20–23]. Additionally, vitamin D supplementation is effective in the management and treatment of autoimmune diseases [24]. In general, vitamin D is an immune regulator with anti-inflammatory activity and causes anti-inflammatory responses by binding to the vitamin D receptor in various cells of the immune system [25]. Vitamin D deficiency can impair muscle function and lead to sarcopenia and, consequently, decreased muscle strength [26]. Some studies suggest that vitamin D deficiency is related to decreased finger muscle strength and function in adult girls [27]; Convincing evidence has suggested that vitamin D might be associated with normal skeletal muscle development and optimizing muscle strength and performance [28]. Epidemiological studies, genetics, and animal models have shown the possibility of the nerve regeneration process following vitamin D supplementation [29]. The COVID-19 outbreak has also increased concerns and reduced quality of life, especially in MS patients. Also, due to quarantine and the fear of getting infected with COVID-19, participation in sports clubs and physical activities has decreased in MS patients. Given the potential effect of aerobic training as well as the aforementioned effect of vitamin D, the question arises as to whether combined Vit D + AT is effective on further improvement of fatigue and quality of life of MS patients during the COVID-19 outbreak?

Methods

Participants and Study Design

This clinical trial study aimed to investigate the effects of 8-week home-based aerobic training and Vit D supplementation fatigue and quality of life in patients with multiple sclerosis. As detailed in Fig. 1, the study population consisted of 60 participants (aged 20–40 years) from the Kermanshah MS center with a disability scale of 3–5.

In this study, 40 women with multiple sclerosis (20–40 years) in Kermanshah were selected using purposive and available sampling method based on G. POWER 3.1 software with a statistical power of 99 %, the effect size of 95%, and significance level at 0.05.

Inclusion criteria included: at least 2 years MS history, disability scale of 3–5, lack of regular exercise, no history of other diseases, no smoking, and no immunosuppressive drug consumption. Exclusion criteria included a history of heart disease, hypertension, orthopedic disorders, and diabetes, consuming other drugs in addition to MS medications that might affect the individual's response to the intervention, lack of regular attendance in the exercise training and testing sessions muscle injuries, inability to perform the exercise, COVID-19 infection, and severe relapses during the study period.

The trial (IR.RAZI.REC.1400.002) was approved by the Ethics Committee of the Kermanshah Razi University; Written informed consent was obtained from all participants, including agreement of the patients to participate as volunteers and feasibility to leave the study. Forty subjects were randomly assigned into four equal (n = 10) groups; aerobic training plus vitamin D supplementation (AT + Vit D), aerobic training (AT), vitamin D supplementation (Vit D), and control (C) using the lottery method.

Intervention

AT experimental groups exercised at home under supervision online three times per week for 2 months. All training sessions were carried out under the supervision of exercise physiologists.

Aerobic Training

Walking aerobics exercise was performed at home under supervision online. The subjects were instructed to do waking aerobics three times a week, starting with 20 min at 50% of HRmax per session, and to increase their total weekly walking time up to 40 min at 70 % of HRmax per session [30] which was recommended by the Multiple Sclerosis Association of America (MSAA) [31] (Table 1). Every session included 10 min of warm-up and 10 min of cooling down period. The walking program was designed to be of moderate intensity.

Table 1
Aerobic training protocol

Variables	Week							
	1	2	3	4	5	6	7	8
Intensity (HR _{max})	50–55%	50–55%	55–60%	55–60%	60–65%	60–65%	65–70%	65–70%
Time (min)	20	25	25	30	30	35	35	40
Borg scale	10	10	10	11	11	11	12	12

At the outset, the HRmax formula was used to determine the target heart rate [$\text{HRmax} = 220 - \text{age}$] [32]. The participants learned to count pulse rate and to monitor heart rate in an instructional session using the pulse palpation method. To assure that the desired heart rate (exercise intensity) was achieved and maintained during the walking aerobics phase, the 6–20 rating of perceived exertion (RPE) scale was considered [33] (Table 1). This walking program was continued for 8 weeks.

Diet and vitamin D supplementation

To attend the training program, the participants filled two questionnaires. First, a questionnaire was determined to assess the readiness of participants including demographic data, health status, and PA. A second questionnaire was a detailed semi-quantitative food frequency questionnaire adapted to the Iranian population and composed common food items, serving sizes, and meals, as designed to record and analyze 3-day food, recalls, before and at the end of the intervention. To determine the food intake and the amount of macronutrient consumption (protein, fat, and carbohydrates), the Food Processor nutritionist 4 software (FPN4) was used. Subjects were asked to consume the same food and macronutrient composition, one day before collecting blood samples in the pre and post-test. In general, the subjects' diet consisted of 55% carbohydrates, 30% fat, and 15% protein.

