

Interleukin-10 and brain-derived neurotrophic factor responses to the Mat Pilates training in women with multiple sclerosis

Respostas da Interleucina-10 e do fator neurotrófico derivado do cérebro ao treinamento de Mat Pilates em mulheres com esclerose múltipla

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ABSTRACT

AIMS: To determine the effect of Mat Pilates on serum levels of interleukin-10 and brain-derived neurotrophic factor in women with multiple sclerosis.

METHODS: Thirty women with multiple sclerosis with mild to moderate disability were recruited and randomly divided into equal Pilates training and Control groups. Patients in the training group accomplished a Pilates program three times a week for eight weeks. The Control group maintained their routine lifestyle. The serum level of interleukin-10 and brain-derived neurotrophic factor were measured before and after the protocol. The differences between groups were assessed by using analysis of covariance test to compare post-tests by considering covariate pre-tests (assuming a p-value <0.05 as significant).

RESULTS: There were no significant changes in interleukin-10 (13.09 ± 5.36 ng/ml in the Pilates training group compared to 13.21 ± 4.76 ng/ml in the Control group, $p=0.81$), whereas an increase in brain-derived neurotrophic factor was observed after eight-week Pilates training (11550.14 ± 2619.60 ng/ml in the Pilates training group compared to 9664.35 ± 3161.66 ng/ml in the Control group, $p=0.03$).

CONCLUSIONS: The results suggest that the intensity and duration of this protocol was not related to significant changes in interleukin-10, but was followed by an increase in brain-derived neurotrophic factor in these patients. Based on this finding, physical activity according to the individual's ability is recommended for patients with multiple sclerosis, in parallel with drug therapy.

KEYWORDS: brain-derived neurotrophic factor; interleukin-10; multiple sclerosis; Pilates training; cytokines; exercise.

RESUMO

OBJETIVOS: Determinar o efeito do Mat Pilates sobre os níveis séricos de interleucina-10 e fator neurotrófico derivado do cérebro em mulheres com esclerose múltipla.

MÉTODOS: Trinta mulheres com esclerose múltipla e deficiência física leve a moderada foram recrutadas e divididas aleatoriamente em grupos iguais, um de treinamento em Pilates e outro de controle. As pacientes do grupo de treinamento cumpriram um programa de Pilates três vezes por semana durante oito semanas. O grupo controle manteve seu estilo de vida de rotina. O nível sérico de interleucina-10 e o fator neurotrófico derivado do cérebro foram medidos antes e após o protocolo. As diferenças entre os grupos foram avaliadas usando o teste de análise de covariância para comparar pós-testes, considerando pré-testes como covariáveis (assumindo p-valor <0,05 como significativo).

RESULTADOS: Não houve alterações significativas na interleucina-10 ($13,09 \pm 5,36$ ng/ml no grupo treinamento em Pilates, em comparação a $13,21 \pm 4,76$ ng/ml no grupo controle, $p=0,81$), mas foi observado um aumento no fator neurotrófico derivado do cérebro após o treinamento de Pilates por oito semanas ($11550,14 \pm 2619,60$ ng/ml no grupo treinamento em Pilates em comparação a $9664,35 \pm 3161,66$ ng/ml no grupo controle, $p=0,03$).

CONCLUSÕES: Os resultados sugerem que a intensidade e duração desse protocolo não se relacionou com mudança significativa na interleucina-10, mas foi seguido por um aumento no fator neurotrófico derivado do cérebro nessas pacientes. Com base neste achado, a atividade física de acordo com a capacidade individual é recomendada para pacientes com esclerose múltipla, paralelamente à terapia medicamentosa.

DESCRIPTORIOS: fator neurotrófico derivado do cérebro; interleucina-10; esclerose múltipla; método Pilates; citocinas; exercício.

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Abbreviations: BDNF, brain-derived neurotrophic factor; C, Control; IL-10, interleukin-10; MS, multiple sclerosis; PT, Pilates training.

