Medical Laboratory Journal
Online ISSN: 2538-4449
Golestan University of Medical Sciences

Original Article

Decreased Serum Neurofilament Light Chain and Fatigue Severity in Patients with Multiple Sclerosis after Home-Based and Outdoor Pilates Training

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Received: 2022/07/02
Revised: 2022/08/02
Accepted: 2022/08/06

DOI: 10.29252/mlj.17.3.55

ABSTRACT

Background and objectives: Studies have reported contradictory results regarding the relationship between serum neurofilament light chain (NFL) and fatigue severity. The aim of our study was to investigate serum NFL and fatigue severity in patients with multiple sclerosis (MS) after home-based and outdoor Pilates training.

Methods: The study population consisted of 44 women with MS (aged 25 to 40 years) with an expanded disability status scale score of 2-5. The patients were randomly divided into three groups: home-based training (HPT, n=15), outdoor training (OPT, n=15), and a control group (n=14). The training groups performed Pilates exercises for 8 weeks individually at home and under the sun. Blood samples and completed Fatigue Severity Scale forms were taken 48 hours before the first session and after the 8-week intervention.

Results: The results showed that OPT caused a more notable increase in serum vitamin D (32.76±5.13, p<0.001) and a decrease in NFL (15.98±2.26, p <0.001) and FSS score (2.51±0.35, p<0.001) compared with HPT. Also, HPT lowered NFL (18.01±2.28, p<0.001) and FSS score (3.84±0.98, p<0.001) compared with the control group.

Conclusion: Pilates training can reduce NFL levels and FSS scores in women with MS. In addition, OPT is more effective than HPT in reducing NFL and FSS and increasing vitamin D levels.

Keywords: Exercise Movement Techniques, Neurofilament Protein, vitamin D, fatigue, Multiple Sclerosis.

INTRODUCTION

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) that is characterized by inflammation, demyelination, axonal degeneration, and glial cell activation (1). The disease causes fatigue, weakness, spasticity, sensorial loss, balance problems, and gait disorders (2). Low circulating levels of 25-hydroxyvitamin D (25(OH)D) due to lack of sun exposure, may influence the disease course either through its immunomodulatory effects (3) or direct effects on resident brain cells (4).

Neurofilament light chain (NFL) is a major component of the cytoskeleton in neuronal axons, which reflects the axonal loss in relapsing-remitting MS (RRMS) from an early disease stage (5) and has been associated with inflammatory disease activity (6). Studies have reported contradictory results regarding the relationship between NFL and fatigue severity. Some studies specifically explored NFL as a biomarker of cognitive performance and fatigue in MS, but others reported no significant association (7–9). Also, few studies have been conducted on the association between vitamin D (VD) and NFL in MS with conflicting results. Sandberg et al. (2016) showed that high VD levels were associated with low levels of cerebrospinal fluid NFL (10). On the other hand, a positive relationship between NFL and VD was reported (11). Thus, the effect of VD on NFL levels is still unclear.

It has been suggested that exercise may improve axonal regeneration and reduce axonal degeneration and astrogliosis (12), but few studies have examined the effect of physical activity on NFL levels in MS patients. In this regard, Amiri et al. (2020) reported no significant change in serum NFL levels of MS patients after an 8-week resistance training program (13). Another study showed that an 8-week aerobic exercise intervention could decrease serum NFL levels in RRMS patients (14).

Pilates training can be done at home with minimal facilities and can adjust the intensity of the exercise according to the individual's capacities. Moreover, home-based Pilates is a safe and acceptable exercise for MS patients (15). Fleming et al. (2020) reported improvement in fatigue symptoms and quality of life of MS patients after 8 weeks of home-based Pilates training (16).

Considering the role of VD in controlling some MS complications and the importance of sunlight exposure as an easy and accessible way to absorb VD, non-pharmacological treatment methods, such as physical activity, should be used to prevent disease progression. Therefore, it seems necessary to provide optimal physical activity for MS patients. The present study aimed to examine the potential effects of 8 weeks of home-based and outdoor Pilates training on the NFL, fatigue, and VD levels of MS patients.