In this study, both the AT+Vit D group and Vit D group received 50000 units of vitamin D supplement (made by the Zahravi Pharmaceutical Company in Iran) once per week for eight weeks [24, 34]. The C and AT groups also received a placebo weekly (made by the Zahravi Pharmaceutical Company, Iran) with the same shape, color, smell, and tastes as vitamin D supplement, for 8 weeks.

Anthropometric Measurements and Body Composition

Three days before the start of the intervention and end of the study, subjects familiarized with the study procedure and primary measurements including anthropometric parameters and body composition were determined. Height was measured to the nearest 0.5 cm using a stadiometer (DETECTO, Model 3PHTROD-WM, USA), and Waist circumference was measured to the nearest 0.5 cm with a non-elastic tape measure. Also, the fat mass of the whole body, BMI, and weight of any patient was determined using INBODY test using bioelectric impedance analysis (Zeus 9.9 PLUS; Jawon Medical Co., Ltd., Kungsang Bukdo, South Korea). To minimize the effect of water consumption on the results, body composition measurements were performed at the beginning and the end of the study early in the morning between 8–9 am after at least 12 hours of fasting overnight and after emptying the bladder. Subjects were asked not to participate in intensive physical activity 48 hours before the test and to refrain from taking diuretic drugs and diuretics.

Fatigue and QoL

Fatigue was assessed using the validated Persian version Modified Fatigue Impact Scale (MFIS) [35], which has been recommended by the MS Council for Clinical Practice Guidelines. The MFIS, extracted from the original 40-item fatigue impact scale, is classified as a multi-dimensional scale and it is planned to analyze variable sides of fatigue by assessing its impact on physical, cognitive, and psychosocial

functions. The combination of nine items for physical status (pMFIS), ten items for cognitive status (cMFIS), and two items for psychosocial function status (psMFIS), depicts the total score of the MFIS. Multiple sclerosis quality of life-54 (MSQOL-54) questionnaire, a disease-specific inventory recently validated in an Iranian population [36], was performed to assess the QoL in the studied cohort. This scale has the advantage of assaying both healthy individuals and MS patient OoL. MSQOL-54 has a high test-retest reliability and an internal consistency with evidence supporting its content and construct validity. It contains a 36-item generic module derived from the SF-36 questionnaire and an 18-item module related to the specific clinical condition. The questionnaires were initially administrated before the first day and after the last day of interventional program. All the performed scales were translated and validated from the source language into Persian [35, 36]. The questionnaires were completed in the same order starting with MSIF followed by MSQOL-54. Each subscale and each composite score ranged from 0 to 100, with a higher score indicating better QoL. Composite scores were extracted by weighted sums of subscale scores.

Data Analysis

All statistical analyses were performed using the SPSS statistical software (version 21; SPSS Inc., Chicago, IL, USA) was used at a significant level of $P < 0.05$. The Shapiro–Wilk's test was used for evaluating the normality of distribution. To compare the mean hepatic risk factors between and within groups, ANOVA and t-test were used, respectively. Tukey's post hoc test was used if significant differences were found.

Results

The mean age, height, and bodyweight of patients are presented in Table 1. The findings on the scores of MFIS and their between-group comparison are presented in Table 2. Based on the results of the t-test, there were significant differences in the mean of scores of MFIS in the post-test compared to the pre-test. After eight weeks, scores of MFIS significantly decreased in all intervention groups, while in the C, these variables increased significantly (Table 2). The results of one-way ANOVA showed no significant difference in scores of MFIS between the groups in the pre-test, however, in the post-test, there was a significant difference in the above variables between the groups. The results of Tukey's post hoc test show that scores of MFIS were significant in AT + Vit D, AT, and Vit D compared to C. also the significant difference in the scores of MFIS was observed between AT + Vit D and AT compare to Vit D. The results indicate no significant difference in the scores of MFIS in AT + Vit D compare to AT alone (Table 2).

Table 2
Mean $\pm$ SD of the scores of MFIS after and before the intervention among the groups

