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Resistance training improves depression in female patients with multiple sclerosis

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Abstract

Introduction: Depression may affect up to 50% of the multiple sclerosis (MS) population and can significantly impact other symptoms such as fatigue and pain, as well as negatively affecting cognition and quality of life. Exercise may be a potential treatment to prevent or reduce depressive symptoms in individuals with MS, but existing studies do not allow solid conclusions. The present study was conducted to determine the effect of 8 weeks resistance exercise on depression, adrenocotrotropic hormone (ACTH) and cortisol concentration in female patients with MS.

Material & Methods: 27 women with MS (mean of age of 32.3 ± 6.9 years) with Expanded Disability Status Scale (EDSS) scores lower than 4.5 were randomly assigned to training or control group. The training group performed progressive resistance training program, 3 days a week for 8 weeks,

whereas control group continued their usual routine activities. Depression was measured by Beck Depression Inventory (BDI) and plasma level of ACTH and cortisol were measured by ELISA kits before and after training. Data were analyzed by ANCOVA.

Results: Results of ANCOVA test indicated that BDI score improves after 8 weeks resistance training (F=12.3, P=0.001). ACTH concentrations were increased (F=26.6, P=0.001) and cortisol levels were decreased (F=26.0, P=0.001) significantly after the intervention.

Conclusions: These results suggest that resistance training improves depression symptoms and its related hormones in female patients with MS.

Keywords: Multiple sclerosis, Depression, Exercise, Hypothalamic-pituitary-adrenal axis

1. Introduction

Depression is one of the most common symptoms in patients with multiple sclerosis (MS) with a point prevalence of major depressive disorder of 13–30% and a lifetime risk of 25–50% (1). Depression in MS has a significant impact on cognitive function (2), quality of life (3), work performance (4), and treatment compliance (5) and is one of the strongest predictors of suicide (6). Despite the high clinical relevance, depression is underdiagnosed and undertreated in MS and its pathogenetic mechanisms remain unclear (7). Depression in MS is not related to the severity of neurological impairment (8), can occur at any stage of the disease (9) and thus does not seem to be simply a psychological reaction to the burden of a serious neurological disorder. Some (10,11) but not all (12) studies have shown associations of depression in MS with lesion load in several brain areas including the frontal, parietal, and temporal lobe, but these efforts failed to reveal a consistent pattern. More consistent associations have been reported with regional atrophy, in particular in the temporal lobe (11,12), but such studies lacked the spatial specificity to pinpoint any particular anatomical structure.

The hypothesis of a neuroendocrine-limbic etiology of depression in MS has received comparatively little attention, despite the fact that the most consistently reproduced biological findings in psychiatric patients with major depressive disorder include hyperactivity of the hypothalamo-pituitary-adrenal (HPA) axis (13) and smaller volumes of the hippocampus (14).

For decades, persons with MS were counseled to avoid excessive physical activity and exercise because of concerns about worsening disease activity. Recent studies indicate that, not only can those with MS tolerate physical exercise, but that it is helpful in managing symptoms, preventing complications and comorbidities, and may possibly have neuroprotective actions (15). A review of the effects of exercise on depression in persons with MS reported heterogeneous results, with several studies using aerobic and resistance training reporting positive effects on depression, and other trials failing to note improvement (16). Dalgas et al. (2010) compared the effects of progressive resistance training and control (usual activity without intervention) on depression measured by the major depression inventory in 38 persons with MS. The results revealed that major depression inventory scores were decreased significantly in the training group, but not in the control condition, and this improvement was sustained over a 12-week follow-up (17). By comparison, Romberg et al. (2005) reported no differential change in depression scores after a 26-week period of primarily home-based resistance training compared with control in persons with MS and noted that there was a possible slight increase in depressive symptoms with resistance exercise training (18).

