






Original Article

## Effect of Eight -Weeks of Resistance Training on Serum Levels of Neurofilament Light Chain and Tau Protein in Women with Multiple Sclerosis

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### ABSTRACT

**Background and objectives:** Multiple sclerosis (MS) is a demyelinating and neurodegenerative disease of the central nervous system that can be tracked through biomarkers of disease status. The present study aimed to examine effect of eight weeks of resistance training on serum levels of neurofilament light chain and tau protein in women with multiple sclerosis (MS).

**Methods:** The study population consisted of 24 women with MS (aged 25 to 40 years) in Bojnourd (Iran) with expanded disability status scale score of 2-5. Patients were randomly divided into two groups of resistance training (n=12) and control (n=12). The training group performed 45-60 minutes of resistance training, three sessions a week for eight weeks. The control group did not partake in sports activity. Blood samples were taken 24 hours before the first session and 48 hours after the last training session. Analysis of covariance was used to analyze data at a significance level of 0.05.

**Results:** The eight-week resistance training intervention significantly decreased serum level of tau protein but had no significant effect on serum level of neurofilament light chain.

**Conclusion:** According to the research results, eight weeks of resistance training could have favorable effects on serum level of tau protein in MS patients.

**Keywords:** [Resistance training](#), [Tau proteins](#), [Multiple sclerosis](#).

## INTRODUCTION

Multiple sclerosis (MS) is a demyelinating and neurodegenerative disease of the central nervous system (CNS) that can be tracked through biomarkers of disease status (1). The etiology of MS is still unknown (2). The clinical symptoms of the disease vary depending on the course of disease and location of the lesions (3). The most obvious pathological findings in the CNS of patients with MS include the local demyelination of white matter, myelin regeneration, inflammation, a variable degree of axonal and gliosis retention/loss as well as extensive gray matter tissue damage (4). Axonal loss seems to be the main pathological factor for the subsequent irreversible disability, which is the predominant feature at the degenerative stage of the disease (5). The mechanisms that lead to axonal degradation in MS are not well-understood (6).

Neurofilaments (NFs) are proteins of intermediate filament family and the main components of the cytoskeleton of neurons, which are abundantly found in axons (7). These proteins are divided into 68-kDa neurofilament light chain (NFL), 160-kDa neurofilament medium chain (NFM) and 205-kDa neurofilament heavy chain (NFH) based on their molecular weights (8). They are affected by post-translational changes, the most important of which is phosphorylation. The phosphorylation of NFs reduces axonal transmission that itself may have a negative effect on the flexibility and conduction velocity of healthy neurons (9).

Due to the axonal destruction in MS, NFs can enter the cerebrospinal fluid (CSF) and then blood (10). According to various studies, NFL level is significantly increased in CSF of patients with MS. On the other hand, numerous studies indicate that serum and CSF NFL levels were highly correlated in MS; hence, the examination of serum levels of NFL can be an important criterion for axonal damage in MS (8). Similar to NFL, the tau protein is released during axonal transport and acts as a potential biomarker of MS (11). Tau is a microtubule-associated protein that can be mainly found in neurons of the CNS (12), especially in axons, and to a lesser extent in cell bodies and dendrites (13). This protein is minimally expressed in astrocytes and oligodendrocytes (14). Strong body of evidence suggests that tau phosphorylation can

lead to sudden neuronal death. The role of tau hyperphosphorylation cannot be denied in nerve damage. Tau damage has been demonstrated in neurodegenerative diseases including Alzheimer's disease, Parkinson's disease and MS (15).

Given that neurodegeneration has not yet been targeted by disease-modifying therapies, and these interventions generally target neuroinflammation (16), some preliminary evidence from animal models, healthy individuals and people with MS suggests that training may have neuroprotective effects (17). Despite the fact that aerobic exercise has neuroprotective properties, recent studies have found that resistance training can also significantly prevent neurological diseases and maintain, develop or improve brain function through neurochemical adaptations. It has been found that resistance training causes brain redox regulation and neuroprotection by increasing the amount of factors such as brain-derived neurotrophic factor (BDNF) and reducing the amount of glutamate (18). An increase in these factors could reduce NFL (19). Furthermore, resistance training activates the PI3K/AKT/mTOR pathway (18), which is associated with the prevention of tau hyperphosphorylation (20). The effects of resistance training on skeletal muscles are well understood, but its effects on the brain have been partially described. To date, no study has investigated the effects of resistance training on biomarkers of axonal degeneration of NFL and tau in MS patients. The present study aimed to investigate effects of eight weeks of resistance training on serum levels of the NFL and tau protein in women with MS.

## MATERIALS AND METHODS

This quasi-experimental and applied study was conducted on 24 women with MS (aged 25 to 40 years) with expanded disability status scale (EDSS) score of 2 to 5 in Bojnord County, Iran. The subjects were randomly divided into two groups of resistance training (n= 12) and control (n=12). Subjects in the training group performed 45-60 minutes of resistance training, three sessions a week for eight weeks, while the control subjects 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 Islamic Azad University of Bojnourd, Iran (ethics code: IR.IAU.BOJNOURD.REC.1398.018).