Variables	AT + Vit D (n = 10)	AT (n = 9)	Vit D (n = 9)	C (n = 10)	P-Value ^a
Age (years)	27.70 $\pm$ 2.68	26.77 $\pm$ 2.27	25.44 $\pm$ 2.29	28.11 $\pm$ 3.62	0.563
Height (cm)	163.40 $\pm$ 2.63	166.03 $\pm$ 2.65	162.33 $\pm$ 1.50	164.20 $\pm$ 1.54	0.467
Body Weight (Kg)	71.90 $\pm$ 1.91	73.12 $\pm$ 1.93	71.11 $\pm$ 2.02	73.01 $\pm$ 1.33	0.086
Physical domain score					
Before	17.23 $\pm$ 2.03	17.33 $\pm$ 1.78	17.11 $\pm$ 2.43	17.01 $\pm$ 3.23	0.234
After	15.62 $\pm$ 3.12 ^{€β}	15.96 $\pm$ 2.24 ^{€β}	16.68 $\pm$ 1.19 ^β	17.48 $\pm$ 1.04	0.001 [¥]
P Value ^b	0.001*	0.001*	0.039*	0.059	
Cognitive domain score					
Before	13.13 $\pm$ 1.93	13.21 $\pm$ 2.03	12.98 $\pm$ 1.06	12.90 $\pm$ 0.66	0.192
After	10.27 $\pm$ 2.11 ^{€β}	10.67 $\pm$ 1.28 ^{€β}	11.97 $\pm$ 0.87 ^β	13.49 $\pm$ 1.33	0.001 [¥]
P Value ^b	0.001*	0.002*	0.011*	0.042*	
Psychosocial domain score					
Before	5.21 $\pm$ 0.41	5.42 $\pm$ 0.24	5.11 $\pm$ 0.15	5.16 $\pm$ 0.38	0.213
After	3.80 $\pm$ 0.23 ^{€β}	3.98 $\pm$ 0.83 ^{€β}	4.66 $\pm$ 0.31 ^β	5.49 $\pm$ 0.24	0.001 [¥]
P Value ^b	0.001*	0.013*	0.034*	0.046*	
Total MFIS score					
Before	35.57 $\pm$ 4.20	35.96 $\pm$ 4.05	35.20 $\pm$ 3.64	35.07 $\pm$ 4.27	0.087
After	29.69 $\pm$ 5.46 ^{€β}	30.61 $\pm$ 4.35 ^β	33.31 $\pm$ 2.37 ^β	36.46 $\pm$ 2.61	0.001 [¥]
P Value ^b	0.001*	0.001*	0.021*	0.048*	

Variables	AT + Vit D (n = 10)	AT (n = 9)	Vit D (n = 9)	C (n = 10)	P-Value ^a
AT + Vit D , Aerobic training + Turmeric supplement, AT , Aerobic training group; Vit D , Turmeric supplement group; C , the control group					
p values superscript with “a” is calculated using one-way analysis of variance test followed by post hoc Tukey's test; p values superscript with “b” is calculated using paired t-test					
*: Significantly different comparing pre and post-test within the groups					
¥: Significantly different comparing pre and post-test between groups					
μ: Significantly different between AT + Vit D compare to the AT group					
€: Significantly different between AT + Vit D compare to the Vit D group					
β: Significantly different between AT + Vit D, AT, and Vit D groups compare to the C group					

The findings on the QoL subscales and their between-group comparison are presented in Table 3. Based on the results of the t-test, there were significant differences in the mean of QoL subscales in the post-test compared to the pre-test. After eight weeks, scores of QoL subscales significantly increased in all intervention groups, while in the C, these variables decreased significantly (Table 3). The results of one-way ANOVA showed no significant difference in scores of QoL subscales between the groups in the pre-test, however, in the post-test, there was a significant difference in the above variables between the groups. The results of Tukey's post hoc test show that scores of QoL subscales were significant in AT + Vit D, AT, and Vit D compared to C. Also, the significant difference in physical health, role limitations due to physical problems, role limitations due to emotional problems, pain, emotional well-being, social function, cognitive function, sexual function, satisfaction with sexual function, and Mental health composite were observed between AT + Vit D compare to AT and Vit D. The results indicate a significant difference in the all scores of QoL subscales in AT + Vit D and AT compare to Vit D lone (Table 3).

Table 3
Mean $\pm$ SD of the scores of multiple sclerosis QoL subscales after and before the intervention among the groups

Variables	AT + Vit D	AT	Vit D	C	P-Value ^a
Physical health					
Before	39.13 $\pm$ 1.43	39.32 $\pm$ 2.23	38.90 $\pm$ 2.10	38.85 $\pm$ 2.32	0.057
After	49.04 $\pm$ 2.17 $\mu\epsilon\beta$	46.14 $\pm$ 1.35 $\epsilon\beta$	41.32 $\pm$ 1.54 β	37.06 $\pm$ 1.60	0.001 $\yen$
P Value ^b	0.001*	0.001*	0.031*	0.087	
Role limitations due to physical problems					
Before	31.67 $\pm$ 2.15	32.13 $\pm$ 2.11	31.95 $\pm$ 3.01	32.32 $\pm$ 1.73	0.330
After	43.21 $\pm$ 3.17 $\mu\epsilon\beta$	40.18 $\pm$ 1.93 $\epsilon\beta$	36.14 $\pm$ 1.19 β	31.73 $\pm$ 1.26	0.001 $\yen$
P Value ^b	0.001*	0.023*	0.039*	0.214	
Role limitations due to emotional problems					
Before	35.23 $\pm$ 1.12	36.22 $\pm$ 2.41	35.97 $\pm$ 3.07	36.04 $\pm$ 1.57	0.213
After	53.36 $\pm$ 1.45 $\mu\epsilon\beta$	48.65 $\pm$ 2.36 $\epsilon\beta$	39.55 $\pm$ 1.24 β	35.21 $\pm$ 1.42	0.001 $\yen$
P Value ^b	0.001*	0.001*	0.034*	0.471	