Evidence suggests that depression in MS is largely biologically mediated by some of the same processes involved in the immunopathogenesis of this neurologic disease. In particular, the increase in proinflammatory cytokines, activation of the HPA axis, and reduction in neurotrophic factors that occur in MS may each account for the increased rate of depression seen in MS (19). Previous studies indicated that upstream of cortisol production (hypercortisolism) and blunted adrenocotrotropic hormone (ACTH) responses are associated with depression levels in MS (20-22). Study results demonstrated that cortisol levels were decreased and ACTH levels were increased in patients with MS after a period of

yoga training (23). We hypothesized that exercise training would regulate HPA axis and improve depression symptoms in patients with MS; therefore, we investigated the effects of 8 weeks resistance exercise on depression symptoms, ACTH and cortisol concentration in female patients with MS.

2. Material & Methods

Subjects

The participants in this study were 27 female between 18 and 48 years of age. All participants were volunteers from the MS Center of Shiraz, Iran. 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.

Study design

This was a cross-sectional study, and each subject was tested during a single session lasting approximately 60 min. The study protocol was approved by the Fars Science & Research 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).

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^2). 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).

Depression assessment

After medical history screening and Anthropometric measurements, participants were asked to complete Beck Depression Inventory (BDI) (24,25) to assess their depression level. BDI was chosen for modification because it has been utilized more than any other depression self-report measure over the last four decades and changes in clinical ratings of depression have been found to be appropriately paralleled by changes in BDI score (25,26). All participants were then assessed immediately prior to (baseline) and following the 8 weeks intervention.

Biochemical analyses

All the subjects fasted at least for 12 hours and a fasting blood sample was obtained by venipuncture. Serum obtained was frozen at –22 °C for subsequent analysis. The plasma ACTH and cortisol levels were measured in duplicate using an enzyme-linked immunosorbent assay (ELISA) kits (Enzo Life Sciences GmbH, Germany and AccuBind™ Monobind Inc, USA respectively). The sensitivity of kits for ACTH and cortisol was <27 pg/ml and < 0.25 µg/dl respectively.

Resistance 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 resistance training 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. Resistance training 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 pre-test were measured again as post-test.

Statistical analysis

Results were expressed as the mean ± SD and distributions of all variables were assessed for normality. Wilcoxon test and paired-sample t-test were used to evaluate the changes of variables before and after the intervention. Differences among groups were assessed by using analysis of covariate (ANCOVA) test. Data were analyzed with SPSS version 17.0, using a significance level of $P<0.05$.

3. Results

Anthropometric and body composition characteristics 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, BMI, body fat mass and body fat percentage decreased ($P<0.05$) after 8 weeks resistance training compared to the control group, while no significant changes in the WHR and lean body mass were found after the training (Table 1). The results demonstrated that mean values of EDSS decreased ($P<0.05$, 27.7%) in the resistance training group, while no significant change in the control group was found (Table 1).

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

	Baseline (mean ± SD)	After intervention (mean ± SD)	Paired t-test (Sig)	ANCOVA
Body weight (kg)				
Exercise (n=14)	66.1 ± 16.2	64.1 ± 16.1*	0.001	0.006
Control (n=13)	65.03 ± 12.5	65.4 ± 13.7	0.5	
BMI (Kg/m^2)				
Exercise (n=14)	25.8 ± 6.5	24.9 ± 6.2*	0.001	0.003
Control (n=13)	25.03 ± 4.9	25.9 ± 4.2	0.4	
Body fat (%)				
Exercise (n=14)	33.8 ± 8.7	32.5 ± 9.09*	0.04	0.04
Control (n=13)	33.8 ± 7.1	34.06 ± 7.2	0.6	
Body fat mass (kg)				
Exercise (n=14)	23.5 ± 10.2	22.3 ± 10.0*	0.01	0.03
Control (n=13)	22.7 ± 8.5	23.2 ± 8.5	0.3	
Lean body mass (kg)				
Exercise (n=14)	39.9 ± 6.4	40.6 ± 6.2	0.07	0.08
Control (n=13)	39.6 ± 4.7	39.1 ± 4.8	0.4	
WHR				
Exercise (n=14)	0.8 ± 0.05	0.77 ± 0.06	0.02	0.3
Control (n=13)	0.81 ± 0.01	0.8 ± 0.04	0.5	
EDSS				
Exercise (n=14)	1.8 ± 1.2	1.3 ± 1.5	0.01	0.04
Control (n=13)	2.1 ± 1.4	2.1 ± 1.5	0.7	

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

Changes of depression score are presented in the Figure 1. Our results indicated that BDI score improves after 8 weeks resistance training ($F=12.3$, $P=0.001$). As shown in the Figure 1, depression score was increased in the control group however it was decreased in the training group after the intervention.