MATERIALS AND METHODS

This was a randomized trial study with a pretest-posttest design. The sample size was determined as 40 using G*Power 3.1 software and based on a previous study (17), with a statistical power of 85%, an effect size of 75%, and a significance level of 0.05. Considering a 10% chance of dropout, the required sample size was estimated at 44. Accordingly, 44 eligible female volunteers with MS in Fasa (Iran) were enrolled. Inclusion criteria were having MS, age of 25-40 years, expanded disability status scale (EDSS) score of 2 to 5, and no history of receiving VD supplements. Exclusion criteria were a history of smoking or alcohol consumption, regular physical activity in the last year, pregnancy, history of relapse (in the last 12 weeks), and lack of cooperation.

The subjects were randomly divided into three groups: home-based Pilates training (HPT; n= 15), outdoor Pilates training (OPT; n=15), and a control group (CON; n=14). Training groups performed 60 minutes of Pilates training at home or under sun exposure, three sessions a week, with at least 48 hours between sessions, for 8 weeks at home. Instruction was provided in form of a DVD. Subjects in the control did not partake in any sports activity.

Written consent was obtained from all participants after fully explaining the research objectives and details. The study received approval from the Research Ethics Committee of Hakim Sabzevari University, Iran (IR.HSU.REC.1400.015).

The training protocol was derived from a study by Fleming et al. (2020). Each training session started with 10 minutes of warm-up, including seven movements, followed by 40 to 45 minutes of main body training including 14 movements, and ended with cool down including 9 movements (16). The OPT group

only performed the main body training under direct sunlight, and the resting was done in the shade to control the temperature and prevent the possibility of relapse due to increased body temperature. Training intensity was controlled by Borg rating of perceived exertion scale and heart rate. Each participant received the DVD and documented details of the Pilates protocol. If a participant was not comfortable with using a DVD player, an online link to the Pilates program was also made available. Four repetitions of each Pilates movement were performed during sessions in the first 2 weeks. Repetitions gradually progressed every 2 weeks, resulting in 10 repetitions in the final 2 weeks. Fidelity, adherence, dose, and compliance were monitored via self-report exercise diaries immediately following the completion of each session. Exercise diaries were supplemented by a weekly telephone call consisting of direct questions about the frequency, intensity, and duration of the Pilates as well as any difficulties experienced during exercise, any adverse events, or relapses. To evaluate fatigue severity, the Fatigue Severity Scale (FSS) was used, which assesses the participants' subjective perception of fatigue and its consequences on daily activities (18).

Serum levels of NFL and VD were measured using a commercial ELISA kit (ZellBio GmbH Co., Germany) and a human VD ELISA kit (Padgin Gostar Isar, Iran), respectively. Fasting blood samples (10 ml) were taken 48 hours before and after the training. Serum was separated and kept at -70 °C for biochemical evaluation.

Data were expressed as mean ± standard deviation. To investigate the effect of groups on NFL, VD, and fatigue, the ANCOVA test was performed. The Bonferroni test was carried out to detect inter-group differences. The Pearson correlation test was done to evaluate the association between variables. All analyses were carried out in SPSS software. (version 26) at a significance level of 0.05.

RESULTS

The demographic characteristics of participants are presented in table 1.

Table 1- Baseline characteristics of participants in each group

Variable	Groups			*p*	Homogeneity
		Before intervention	After the intervention		
Age (years)	OPT	35.16±4.44	-	0.93	0.11
	HPT	35.75±5.15	-		
	CON	35.50±3.62	-		
Weight (kg)	OPT	68.41±3.77	61.95±2.19	0.001*	0.85
	HPT	71.41±3.52	67.0±3.54		
	CON	70.60±5.71	71.70±5.70		
Height (cm)	OPT	161.75±5.59	-	0.90	0.90
	HPT	162.75±6.12	-		
	CON	162.0±5.05	-		
Body mass index (BMI)	OPT	26.41±2.05	23.91±3.08	0.001*	0.38
	HPT	27.25±3.01	25.57±2.47		
	CON	26.94±4.68	27.13±4.11		

OPT: Outdoor Pilates training, HPT: Home-based Pilates training, CON: control, *p<0.05 according to ANCOVA test

The results showed that there was a significant difference between the groups in serum levels of NFL and VD and FSS scores following the 8-week OPT and HPT training in all groups (p<0.001). The post hoc test also showed that OPT caused a greater decrease in FSS score (41.76%) and NFL levels (-25.15%) and a greater increase in VD levels (78.43%) compared with HPT (17.77%, -18.17%, and 9.61%, respectively) and CON groups (p≥0.001). In addition, VD level of patients did not differ significantly between the HPT and CON groups (p=0.87) (Table 2).