AT + Vit D, Aerobic training + Turmeric supplement, **AT**, Aerobic training group; **Vit D**, Turmeric supplement group; **C**, the control group

p values superscript with "a" is calculated using one-way analysis of variance test followed by post hoc Tukey's test; p values superscript with "b" is calculated using paired t-test

*: Significantly different comparing pre and post-test within the groups

$\yen$: Significantly different comparing pre and post-test between groups

μ : Significantly different between AT + Vit D compare to the AT group

ϵ : Significantly different between AT + Vit D compare to the Vit D group

β : Significantly different between AT + Vit D, AT, and Vit D groups compare to the C group

Variables	AT + Vit D	AT	Vit D	C	P-Value ^a
Pain					
Before	65.42 ± 1.26	66.03 ± 1.31	65.76 ± 2.09	66.20 ± 2.13	0.616
After	74.36 ± 2.01 ^{μ€β}	69.37 ± 2.19 ^{€β}	67.25 ± 1.26 ^β	65.18 ± 1.39	0.001 [¥]
P Value ^b	0.001*	0.035*	0.049*	0.327	
Emotional well being					
Before	41.54 ± 1.19	41.12 ± 2.25	40.95 ± 2.16	42.33 ± 1.70	0.259
After	49.18 ± 2.11 ^{μ€β}	46.13 ± 2.48 ^{€β}	43.14 ± 1.44 ^β	42.04 ± 0.98	0.001 [¥]
P Value ^b	0.001*	0.017*	0.028*	0.514	
Energy					
Before	30.56 ± 1.42	31.26 ± 2.65	30.88 ± 2.15	31.84 ± 1.38	0.248
After	38.06 ± 2.24 ^{€β}	36.77 ± 1.83 ^{€β}	33.27 ± 1.46 ^β	30.09 ± 0.78	0.001 [¥]
P Value ^b	0.001*	0.001*	0.037*	0.491	
Health perception					
Before	42.56 ± 2.08	43.13 ± 1.76	43.34 ± 1.96	42.33 ± 2.11	0.340

AT + Vit D, Aerobic training + Turmeric supplement, **AT**, Aerobic training group; **Vit D**, Turmeric supplement group; **C**, the control group

p values superscript with “a” is calculated using one-way analysis of variance test followed by post hoc Tukey's test; p values superscript with “b” is calculated using paired t-test

*: Significantly different comparing pre and post-test within the groups

¥: Significantly different comparing pre and post-test between groups

μ: Significantly different between AT + Vit D compare to the AT group

€: Significantly different between AT + Vit D compare to the Vit D group

β: Significantly different between AT + Vit D, AT, and Vit D groups compare to the C group

Variables	AT + Vit D	AT	Vit D	C	P-Value ^a
After	51.12 ± 1.67 ^{€β}	50.16 ± 1.78 ^{€β}	47.10 ± 1.21 ^β	42.08 ± 1.04	0.001 [¥]
P Value ^b	0.001*	0.001*	0.021*	0.647	
Social function					
Before	60.44 ± 1.23	61.11 ± 2.76	61.32 ± 3.04	60.88 ± 2.13	0.326
After	67.20 ± 1.46 ^{μ€β}	65.27 ± 1.29 ^{€β}	63.15 ± 1.36 ^β	60.55 ± 1.39	0.001 [¥]
P Value ^b	0.001*	0.015*	0.029*	0.723	
Cognitive function					
Before	65.23 ± 1.21	66.17 ± 1.73	65.22 ± 2.06	66.27 ± 2.16	0.424
After	72.20 ± 1.46 ^{μ€β}	70.04 ± 1.33 ^{€β}	68.06 ± 1.05 ^β	66.02 ± 1.44	0.001 [¥]
P Value ^b	0.001*	0.019*	0.034*	0.650	
Health distress					
Before	70.32 ± 1.56	71.13 ± 1.21	70.66 ± 3.19	70.30 ± 2.14	0.616
After	77.36 ± 2.01 ^{€β}	76.27 ± 1.29 ^{€β}	73.45 ± 2.16 ^β	70.21 ± 2.09	0.001 [¥]
P Value ^b	0.001*	0.035*	0.049*	0.421	

