

## **Resistance training improves hormonal related fatigue and physical fitness in female patients with multiple sclerosis**

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### **Abstract:**

*Introduction:* Fatigue occurs in the majority of patients with multiple sclerosis (MS) and MS – related fatigue is strongly linked to impaired physical activity. Exercise may have beneficial effects on both fatigue and physical performance in MS patients however it is not well known. The aim of this study was to examine the effects of 8 weeks resistance training (RT) on fatigue levels, hormonal related fatigue and physical fitness in female patients with MS.

*Material & Methods:* Twenty seven female with MS disease in a range of 18-48 year of old and EDSS lower than 4.5 participated in this study as the subject. Subjects were

divided into control group (n=13) or training group (n=14) randomly. The training group performed progressive RT program, 3 days a week for 8 weeks.

*Results:* The results showed that fatigue levels decreased and right leg balance (RLB), left leg balance (LLB) and muscular endurance improved after 8 weeks RT compare to the control group ( $P<0.05$ ). For serum levels of dehydroepiandrosterone sulfate (DHEA-S) no significant differences were observed after the intervention.

*Conclusions:* The results suggest RT with specific intensity and duration utilized in this study improves decrease fatigue levels and improved physical fitness in female patients with MS.

**Key words:** Multiple sclerosis, Resistance training, Fatigue, Physical fitness, DHEA-S.

## 1. Introduction

Multiple sclerosis (MS) is thought to be an autoimmune disorder that leads to the destruction of myelin, oligodendrocytes and axons (1). Functional impairments in MS such as abnormal walking mechanics, poor balance, muscle weakness and fatigue typically result from axonal degeneration and conduction block. Although the exact etiology of MS remains unknown, a combination of genetic, infectious, environmental and/or autoimmune factors likely contributes to disease onset. About 1-2.5 million people around the world are estimated to be affected, depending on the publication (2). The prevalence of MS is more common in women than men (female to male ratio approximately 2-3:1). MS usually presents between the age of 18 to 35 years, rarely much earlier during childhood, or in old age (3).

Functional deficits and impairments, such as muscle weakness, fatigue, and impaired ventilation, have long been recognized as major causes of morbidity and mortality in individuals with advanced MS (4). Fatigue unrelated to physical activity is a common symptom in MS that has been observed since the initial descriptions of this disease.

Approximately 65% of individuals with MS report fatigue limitations (5) and as many as 40% describe it as the single most disabling symptom – a higher percent age than weakness, spasticity, balance or bowel/bladder problems (6). So this life style which reduces mobility can lead to secondary sequels such as obesity, osteoporosis, and/or cardiovascular damage (7). Dehydroepiandrosterone (DHEA) is an androgenic steroidal hormone produced by the adrenal gland and DHEA-S is a metabolite of DHEA. Its specific physiological functions, other than serving as a precursor to other steroid hormones (such as testosterone), are not yet established. It is possible that DHEA-S plays an important role in physical development during puberty (8). Previous studies demonstrated that reduced levels of DHEA-S linked with fatigue in MS (9,10). Multiple sclerosis– related fatigue is strongly linked to impaired physical activity and quality of life (11). Deficit in balance control is a common and often an initial disabling symptom of MS (12) and previous studies demonstrated that aerobic performance is significantly reduced in persons with MS, (13,14) which may suggest an increased risk of mortality and limited mobility. Regular physical activity may alleviate fatigue while enhancing functional reserve capacity (15). It is not clearly established whether exercise training can positively influence on DHEA-S and fatigue in MS patients. The findings show inconsistency because some studies show an effect, (16,17) whereas others do not (18). On the other hand, there are limited data on physical performance in individuals with MS and determining factors that contribute to muscular endurance, balance and fatigue in people with MS will assist therapists in planning treatment for these individuals. Therefore, we investigated the effects of 8 weeks resistance training (RT) on DHEA-S, fatigue levels and physical fitness in female patients with MS.

## 2. Materials and Methods

### *Subjects*

Twenty seven female patients with MS from the MS Center of Shiraz, Iran participated in this study as the subject. The inclusion criteria for the subjects with MS were diagnosis with relapsing-remitting MS by modified McDonald criteria, presenting any type of orthopedic, any

cardiovascular or pulmonary disease, pregnancy, cancer, bone fracture of less than 6 months, use of prostheses, any serious nervous system disorder, any health problems to prevent effort on the physical test and taking part in regular physical activities before this study and age between 18 and 50 years. Their mean Expanded Disability Status Scale (EDSS) score was 2, with a range of 1 to 4.5. The study protocol was approved by the Marvdasht branch, Islamic Azad University, Fars, Iran and all study participants provided written informed consent before testing. Before the examinations a neurologist assessed EDSS and participants were randomly divided into an exercise group (n=14) and control group (n=13).