Bivariate correlation analysis for NFL demonstrated a moderate positive association with fatigue (r=0.45; p<0.001) and a moderate negative association with VD (r=0.46, p<0.001); however, there was a moderate negative association between fatigue and VD changes (r=-0.54, p<0.001) (Table 3).

Table 2-Results of ANCOVA and posthoc test on the levels of NFL, VD, and fatigue in patients with MS

Variable	Groups	Baseline	PosttestPost-test	*p*	F
NFL	OPT	21.35±2.74	15.98±2.26**	0.001*	58.01
(ng/ml)	HPT	22.01±3.01	18.01±2.28#		
	CON	21.12±3.05	21.92±3.09##		
Vitamin D	OPT	18.36±2.87	32.76±5.13**	0.001*	12.22
(ng/ml)	HPT	19.44±2.40	21.31±2.32		
	CON	18.64±3.52	19.22±3.64##		
Fatigue	OPT	4.31±0.98	2.51±0.35**	0.001*	32.66
	HPT	4.67±0.71	3.84±0.98#		
	CON	4.24±1.04	4.96±0.67##		

OPT: outdoor Pilates training, HPT: home-based Pilates training, CON: control, *difference between groups according to ANCOVA test, **difference between OPT and HPT, #difference between HPT and CON, ## difference between OPT and CON

Table 3- Correlation test results on variables

Variable	*p*	r
NFL Vitamin D	0.001	-0.46
NFL Fatigue	0.001	0.45
Vitamin D Fatigue	0.001	-0.54

DISCUSSION

This study is the first that examined the effects of long-term training on NFL, fatigue, and VD in people with MS. Our results revealed that OPT and HPT significantly alter NFL, VD, and fatigue levels, while the greatest increase in VD levels was achieved by OPT, which consequently resulted in a further reduction of fatigue and NFL levels. We also found a significant negative correlation between NFL and VD and a positive correlation between NFL and fatigue.

In this regard, Joisten et al. (2021) observed that repetitive acute exercise bouts reduce persistent acute NFL levels in MS patients in an intensity-dependent manner, but a 3-week high-intensity interval training did not affect NFL levels. They also reported that baseline plasma NFL levels had a negative correlation with participants' cognitive performance (19). The difference between our findings and the results of the mentioned study may be attributed to the difference in the NFL measurement method as well as the type of blood sample used. For instance, in the study by Joisten et al., plasma samples were assessed by the single-molecule array method. In line with our findings, Ercan et al. (2021) reported a significant decrease in NFL levels after an 8-week aerobic training intervention in RRMS patients (14). However, a study demonstrated that an 8-week resistance training intervention had no significant effect on NFL levels (13). The discrepancies between these results may be associated with the difference in exercise types and characteristics of the participants.

Recently, it has been postulated that glutamate excitotoxicity could be a missing link between inflammatory and neurodegenerative processes in MS patients (20). An increase in the concentration of extracellular glutamate leads to the over-activation of glutamate receptors (21) and the transfer of large amounts of calcium ions into the cell, which in turn might increase NFL phosphorylation (22). On the other hand, an increase in brain-derived neurotrophic factor (BDNF) leads to a decrease in NFL level (23). Given the role of Pilates training in increasing the level of BDNF (24), this type of exercise, by increasing neuroprotective factors and decreasing oxidative factors, may reduce the rate of NFL phosphorylation and therefore slow down disease progression. However, in this study, neurotrophic indicators were not measured, which needs to be addressed in future research.