AT + Vit D, Aerobic training + Turmeric supplement, **AT**, Aerobic training group; **Vit D**, Turmeric supplement group; **C**, the control group

p values superscript with “a” is calculated using one-way analysis of variance test followed by post hoc Tukey's test; p values superscript with “b” is calculated using paired t-test

*: Significantly different comparing pre and post-test within the groups

¥: Significantly different comparing pre and post-test between groups

μ: Significantly different between AT + Vit D compare to the AT group

€: Significantly different between AT + Vit D compare to the Vit D group

β: Significantly different between AT + Vit D, AT, and Vit D groups compare to the C group

Variables	AT + Vit D	AT	Vit D	C	P-Value ^a
Sexual function					
Before	68.22 ± 2.31	68.76 ± 1.82	69.11 ± 2.34	69.30 ± 2.24	0.730
After	76.36 ± 2.01 ^{μ€β}	73.27 ± 1.07 ^{€β}	71.35 ± 1.34 ^β	69.21 ± 2.19	0.001 [¥]
P Value ^b	0.001*	0.021*	0.044*	0.627	
Change in health					
Before	43.15 ± 1.38	42.67 ± 2.76	43.04 ± 1.96	42.73 ± 2.33	0.247
After	47.12 ± 1.57 ^{€β}	46.30 ± 1.34 ^{€β}	45.10 ± 0.92 ^β	42.38 ± 1.24	0.001 [¥]
P Value ^b	0.001*	0.027*	0.043*	0.501	
Satisfaction with sexual function					
Before	55.34 ± 2.27	56.16 ± 1.64	55.77 ± 1.40	56.33 ± 2.21	0.421
After	63.20 ± 1.33 ^{μ€β}	60.22 ± 2.30 ^{€β}	59.14 ± 1.51 ^β	55.80 ± 1.43	0.001 [¥]
P Value ^b	0.001*	0.017*	0.036*	0.320	
Overall QoL					
Before	54.74 ± 1.47	55.19 ± 1.54	55.47 ± 0.88	54.68 ± 1.20	0.394

AT + Vit D, Aerobic training + Turmeric supplement, **AT**, Aerobic training group; **Vit D**, Turmeric supplement group; **C**, the control group

p values superscript with “a” is calculated using one-way analysis of variance test followed by post hoc Tukey's test; p values superscript with “b” is calculated using paired t-test

*: Significantly different comparing pre and post-test within the groups

¥: Significantly different comparing pre and post-test between groups

μ: Significantly different between AT + Vit D compare to the AT group

€: Significantly different between AT + Vit D compare to the Vit D group

β: Significantly different between AT + Vit D, AT, and Vit D groups compare to the C group

Variables	AT + Vit D	AT	Vit D	C	P-Value ^a
After	59.20 ± 1.33 ^{€β}	58.27 ± 2.36 ^{€β}	56.13 ± 1.47 ^β	54.19 ± 1.59	0.001 [¥]
P Value ^b	0.001*	0.001*	0.039*	0.670	
Physical health composite					
Before	48.15 ± 2.08	48.77 ± 2.76	47.14 ± 2.06	48.59 ± 1.50	0.301
After	57.11 ± 1.36 ^{€β}	56.32 ± 2.31 ^{€β}	53.16 ± 1.58 ^β	48.21 ± 2.23	0.001 [¥]
P Value ^b	0.001*	0.001*	0.022*	0.709	
Mental health composite					
Before	53.24 ± 1.30	54.17 ± 1.66	53.37 ± 1.43	54.33 ± 2.48	0.624
After	62.21 ± 1.40 ^{μ€β}	59.73 ± 2.30 ^{€β}	57.12 ± 1.49 ^β	53.80 ± 1.43	0.001 [¥]
P Value ^b	0.001*	0.027*	0.034*	0.420	
AT + Vit D , Aerobic training + Turmeric supplement, AT , Aerobic training group; Vit D , Turmeric supplement group; C , the control group					
p values superscript with “a” is calculated using one-way analysis of variance test followed by post hoc Tukey's test; p values superscript with “b” is calculated using paired t-test					
*: Significantly different comparing pre and post-test within the groups					
¥: Significantly different comparing pre and post-test between groups					
μ: Significantly different between AT + Vit D compare to the AT group					
€: Significantly different between AT + Vit D compare to the Vit D group					
β: Significantly different between AT + Vit D, AT, and Vit D groups compare to the C group					