INTRODUCTION

Cytokines have a crucial role in the pathogenesis of multiple sclerosis (MS) an inflammatory disease so that pro-inflammatory cytokines exacerbate MS, and anti-inflammatory cytokines improve it [1]. Interleukin (IL)-10 also known as the human cytokine synthesis inhibitory factor, is key in understanding the pathogenesis of MS. Correlation between the MS disease classification (mild/moderate/severe) and levels of IL-10 in serum and cerebrospinal fluid have been observed [2]. IL-10 therapy is an effective treatment method for neuro-immune diseases [1]. IL-10 has an important role in immune and inflammatory responses which are regulated by growth and /or differentiation of B cell, T helper cell, and T regulatory cell [3]. The altered function of T cells in MS is characterized by the lack of IL-10 secretion that could contribute to the inflammatory process, whereas interferon-beta regulates IL-10 [4]. IL-6, as a myokine released by contracting the skeletal muscle, causing an increase in IL-10 [5,6]. Contraction of skeletal muscle is another major source of IL-10 and leads to its increase during moderate exercise [7].

Brain-derived neurotrophic factor (BDNF) which has a neuroprotective role in MS [8], is synthesized in the dentate gyrus of the hippocampus [9], T cell, B cells and monocytes [10], which are affected by released myokines from contracted skeletal muscles (IL-6) [9]. There is a decrease in the base level of BDNF in patients with relapsing-remitting MS compared with healthy populations [11] whereas there is an increase of BDNF in immune modulation in MS [12]. Physical activity, by moderating BDNF in the MS patient, has a neuroprotective effect that could be a novel and therapeutically determining factor [9, 13, 14].

Few studies assessed plasma IL-10 [15] and plasma BDNF in relation to exercise in MS patients [9, 13, 14]. The importance of studying Mat Pilates rather than other exercises is due to the ability to adjust the suitable intensity of training, to avoid hyperthermia during exercise. In addition, Pilates allows control of the patient's position during training and also decrease relapsing-remitting during the study. This study investigated the effect of Mat Pilates on the IL-10 and BDNF levels in patients with MS.

METHODS

A randomized controlled trial was conducted from April 2015 to June 2015 at the Najafabad Branch, Islamic Azad University, and the Goldasht Multiple Sclerosis Center. The participants had registered at Goldasht Multiple Sclerosis Center and were chosen on a volunteer basis. The study protocol was approved by the Isfahan University of Medical Sciences Ethics Committee (number 494120). All participants signed the written informed consent.

The sample included women suffering from relapsing-remitting MS with expanded disability status scale 2-6, based on McDonalds criteria (use of imagining to demonstrate the dissemination of central nervous system lesions, which can be established by a single scan) [16]. The patients received interferon-beta (interferon-beta-1b: Betaseron and Betaferon, interferon-beta-1a: Avonex). Participants were excluded if they took part in regular exercise during the last three months, were pregnant, had back problems, epilepsy, or cancer. This research used a simple random sampling and the size was chosen according to the literature [13-15].

All subjects were randomly assigned to either a Pilates training (PT) group or a Control (C) group by using closed envelopes. Subjects in the PT group participated in the protocol of training for eight weeks and the C group had their routine lifestyle. A portable wall-mounted ruler was used to measure height in the upright position (accuracy 0.1 cm), a portable scale was used to measure body weight (Seca Voge &Halke, German model: 760 1029009), and body mass index (kg/m²) was calculated for each subject at pre and post-test.

Blood sampling was done between 8-9 AM to determine the serum levels of IL-10 and BDNF as pre and post-test. The post-test blood sampling was collected 48 hours after last Pilates session to avoid interference of acute effect of the training (because the aim of our research was the evaluation of the chronic effect of Mat Pilates training).

The training group completed Mat Pilates training for eight consecutive weeks on the progressive program. Our protocol was designed with special exercise-based core stability with low to moderate intensity (for the beginner) according to patient's performance capacity, which was focused on proper breathing, balance, correct body alignment, and range of motion in joints. Three sessions were held in the week with 48-hour rest between sessions for eight weeks. The intensity of the exercise gradually increased with including more