### *Exercise training*

All subjects performed 10 min warm-up at the beginning of each training session consisting of static stretching movements for like extended arm side stretch, biceps stretch, triceps side stretch, quadriceps stretch and hamstring stretch. The duration of each static stretching movement was at least 8 seconds. Subjects executed seven RT selected to stress the major muscle groups in the following order: biceps curls with dumbbell, side arm raisers with resistance band, back arm opener with resistance band, pelvic lift, towel crunches and twists, calf and ankle stretch with resistance band, and squad with dumbbell. RT consisted of 50-60 min of station weight training per day, 3 days a week, for 8 weeks. This training was performed in 7 stations and included 3 sets with 5-12 maximal repetitions at 50-70% of 1-RM in each station. 2 min rest was considered between each position and each training session was followed by cool-down. Subjects completed the protocol under the supervision of an exercise physiologist and a physician. At the end of the study all of the variables that were measured as pretest were measured again as posttest.

### *Measurements*

#### *Anthropometric and body composition measurements*

Height and weight were measured, and body mass index (BMI) was calculated by dividing weight (kg) by height (m<sup>2</sup>). Waist circumference was determined by obtaining the minimum circumference (narrowest

part of the torso, above the umbilicus) and the maximum hip circumference while standing with their heels together. The waist to hip ratio (WHR) was calculated by dividing waist by hip circumference (cm). Body fat mass, body fat percentage and lean body mass were assessed by bioelectrical impedance analysis using a Body Composition Analyzer (BoCA x1, Johannesburg, South Africa).

### *Fatigue Assessment*

Fatigue measured by Fatigue Severity Scale (FSS). FSS is widely used in MS studies and shows high reliability, validity and internal consistency (19). This scale is specifically designed to differentiate fatigue from clinical depression, since both may share common symptoms. A score of 4.5 is on average seen in people with depression alone, but people with fatigue-related MS, score an average of 6.5 (19). The FSS is a 9-item questionnaire, each item rating from 1-7, and requires the subject to rate his or her own level of fatigue. Each participant was asked to answer the questions depending on how appropriate they felt the statement applied to them over the preceding week. A low value indicates low agreement with the statement whereas a high values indicates high agreement (19). The score is calculated by adding all 9-items and dividing it by 9.

### *Balance Assessment*

To assess balance and monitor mobility, the standing balance test was used (20). The subjects stood on one leg for as long as possible. The subject was permitted to practice their balancing before starting the test for one minute. The timing stopped, when the elevated foot touched the ground or the subjects lost their balance position. The best of three attempts was recorded. The test was repeated on the other leg.

### *Muscular endurance measurement*

1-minute bent-knee sit-ups test was used to assess abdominal muscular endurance. The bent knee sit-ups test required the subjects to lock their hands behind their head and touch their elbows to the thigh with a partner holding the ankles.

### *Biochemical analysis*

Fasted, resting morning blood samples (7 ml) were taken at the same time before and after 8 weeks intervention. All the subjects fasted at least for 12 hours and a fasting blood sample was obtained by venipuncture. Serum obtained was frozen at  $-22^{\circ}\text{C}$  for subsequent analysis. The serum DHEA-S levels were measured in duplicate using an enzyme-linked immunosorbent assay (ELISA) kits (Demeditec Diagnostics GmbH, Germany).

### *Statistical analysis*

Results were expressed as the mean  $\pm$  SD and distributions of all variables were assessed for normality. Paired t-test was used to compute mean ( $\pm$  SD) changes in the variables in control and training group pre and after the intervention. Differences among groups were assessed by using analysis of covariate (ANCOVA) test. The level of significance in all statistical analyses was set at  $P \leq 0.05$ . Data analyses were performed using SPSS software for windows (version 17, SPSS, Inc., Chicago, IL).

## **6. Results**

Anthropometric and body composition characteristics and disability status (EDSS) of the subjects at baseline and after training are presented in Table 1. Before the intervention, there were no significant differences in any of variables among the two groups. Body weight, body mass index (BMI), body fat mass, body fat percentage and EDSS decreased ( $P < 0.05$ ) after 8 weeks RT compared to the control group, while no significant changes in the waist hip ratio (WHR) and lean body mass were found after the training (Table 1).