Discussion

To the best of our knowledge, this study is the first, single-blind randomized controlled trial specifically designed to assess the effectiveness of combined aerobic training and vitamin D supplementation on MS-related fatigue and QoL in patients with MS. The eight weeks of aerobic training and vitamin D

supplementation significantly improved fatigue, increased QoL, and vitamin D levels in favor of combined aerobic training and vitamin D. Consistent with the results of the present study, Beckman et al. (2020) reported that increasing vitamin D levels reduces fatigue and increases the QoL in MS patients [37], Rezaei et al (2016), also reported the effectiveness of combined Core Stability exercise training and vitamin D compared with exercise or vitamin D alone [38]. Several mechanisms have been proposed to explain the possible beneficial effects of aerobic training. Increased metabolism during and after aerobic training has been reported as a primary mechanism for improved fatigue in MS patients. Accordingly, aerobic training-induced increased metabolism increases blood flow (oxygen and nutrients delivery), reduces muscle weakness, and ultimately improves the nervous system function [39]. Since aerobic training increases the delivery of oxygen to the working skeletal muscles, it, in turn, increases muscle oxidation capacity and stimulates the aerobic biochemical system to establish adaptive responses [40]. In general, aerobic training stimulates structural and functional changes in muscles and increases capillary availability, myoglobin storage, mitochondrial function, and oxidative enzymes by the consecutive recruitment of muscle fibers. Therefore, aerobic training in MS patients with more blood supply to muscles and muscle efficiency might reduce fatigue [40]. Studies have suggested that aerobic training could improve fatigue probably by managing the immune system, altering inflammatory and anti-inflammatory cytokines, normalizing the hypothalamic-pituitary-adrenal axis imbalances [41, 42]. Also, aerobic training might affect the QoL by reducing epinephrine, norepinephrine, cholesterol, and triglycerides levels, improving the immune system, endorphin secretion, and ultimately mood state [43]. Also, according to available studies, the production of free radicals (e.g., nitric oxide) in MS patients is probably increased due to disruption of the nicotinamide adenine dinucleotide phosphate (NADP+) system, which intensifies inflammatory responses and, consequently, exacerbates brain damage. Therefore, vitamin D might prevent the progression of MS by inhibiting nitric oxide production [44], reducing myostatin expression (a negative regulator of skeletal muscle growth), and increasing myogenic cell differentiation. Accordingly, studies have shown that possibly due to the presence of vitamin D receptors in skeletal muscle, vitamin D metabolites affect muscle metabolism by stimulating protein synthesis, increasing the ratio of type 2 muscle fibers, and improving muscle function [45]. Overall, our findings support the hypothesis that vitamin D supplementation reduces fatigue and QoL in individuals with vitamin D deficiency which could be increased when combined with aerobic training. The limitations of this study include being cross-sectional, the small sample size, and the exposure of the subjects to sunlight.

Eight weeks of aerobic training and vitamin D supplementation in MS patients lead to a clinically meaningful improved fatigue, enhanced QoL, and increased vitamin D levels when compared with each AT or Vit D alone and control. Therefore, lifestyle changes can be effective in improving the condition of patients with MS. However due to some contradictory reports, further research in larger sample size is needed.

Declarations

Authors' contributions

RH designed the study. EB experimented. RH analyzed the data and wrote the manuscript. EA involved in the interpretation of data, reviewed and edited the manuscript. All authors read and approved the final manuscript.

Funding:

The author(s) received no specific funding for this work.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate.

This study was approved by the ethics committee of Razi University of Kermanshah (IR.RAZI.REC.1400.002) and registered in the Iranian Clinical Trial Registration Center under the code IRCT20201129049525N1.

Competing interests

The authors declare no competing interests.

Conflict of interest

The authors report no conflicts of interests.

References

1. Wendebourg MJ, Heesen C, Finlayson M, Meyer B, Pöttgen J, Köpke S: Patient education for people with multiple sclerosis-associated fatigue: a systematic review. *PLoS One* 2017, 12:e0173025.
2. Dobryakova E, Genova HM, DeLuca J, Wylie GR: The dopamine imbalance hypothesis of fatigue in multiple sclerosis and other neurological disorders. *Frontiers in neurology* 2015, 6:52.
3. Mazumder R, Murchison C, Bourdette D, Cameron M: Falls in people with multiple sclerosis compared with falls in healthy controls. *PLoS One* 2014, 9:e107620.
4. Cameron MH, Peterson V, Boudreau EA, Downs A, Lovera J, Kim E, McMillan GP, Turner AP, Haselkorn JK, Bourdette D: Fatigue is associated with poor sleep in people with multiple sclerosis and cognitive impairment. *Multiple sclerosis international* 2014, 2014.
5. Urits I, Adamian L, Fiocchi J, Hoyt D, Ernst C, Kaye AD, Viswanath O: Advances in the understanding and management of chronic pain in multiple sclerosis: a comprehensive review. *Current pain and headache reports* 2019, 23:1-11.