repetitions (3-10), decreasing rest time, and increasing the number of sets (1-2). However, the subjects' ability levels were a determining factor of intensity, to avoid exacerbation, hyperthermia, and fatigue. Each session began with a five-minute warm-up consisting of two repetitions of Breathing, Imprint and Release, Supin Spinal, Head Node, Shoulder Shrugs, Scapula Isolation, Arm Circle, Spinal Rotation, Hip Release, Cat Stretch, and Hip Rolls. Participants were instructed to do the main exercises for 30-40 minutes. The main exercises included Hundred, Roll-Up, Roll-Down, and Single Leg Circle movements. In the first month one set, and in the second month two sets of repetitions (which started with three to four repetitions and gradually increased reached up to 10) of movements were done. Movements consisted of 10 seconds exercise, 10 seconds rest, 30 seconds rest between each movement, and 60 seconds rest between each set (each exercise took nearly seven minutes). The cool-down performed like the warm-up. The C group had their routine lifestyle.

Venous blood samples were obtained from the antecubital vein, centrifuged in order to separate plasma from the cells, and stored at -80°C until analyzed by commercially available enzyme-linked immunosorbent assay (ELISA). The serum levels of IL-10 estimated by Human IL-10 ELISA Kit (Boster Biological Technology Ltd), and BDNF was measured by using the Human BDNF ELISA Kit (Boster Biological Technology Ltd).

Statistical analysis was performed by using IBM SPSS Statistics version 20 on a personal computer. Descriptive analysis was adopted for demographic and clinical characteristics and are reported as the

mean \pm standard deviation. The T-independence test was used to show differences between demographic variables as the pre-test in PT and C groups (p -value < 0.05). Kolmogorov-Smirnov test was used for determination of normality of the distribution, and Levene's test was used to show homogeneity of variance between two-group before the start of the protocol (p -value > 0.05). The differences between groups were assessed by using analysis of covariance (ANCOVA) test to compare post-tests by considering covariate pre-tests (p -value < 0.05).

RESULTS

From the 30 female patients with relapsing-remitting MS of the initial sample (age 33 ± 8.08 years, body mass index $24.52 \pm 4.93 \text{ kg/m}^2$, expanded disability status scale 2-6), five subjects dropped out (PT=2, C=3). Thus, 25 participants (PT=13, C=12) took part in the entire study and were considered in the statistical analysis. T-independence test indicated no significant differences between age, weight, and body mass index as the pre-tests in PT and C groups. The subjects' characteristics at baseline are shown in **Table 1**.

The mean \pm standard deviation values of pre-test and post-test of IL-10 and BDNF in PT and C groups are shown in **Table 2**. The Levene's test to show homogeneity of variance between two groups before the starting the protocol reported IL-10 ($F=1.85$, $p=0.18$), BDNF ($F=0.09$, $p=0.76$). The ANCOVA test (comparing post-tests of PT and C groups by covariation pre-tests) were adjusted in **Table 2**.

Table 1. Mean and standard deviation of subjects' characteristics who completed the study protocol, and the T-independence test to show differences between two groups at baseline

Characteristic	Mean \pm standard deviation		t	df	p-value
	PT group (n = 13)	C group (n = 12)			
Age (years)	34.46 ± 7.29	31.41 ± 8.89	0.94	23	0.36
Weight (kg)	58.92 ± 12.02	63.70 ± 12.35	-0.98	23	0.34
Body mass index (kg/m^2)	24.38 ± 5.36	24.66 ± 4.64	-0.14	23	0.89

PT, Pilates training; C, Control; t, t-test; df, degree of freedom.

Table 2. Characteristic of pre and post-test of variables and the analysis of covariance (ANCOVA) test in studying subjects

Tested factor	Group	Mean \pm standard deviation		ANCOVA Test			
		Pre-test	Post-test	F	p-value	η	Op
IL-10 (ng/ml)	PT (n = 13)	13.09 ± 5.36	12.36 ± 7.20	0.05	0.81	0.00	0.05
	C (n = 12)	13.21 ± 4.76	11.78 ± 4.83				
BDNF (ng/ml)	PT (n = 13)	10678.85 ± 2260.17	11550.14 ± 2619.60	5.12	0.03	0.18	0.58
	C (n = 12)	11377.49 ± 3860.61	9664.35 ± 3161.66				

PT, Pilates training; C, Control; F, F-Test; η , partial eta-squared (demonstrated the changes of the variable); Op, observed power (the estimate of power of study based on the effect size in our study); df (1,23).