Table 1. Body composition characteristics and disability status of the subjects

	Baseline (mean $\pm$ SD)	After intervention (mean $\pm$ SD)	Paired t-test (Sig)	ANCOVA
<b>Body weight (kg)</b>				
Exercise (n=14)	66.1 $\pm$ 16.2	64.1 $\pm$ 16.1*	0.001	0.006
Control (n=13)	65.03 $\pm$ 12.5	65.4 $\pm$ 13.7	0.5	
<b>BMI (Kg/m)</b>				
Exercise (n=14)	25.8 $\pm$ 6.5	24.9 $\pm$ 6.2*	0.001	0.003
Control (n=13)	25.03 $\pm$ 4.9	25.9 $\pm$ 4.2	0.4	
<b>Body fat (%)</b>				
Exercise (n=14)	33.8 $\pm$ 8.7	32.5 $\pm$ 9.09*	0.04	0.04
Control (n=13)	33.8 $\pm$ 7.1	34.06 $\pm$ 7.2	0.6	
<b>Body fat mass (kg)</b>				
Exercise (n=14)	23.5 $\pm$ 10.2	22.3 $\pm$ 10.0*	0.01	0.03
Control (n=13)	22.7 $\pm$ 8.5	23.2 $\pm$ 8.5	0.3	
<b>Lean body mass (kg)</b>				
Exercise (n=14)	39.9 $\pm$ 6.4	40.6 $\pm$ 6.2	0.07	0.08
Control (n=13)	39.6 $\pm$ 4.7	39.1 $\pm$ 4.8	0.4	
<b>WHR</b>				
Exercise (n=14)	0.8 $\pm$ 0.05	0.77 $\pm$ 0.06	0.02	0.3
Control (n=13)	0.81 $\pm$ 0.01	0.8 $\pm$ 0.04	0.5	
<b>EDSS</b>				
Exercise (n=14)	1.8 $\pm$ 1.2	1.3 $\pm$ 1.5	0.01	0.04
Control (n=13)	2.1 $\pm$ 1.4	2.1 $\pm$ 1.5	0.7	

Data are the mean  $\pm$  SE of baseline and final values and of the body composition parameters and disability status in each group. Paired t-test was used to compute mean ( $\pm$  SD) changes in the variables in control and training group pre and after the intervention. Comparison different significance between groups after 8 weeks RT was determined by using the ANCOVA test. \* P<0.05

Changes of fatigue level, serum DHEA-S and physical performance of the subjects are illustrated in Table 2. The results showed that the mean score of fatigue decreased (P<0.05, 20.5%) after 8 weeks RT compared to the control group. After 8 weeks of RT the exercise group showed significant increase in RLB (77.07%), LLB (33.4 %) and muscular endurance (88.1 %) while no significant change in the control group was found (Table 2). Our results demonstrated that DHEA-S levels had no significant differences after the RT.

**Table 2.** Fatigue level and physical performance status of the subjects

	Baseline (mean $\pm$ SD)	After intervention (mean $\pm$ SD)	Paired t-test (Sig)	ANCOVA
<b>Fatigue level</b>				
Exercise (n=14)	3.4 $\pm$ 1.3	2.7 $\pm$ 1.3*	0.01	0.001
Control (n=13)	4.2 $\pm$ 1.34	4.2 $\pm$ 1.30	0.7	
<b>Serum DHEA-S (ng/ml)</b>				
Exercise (n=14)	1.0 $\pm$ 0.6	1.1 $\pm$ 0.6	0.2	0.09
Control (n=13)	1.2 $\pm$ 1.4	0.7 $\pm$ 0.5	0.1	
<b>RLB (s)</b>				
Exercise (n=14)	31.4 $\pm$ 37.1	55.6 $\pm$ 51.3*	0.02	0.001
Control (n=13)	22.4 $\pm$ 23.8	18.6 $\pm$ 24.6	0.1	
<b>LLB (s)</b>				
Exercise (n=14)	39.2 $\pm$ 67.7	52.3 $\pm$ 53.2*	0.04	0.04
Control (n=13)	15.9 $\pm$ 15.7	13.6 $\pm$ 17.5	0.4	
<b>Sit up test (rpts)</b>				
Exercise (n=14)	12.7 $\pm$ 8.4	23.9 $\pm$ 7.7*	0.002	0.008
Control (n=13)	11.3 $\pm$ 12.2	12.6 $\pm$ 11.8	0.7	