Given the immunomodulatory role of VD and its effects on T lymphocytes, this vitamin has been linked with the etiology of MS. It is well-established that VD deficiency can be an independent factor associated with MS progression and patients disability. It has been suggested that nitric oxide (NO) production via inducible nitric oxide synthase (iNOS) plays an important role in the pathogenesis of several systemic autoimmune disorders, including MS. Active VD regulates the production of oxidative stress markers, NO, and/or the expression of iNOS in different cells, such as microglial cells, macrophages, and astrocytes (25). Furthermore, the activated inflammatory cells can produce 25-(OH)2D3, which subsequently exhibits anti-inflammatory activities directed against these cells (26). It was shown that patients with subclinical disease activity might have higher NFL levels than patients without magnetic resonance imaging (MRI) activity, and NFL levels correlated with enhancing lesion volume. Although a negative association between increased 25(OH)D levels and inflammatory MRI disease activity and a positive association between inflammatory MRI disease activity and NFL levels have been reported (27), it is certain that axonal degeneration is not only driven by neuroinflammation (28). Lastly, it may be speculated that inter-individual differences in serum levels of 25(OH)D at a given time point are related to varying inflammatory disease activity (29), and that seasonal variation in inflammatory MRI disease activity and NFL levels are due to seasonal beneficial factors for both neuroinflammation and neurodegeneration not related to 25(OH)D or ultraviolet ray exposure (29). A previous study found no significant association between serum VD and NFL levels in a 2-year study period (30). An epidemiologic study reported that outdoor physical activities could induce a higher increase in VD levels (31). This may contribute to the maintenance of VD status by increasing the rate of lipolysis, which enhances its mobilization from adipose tissue, other than merely by increasing the exposure of the skin to sunlight (32). In our study, one of the reasons for increasing VD levels and further reduction of BMI in the OPT group can

be the sufficient duration of exposure to sunlight and its possible effects on lipolysis and adipose tissue.

The most commonly proposed primary mechanisms of fatigue in MS involve the immune system or sequelae from CNS damage. Specific causes are thought to include pro-inflammatory cytokines, endocrine influences, axonal loss, and altered patterns of cerebral activation (33). The potential mechanisms through which Pilates affects symptoms of MS including anxiety, depression, and fatigue remain poorly understood. Evidence supports the plausibility of a myriad of psychological and biological mechanisms, including reduced sympathetic nerve activity in response to Pilates' breathing principles, improved serotonin system regulation, and social interaction (34). It was stated that a 4-week upper body and breathing exercise could help strengthen the upper body and respiratory muscles and increase training capacity, thereby reducing initial fatigue and improving quality of life (35). In line with our results, Beckman et al. (2020) reported that increasing VD levels could reduce fatigue and increase the quality of life in MS patients (36). In another study, an 8-week aerobic exercise and VD supplementation intervention improved fatigue and quality of life in MS (37).

It is well-demonstrated that VD deficiency induces muscle weakness and myalgia, especially in patients with neurological impairment. Adequate VD levels promote the expression of insulin-like growth factor 1, which has neuroprotective effects against axonal and dendrite degeneration (38). Furthermore, VD therapy improves muscle mitochondrial oxidative phosphorylation that potentially results in fatigue modulation (39). Previous research indicates that 25(OH)D concentrations and calcium might prevent fatigue by regulating the biosynthesis of creatine kinase, lactate dehydrogenase, troponin I, and hydroxyproline via a proposed anti-free radical mechanism caused by a higher total antioxidant capacity (40).

Our study has some limitations including the lack of accurate control of the subjects' diet during the research period and enrolling RRMS individuals with EDSS scores between 2 and 5. Thus, our results cannot be generalized because we did not include other types of MS and individuals with high levels of disability. The lack of significant differences in the baseline characteristics of the groups and the fact that they were randomized were some strengths of our study. It is not known how the effect of exercise on these variables will change when the type, intensity, and duration of the exercise are changed. Therefore, studies with a larger study population are needed to determine the effects of exercise on MS patients from the perspective of the stated biomarkers.

CONCLUSION

Our findings indicate that HPT and OPT can significantly reduce NFL levels and fatigue in women with MS. This indicates the positive effects combination of Pilates exercise and sunlight exposure in MS patients. However, further studies are required to confirm these findings.

ACKNOWLEDGMENTS

The authors would like to thank all participants in the study for their cooperation.

DECLARATIONS

FUNDING

The authors received no financial support for the research, authorship, and/or publication of this article.

Ethics approvals and consent to participate

Written consent was obtained from all participants after fully explaining the research objectives and details. The study received approval from the Research Ethics Committee of Hakim Sabzevari University, Iran (IR.HSU.REC.1400.015). The study has been also registered with the Iranian Registry of Clinical Trials (code: IRCT20220324054348N1).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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How to Cite:
Balaghi Inaloo F, Askari F, Haghighi AH, Kashani K, Friedemann P [Decreased Serum Neurofilament Light Chain and Fatigue Severity in Patients with Multiple Sclerosis after Home-Based and Outdoor Pilates Training]. mljgoums. 2023; 17(3): 55-62 DOI: 10.29252/mlj.17.3.55