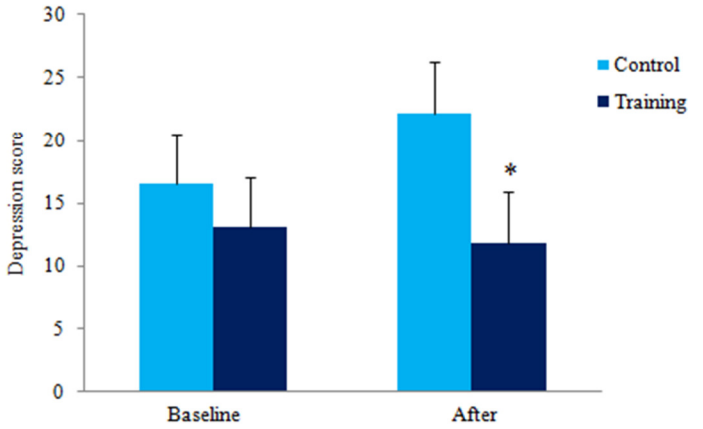

Figure 1. Changes of depression score after 8 weeks resistance training
Data are the mean ± SE of baseline and final values of the depression level in each group.
* Significant differences (P<0.05)

Changes of cortisol level are presented in the Figure 2. ANCOVA test demonstrated that cortisol concentration decreased significantly after 8 weeks resistance training (F=26.0, P=0.001). As shown in the Figure 2, cortisol concentration was decreased in the training group and it was increased in the control group after 8 weeks.

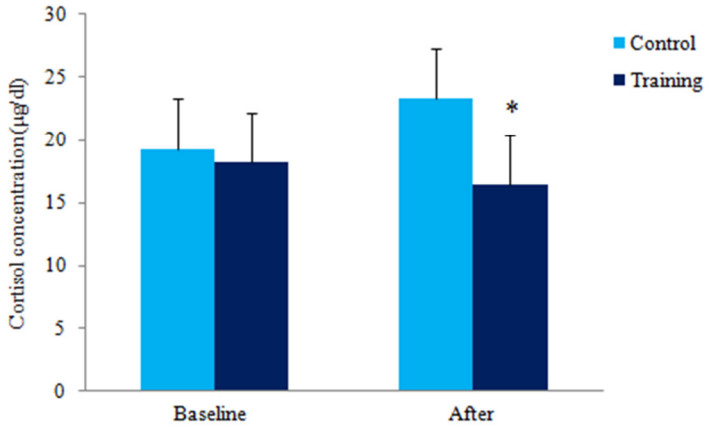

Figure 2. Changes of cortisol level after 8 weeks resistance training
Data are the mean ± SE of baseline and final values of the cortisol level in each group.
* Significant differences (P<0.05)

Figure 3 shows the changes of ACTH concentration after 8 weeks resistance training. The results revealed that ACTH level increased significantly after the intervention (F=26.6, P=0.001). As shown in the Figure 3, ACTH concentration was increased in the training group; however it had not significant change in the control group.

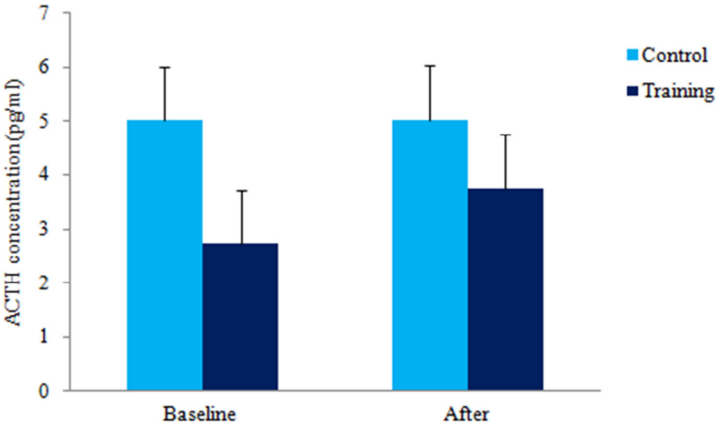

Figure 3. Changes of ACTH concentration after 8 weeks resistance training
Data are the mean ± SE of baseline and final values of the ACTH level in each group.
* Significant differences (P<0.05)