Data are the mean  $\pm$  SE of baseline and final values and of the DHEA-S level, fatigue level and physical performance status in each group. The result demonstrated that fatigue levels decreased (20.5 %) and RLB, LLB and muscular endurance increased (77.07, 33.4 and 88.1 % respectively) in the training group compared with the control group. For DHEA-S levels no significant differences were observed. \*  $P < 0.05$

#### 4. Discussion

Fatigue occurs in the majority of multiple sclerosis patients and therapeutic possibilities are few. Randomized controlled trials have indicated that exercise training is associated with increased fitness, reduced motor fatigue, improved quality of life, and psychological conditions in MS patients (21,22). Exercise therapy has the potential to induce a positive effect on MS fatigue, but findings are heterogeneous. Exercise studies have demonstrated benefits in fitness level, quality of life, balance, and walking capacity in people with MS (3,15) however, no consistent effect on fatigue has been reported. Some multifaceted rehabilitation studies have shown improvements in fatigue (21,23) but others have shown no effect (24). Mean score of fatigue decreased ( $P < 0.05$ ) after 8 weeks RT compared to the control group in our study. The decrease of fatigue level in our study matches the results of other studies. Previous studies also demonstrated that fatigue levels were



decreased after aquatic exercise training (21,25), RT (26) and endurance training (15). In healthy subjects RT improves central motor activation and in MS patients RT enhances the efferent motor drive and in MS patients RT seems to reduce MS fatigue (27,28). The perception of worsened fatigue after overtraining may occur as a consequence of afferent inhibition from strained muscles. Another plausible mechanism behind the effect of exercise on MS fatigue is a training-induced up-regulation of neuroendocrine growth factor production, which increases neuronal plasticity and thereby possibly improves compensatory cortical activation (29). Also, an exercise-induced up-regulation of anti-inflammatory cytokines, may have a beneficial effect on MS fatigue (30).

Our results demonstrated that DHEA-S levels had no significant differences after the RT. Previous studies indicated that exercise induced-increases in DHEA-S might due to increased secretion rate by the adrenal cortex as a result of ACTH stimulation (31) and decreased metabolic clearance due to a reduction in hepatic blood flow during exercise (32). Thus it seems that our RT can not stimulate sufficient ACTH and hepatic blood flow. On the other hand, no significant relationship was observed between DHEA-S and fatigue after the intervention, thus it seems that other mechanisms might decrease fatigue in female patients with MS.

MS patients are less able to develop physical performance. The lesser physical performance of MS patients is due to muscular metabolic disturbances, such as a lower oxidation capacity (33), smaller section, fiber atrophy, and reduced activity of the enzyme succinate dehydrogenase, all factors indicating muscular unfitness derived from physical inactivity (33). In any event, there are factors directly linked to the nervous affection characteristic of the illness, such as difficulty in achieving complete muscular action, greater tension from the cross-bridge mechanism, nerve conductivity blocking, and the normal fatigue brought on by MS, which prevents sufferers from keeping up muscular tension for any length of time (34). Some studies have indicated a loss of muscle mass in MS patients (35,36) that is due to decreased muscle strength and may affect balance defect (35). The mechanisms of strength deficit are probably of both muscular (35) and neural origin (37). In our study comparing control and exercise group, it has shown significant

difference in left foot standing balance, and right foot standing balance. The results are in agreement with previous reports showing that RLB and LLB increased after RT ( $P < 0.05$ ). Improvements in muscle strength, endurance, range of motion, and coordination may improve balance in individuals with MS (38). Roelandts et al. (2007) has shown that balance improved after 10 weeks RT and vibration in MS patients (39). Eftekhari et al. (2012) also demonstrated that 8 weeks RT and vibration improve muscle balance in female patients with MS (3), whereas DeBolt and McCubbin (2004) indicated 8 weeks home-based resistance exercise had no significant effect on balance in adults with MS (40). These discrepant results may be attributed to variation in the exercise protocols and differences in subject populations.

It has been suggested that MS patients could improve their muscular strength and endurance by means of progressive RT (41). Our results demonstrated that muscular endurance increased ( $P < 0.05$ ) after 8 weeks RT compared with the control group. Previously, Ayán Pérez et al. (2007) also noted that muscular endurance measured by bent-knee sit-ups test was improved after 6 weeks RT in MS Spanish patients (41). This should be expected from a strength-training program designed to enhance muscle strength and endurance. Our results confirm the usefulness of RT for the rehabilitation of MS patients. Physical performance and the normal fatigue brought on by MS improved after 8 weeks RT in female patients with MS. On the other hand, it reveals the need for physical exercise to be prescribed individually for these people and that the effects of RT may have a major impact on the daily life of the patients, while also showing the need for further research.

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