6. Heydarpour P, Khoshkish S, Abtahi S, Moradi-Lakeh M, Sahraian MA: Multiple sclerosis epidemiology in Middle East and North Africa: a systematic review and meta-analysis. *Neuroepidemiology* 2015, 44:232-244.
7. Eskandarieh S, Heydarpour P, Elhami S-R, Sahraian MA: Prevalence and incidence of multiple sclerosis in Tehran, Iran. *Iranian journal of public health* 2017, 46:699.
8. Mousavizadeh A, Dastoorpoor M, Naimi E, Dohrabpour K: Time-trend analysis and developing a forecasting model for the prevalence of multiple sclerosis in Kohgiluyeh and Boyer-Ahmad Province, southwest of Iran. *Public health* 2018, 154:14-23.
9. Sorensen PS: Multiple sclerosis: pathophysiology revisited. *The Lancet Neurology* 2005, 4:9-10.
10. Elhami S-R, Mohammad K, Sahraian MA, Eftekhari H: A 20-year incidence trend (1989–2008) and point prevalence (March 20, 2009) of multiple sclerosis in Tehran, Iran: a population-based study. *Neuroepidemiology* 2011, 36:141-147.
11. Carroll CC, Gallagher PM, Seidle ME, Trappe SW: Skeletal muscle characteristics of people with multiple sclerosis. *Archives of physical medicine and rehabilitation* 2005, 86:224-229.
12. Morrow SA, Rosehart H, Johnson AM: The effect of Fampridine-SR on cognitive fatigue in a randomized double-blind crossover trial in patients with MS. *Multiple sclerosis and related disorders* 2017, 11:4-9.
13. Hasanpour-Dehkordi A, Jivad N, Solati K: Effects of yoga on physiological indices, anxiety and social functioning in multiple sclerosis patients: A randomized trial. *Journal of clinical and diagnostic research: JCDDR* 2016, 10:VC01.
14. Ghazagh M, Zadhasan Z: The Effect of Group Mindfulness-Based Stress Reduction Program on the Quality of Life and Fatigue in Patients With Multiple Sclerosis. *Avicenna Journal of Nursing and Midwifery Care* 2019, 27:35-44.
15. Salehpour G, Rezaei S, Hosseini-neshad M: Quality of life in multiple sclerosis (MS) and role of fatigue, depression, anxiety, and stress: A bicenter study from north of Iran. *Iranian journal of nursing and midwifery research* 2014, 19:593.
16. Mostert S, Kesselring J: Effects of a short-term exercise training program on aerobic fitness, fatigue, health perception and activity level of subjects with multiple sclerosis. *Multiple Sclerosis Journal* 2002, 8:161-168.
17. Hermann BP, Vickrey B, Hays RD, Cramer J, Devinsky O, Meador K, Perrine K, Myers LW, Ellison GW: A comparison of health-related quality of life in patients with epilepsy, diabetes and multiple sclerosis. *Epilepsy research* 1996, 25:113-118.

18. Motl RW, McAuley E, Snook EM: Physical activity and quality of life in multiple sclerosis: Possible roles of social support, self-efficacy, and functional limitations. *Rehabilitation Psychology* 2007, 52:143.
19. Motl RW, McAuley E, Snook EM, Gliottoni RC: Physical activity and quality of life in multiple sclerosis: intermediary roles of disability, fatigue, mood, pain, self-efficacy and social support. *Psychology, health & medicine* 2009, 14:111-124.
20. Soleimany M, Ziba FN, Kermani A, Hosseini F: Comparison of sleep quality in two groups of nurses with and without rotation work shift hours. *Iran Journal of Nursing* 2007, 20:29-38.
21. Petajan JH, Gappmaier E, White AT, Spencer MK, Mino L, Hicks RW: Impact of aerobic training on fitness and quality of life in multiple sclerosis. *Annals of neurology* 1996, 39:432-441.
22. Ardakani MD: Effect of Aerobic Exercise Program on Quality of Life in Male Patients with Multiple Sclerosis. *Journal of Shahid Sadoughi University of Medical Sciences* 2020.
23. Stuifbergen AK, Blozis SA, Harrison TC, Becker HA: Exercise, functional limitations, and quality of life: A longitudinal study of persons with multiple sclerosis. *Archives of physical medicine and rehabilitation* 2006, 87:935-943.
24. VanAmerongen B, Dijkstra C, Lips P, Polman C: Multiple sclerosis and vitamin D: an update. *European journal of clinical nutrition* 2004, 58:1095-1109.
25. Verstuyf A, Carmeliet G, Bouillon R, Mathieu C: Vitamin D: a pleiotropic hormone. *Kidney international* 2010, 78:140-145.
26. Solomon A, Bouloux P: Modifying muscle mass—the endocrine perspective. *Journal of Endocrinology* 2006, 191:349-360.
27. Ward KA, Das G, Berry JL, Roberts SA, Rawer R, Adams JE, Mughal Z: Vitamin D status and muscle function in post-menarchal adolescent girls. *The Journal of Clinical Endocrinology & Metabolism* 2009, 94:559-563.
28. Houston DK, Tooze JA, Hausman DB, Johnson MA, Nicklas BJ, Miller ME, Neiberg RH, Marsh AP, Newman AB, Blair SN: Change in 25-hydroxyvitamin D and physical performance in older adults. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences* 2011, 66:430-436.
29. MOSAYEBI G, Ghazavi A, Payani M: The effect of vitamin D3 on the inhibition of experimental autoimmune encephalomyelitis in C57BL/6 mice. 2006.
30. Monazamnezhad A, Habibi A, Majdinasab N, Ghalvand A: The effects of aerobic exercise on lipid profile and body composition in women with multiple sclerosis. *Jundishapur Journal of Chronic Disease Care* 2015, 4.