4. Discussion

Several studies have explained on cognitive impairment in the MS patients. Research reports have shown that depression and fatigue are commonly seen with cognitive dysfunction (27). Some studies indicated that anxiety and depression correlated with disability in people with MS (11). Exercise may be a potential treatment to prevent or reduce depressive symptoms in individuals with MS, thus the present study was conducted to determine the effect of 8 weeks resistance exercise on depression in female patients with MS. In agreement with the previous studies, our results indicated that depression symptoms were decreased in the training group after the intervention (16,17,26). For example, Dalgas et al. (2010) compared the effects of progressive resistance training and control on depression level in 38 persons with MS. The sample had moderate disability based on EDSS scores of 3.0–5.5 and baseline major depression inventory scores in the normal range,

indicating no elevated depressive symptoms. The supervised progressive resistance training targeted lower extremities and was delivered 2 days/week with an intensity of between 8 and 15 repetition maximum over 12 weeks. There was a significant reduction in major depression inventory scores in the group receiving resistance training, but not in the control condition, and this improvement was sustained over a 12-week follow-up (17). Interestingly, the mechanisms by which exercise may improve depression remain uncertain. Although it would be expected that improvements in mood should occur in conjunction with improvements in fitness, only half of studies demonstrate such a correlation (28). Another possibility is that exercise impacts on depression via cognitive changes. There is a large body of evidence suggesting that regular exercise is associated with neurogenesis, angiogenisis, enhanced central nervous system metabolism and other changes in the brain that improve memory and learning (29). The degree to which exercise can impact on cognition in depressed patients has been largely unexamined, although a research demonstrates promise: a leading study by Déry et al. (2013) evidenced opposing effects of depression compared to sustained exercise on a putative neurogenesis-dependent learning task (30). Observed equivalency in depression outcomes between pharmacotherapy and exercise in clinical trials may suggest potentially overlapping biological mechanisms of action, including putative serotonin synthesis and metabolism, although this remains to be directly tested (31). Finally, a great deal of evidence suggests involvement of the HPA axis in the development of depression (19). Both excess cortisol and dexamethasone suppression test nonsuppression have been reported for many years to be associated with mood disorders (32), and dexamethasone suppression test nonsuppression is related to the number of depressive episodes (33). Furthermore, dexamethasone suppression test nonsuppression normalizes as mood symptoms subside, with persistent non-suppression associated with a higher probability of relapse (34). Upstream of cortisol production, patients suffering from depression display elevated levels of corticotropin-releasing hormone in the cerebrospinal fluid and a blunted ACTH response to administered corticotropin-releasing hormone, presumably due to chronic high levels of corticotropin-releasing hormone causing downregulation of pituitary

corticotropin-releasing hormone receptors as well as negative feedback from high levels of circulating cortisol (35,36). These changes in both corticotropin-releasing hormone and ACTH normalize after the depression is treated (20,21). The results of the present study indicated that cortisol concentration was decreased and ACTH level was increased after 8 weeks resistance training. Previously, Najafi and Moghadasi (2017) also indicated that cortisol levels were decreased and ACTH levels were increased in response to 8 weeks of yoga training in female patients with MS (23). Although acute high intensity physical activity leads to increased levels of stress hormones corticotropin and cortisol, long-term exercise attenuates the human stress response (37). Exercise can be a stressful stimulus itself depending on the intensity and duration of the activity (38) so that stressful stimulations like exercise need to be followed by adaptations of the organism. If the organism becomes adapted to exercise, then the subsequent response of catecholamine release to stressful intensities of exercise is less than that observed in nontrained subjects (39).

5. Conclusion

The results of the present study indicated that 8 weeks resistance training regulates HPA axis and improve depression symptoms in female patients with MS; therefore, our results suggested that resistance training with mode and duration that utilized in the present study may be appropriate and beneficial for this patient population.

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Conflict of interests: None of the authors declare competing financial interests.

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