There were no significant changes in IL-10 (13.09 ± 5.36 ng/ml in PT compared to 13.21 ± 4.76 ng/ml in C group, $p=0.81$), whereas an increase in BDNF was observed after 8-week Pilates training (11550.14 ± 2619.60 ng/ml in PT compared to 9664.35 ± 3161.66 ng/ml in C group, $p=0.03$) in MS patients.

DISCUSSION

The IL-10 responses to exercise training are inconsistent in MS patients. We found no difference in the serum concentration of IL-10 after eighth-week Mat Pilates program. It was in line with Mokhtarzade et al., which reported no significant change in IL-10 after eight-week of upper and lower limb aerobic interval training [15], Deckx et al. after 12-week of combined endurance and resistance training program [17], Ozkul et al. after eight weeks of combined exercise training program in MS patients [18], and Hessen et al. in response to eight-week aerobic training twice per week [20] in MS patients, whereas White et al. reported reduced IL-10 after eight weeks of progressive training twice per week in women MS patients [19]. The responses of IL-10 to exercise training are different in MS patients, healthy people or athletes [6, 7, 15, 17-20]. No significant change or decrease in IL-10 (as anti-inflammatory) is reported in MS patients [15, 17-20], whereas significant increase was seen in healthy people or athletes after physical stress [6, 7]. In fact, the intensity of exercise is the efficiency factor and could justify the distinct results of these research papers. The moderate to severe intensity exercise could be the stressor factor to increase pro-inflammatory cytokines which will be balanced by releasing the anti-inflammatory cytokines such as IL-10. So low-intensity exercise which is recommended for MS patients could not be changed in IL-10 as anti-inflammatory cytokines. The drug therapy such as interferon-beta by increasing IL-10 [21], which probably more effective factor to increase IL-10. Also, the lack of physical activity, change in body composition and the plasma adiponectin in MS patients as special characters, which could be an effective factor in the responses of IL-10 to physical activity by comparing with healthy subjects, as Jung et al. noted to increase IL-10 following caloric restriction and weight loss [22].

The results of our study demonstrated a significant increase in BDNF after eight-week Mat Pilates training. Numerous studies have been done on the modulation of BDNF with physical activity in MS patients [13, 14, 23].

Increase in BDNF in MS patients was reported by Sarvaria et al. after 30-minute bicycling [14], Bansil et al. after three-week endurance training conducted at an aquatic bike training at $60\% \text{Vo}_{2\text{max}}$ daily 30 minutes [23], and Wens et al. after 24-week endurance and resistance training [13]. Physical activity leads to increase plasma BDNF two to three-fold during exercise and decrease after one hour of recovery in human [24]. The BDNF as an index of the hippocampal response [25], which presents at the neuromuscular junction [26], and muscle as a source to produce BDNF [26], so muscle contraction could justify the increase of BDNF levels [24]. In the C group, we had decrease BDNF level. Decrease BDNF in newly diagnosed MS was reported [11]. The difference in the methodology of studies, exercise intensity, basic peripheral BDNF concentration, physical fitness of subjects could justify the different changes [24, 27, 28]. Although the intensity of our designed protocol, in such a way to avoid reaching lactate accumulation and fatigue, showed increase peripheral BDNF in these patients which reflect the central BDNF level and could induce neuroprotective effects [29].

This intensity of Mat Pilates training designed based on the specific conditions of patients -to avoid fatigue and hyperthermia to prevent the relapsing-remitting and control their balance- had no significant effect on IL-10, whereas showed a significant increase in BDNF. Regarding BDNF neurotrophic and neuroprotective effect, low-intensity physical activity based on the patient's ability is recommended in parallel with drug therapy for these patients.

NOTES

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Conflicts of interest disclosure

The authors declare no competing interests relevant to the content of this study.

Authors' contributions

The authors declare to have made substantial contributions to the conception, or design, or acquisition, or analysis, or interpretation of data; and drafting the work or revising it critically for important intellectual content; and to approve the version to be published.

Availability of data and responsibility for the results

The authors declare to have had full access to the available data and they assume full responsibility for the integrity of these results.

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