31. Rae-Grant A, Day GS, Marrie RA, Rabinstein A, Cree BA, Gronseth GS, Haboubi M, Halper J, Hosey JP, Jones DE: Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 2018, 90:777-788.
32. Branco BHM, de Oliveira Mendes F, Ladeia GF, Bertolini SMMG, Badilla PV, Andreato LV: Maximum heart rate predicted by formulas versus values obtained in graded exercise tests in Brazilian jiu-jitsu athletes. *Sport Sciences for Health* 2020, 16:39-45.
33. Kalb R, Brown TR, Coote S, Costello K, Dalgas U, Garmon E, Giesser B, Halper J, Karpatkin H, Keller J: Exercise and lifestyle physical activity recommendations for people with multiple sclerosis throughout the disease course. *Multiple Sclerosis Journal* 2020, 26:1459-1469.
34. Tuyserkani H, Rezaei M: Role of Vitamins D and A in Immune System of Multiple Sclerosis Patients: An Updated Mini-Review. *Journal of Reviews in Medical Sciences* 2020, 1:45-48.
35. Ghajarzadeh M, Jalilian R, Eskandari G, Ali Sahraian M, Reza Azimi A: Validity and reliability of Persian version of Modified Fatigue Impact Scale (MFIS) questionnaire in Iranian patients with multiple sclerosis. *Disability and rehabilitation* 2013, 35:1509-1512.
36. Ghaem H, Haghighi AB, Jafari P, Nikseresht A: Validity and reliability of the Persian version of the multiple sclerosis quality of life questionnaire. *Neurology India* 2007, 55:369.
37. Beckmann Y, Türe S, Duman SU: Vitamin D deficiency and its association with fatigue and quality of life in multiple sclerosis patients. *EPMA Journal* 2020, 11:65-72.
38. Rezaee H, Koushkie Jahromi M, Salesi M, Izadi S: The Influence of Core Stability Exercise and Vitamin D on Some of Physical Fitness Indices in Young Multiple Sclerosis (MS) Women. *Sport Physiology* 2017, 9:17-34.
39. De Groot MH, Phillips SJ, Eskes GA: Fatigue associated with stroke and other neurologic conditions: implications for stroke rehabilitation. *Archives of physical medicine and rehabilitation* 2003, 84:1714-1720.
40. Kargarfard M, Etemadifar M, Baker P, Mehrabi M, Hayatbakhsh R: Effect of aquatic exercise training on fatigue and health-related quality of life in patients with multiple sclerosis. *Archives of physical medicine and rehabilitation* 2012, 93:1701-1708.
41. White LJ, Castellano V: Exercise and brain health—implications for multiple sclerosis: Part II—immune factors and stress hormones. *Sports medicine* 2008, 38:179-187.
42. White LJ, Castellano V: Exercise and brain health—implications for multiple sclerosis. *Sports medicine* 2008, 38:91-100.

43. Fayazi B, Parnow A, Ahsan B: Effect Aerobic Exercises on fatigue and quality of life in Women with Multiple Sclerosis. *Journal of Holistic Nursing And Midwifery* 2016, 26:30-40.
44. Ibrahim MH, Alloush TK, Rahim MKA: Vitamin D Level in Multiple Sclerosis Patients. Could Vitamin D Level Be Routine Investigation for Multiple Sclerosis Patients? *Neuroscience & Medicine* 2014, 5:201.
45. Saremi A, Shavandi N, Vafapour H: Eight-week resistance training with vitamin D supplementation in postmenopausal women: Effects on skeletal muscle. *Pajoohandeh Journal* 2013, 18:57-63.

Figures

Figure 1

Flow chart of the study population AT+Vit D, Aerobic training + vitamin D supplement, AT, Aerobic training group; Vit D, vitamin D supplement; C, the control group