Each training session started with 10 minutes of general warm-up (slow walking, stretching and flexibility), followed by 3-5 minutes of special warm-up and ended with 10 minutes of cool down. The training protocol included leg press, leg extension, leg curl, bench press, lat pull down, lateral raise, triceps push down, arm curl and two basic abdominal crunch protocols (21). To control exercise intensity, the exercises were performed in two sets of 10-12 repetitions with an intensity of 45% of a maximum repetition (1-RM) in the first eight sessions, in two sets of 10-12 repetitions with an intensity of 50% of 1-RM in the second eight sessions, and in two sets of 10-12 repetitions with an intensity of 55% of 1-RM in the third eight sessions. There was a 1-2-minute rest interval between each set. The participants rested for 2 minutes between movements. It should be noted that 1-RM of participants was recorded in all movements every two weeks. Fasting blood samples (5 ml) were taken 24 hours before the first session

and 48 hours after the last training session. Serum was separated and kept at  $-20^{\circ}\text{C}$  for biochemical evaluation. Serum level of tau protein was measured using a commercial ELISA kit (MyBioSource company) with sensitivity of 2.0 pg/ml and a detection range of 15.6 to 500 pg/ml. Serum level of NFL was measured using a commercial ELISA kit (ZellBio GmbH company) with sensitivity of 0.390 ng/ml and a detection range of 3.125 to 100 ng/ml.

Data were expressed as mean  $\pm$  standard deviation. Normality of data was assessed using the Shapiro-Wilk test. Analysis of covariance (ANCOVA) was carried out in SPSS 23 and at significant level of 0.05.

## RESULTS

[Table 1](#) shows the mean level of tau protein and NFL in the study groups at baseline and posttest.

Based on the ANCOVA test, the eight-week resistance training significantly decreased serum level of tau protein ( $P=0.000$ ) but had no significant effect on NFL level ( $P=0.110$ ) compared to the control group ([Table 2](#)).

Table 1-Mean level of study variables in the pretest and posttest stages

Variable		Resistance training (n=12)	Control group (n=12)
Tau protein (pg/ml)	Pre-test	44.33 $\pm$ 5.54	44.00 $\pm$ 5.62
	Post test	35.48 $\pm$ 5.52*	43.25 $\pm$ 6.06
	Percent change	-19.96*	-1.70
NFL(ng/ml)	Pre-test	65.92 $\pm$ 7.94	72.24 $\pm$ 12.68
	Post test	62.36 $\pm$ 5.75	69.25 $\pm$ 12.98
	Percent change	-5.39	-4.13

Table 2-Effects of resistance training on serum NFL and tau protein

Variable	Stage	Cube square	df	Mean square	F	Significance level	Partial Eta squared
Tau protein (pg/ml)	Pre-test	706.889	1	706.889	435.869	0.000	0.954
	Posttest	393.369	1	393.369	242.552	0.000*	0.920
NFL(ng/ml)	Pre-test	10.739	1	10.739	0.102	0.752	0.005
	Posttest	292.032	1	292.032	2.778	0.110	0.117

## DISCUSSION

Based on the findings of the present study, eight weeks of resistance training significantly reduced tau protein level in women with MS. This is in line with findings of previous studies that reported change in tau concentrations in plasma and CSF samples from athletes, healthy individuals, Alzheimer's disease patients, those with brain injuries and animals (20). In this regard, Daniele et al. (2018) examined the accumulation of alpha-synuclein With tau and amyloid beta in human platelets

of healthy individuals after physical exercise. They reported a decrease in tau concentrations in athletes but no change in amyloid beta and alpha-synuclein (22). GharariArefi et al. (2016) investigated the role of aerobic exercise and omega-3 supplementation on the level of phosphorylated-tau protein in the hippocampus of homocysteine-infected rats with Alzheimer's disease. The training was performed on 60 male Wistar rats for eight weeks. They reported that aerobic exercise and

omega-3 supplementation could separately reduce the level of phosphorylated-tau protein in the hippocampus of the rats (23). Leem et al. (2009) reported that three months of endurance training reduced phosphorylated-tau protein levels in the hippocampus of rats with Alzheimer's disease. They concluded that prolonged endurance training might induce a therapeutic effect and reduce the pathology of the tau protein (24). In consistent with our findings, Liang et al. (2010) found no significant difference in the level of tau protein and hyperphosphorylated-tau between active and sedentary elderly people with Alzheimer's disease (25). Therefore, the amount of tau protein may depend on the intensity and type of training (15). Given that resistance training activates the PI3K/AKT/mTOR pathway and can prevent the hyperphosphorylation of tau protein (18), it may also suppress the generation of neurofibril aggregates. The reduction of phosphorylated tau may be due to the inhibition or activation of other tau-protein kinases, including mitogen-activated protein kinases, protein kinase C and protein kinase A. Such changes lead to a considerable decrease in the phosphorylated tau concentration (15). We found no significant change in serum NFL level following the exercise intervention. This is in line with findings of a study by Jensen et al. (2017) that reported no significant change in the CSF concentrations of NFL, neurogranin, visinin like protein 1 and chitinase-3 like protein-1 between patients with Alzheimer's disease and healthy individuals. The mentioned study also found no significant change in the biomarkers after moderate and high intensity training (26). Inconsistent with our findings, Garcia et al. (2012) reported that acrobatic training could affect the expression of structural and synaptic proteins mainly in the striatum and motor cortex. In addition, treadmill running significantly altered the level of structural proteins in all three areas, especially in the cerebellum that are involved in learned and automated tasks (27). The discrepancy between the results of the present study and previous studies may be associated with the type of training and characteristics of the study population. Recently, It has been postulated that glutamate excitotoxicity could be a missing link between inflammatory and neurodegenerative processes evident in MS (28). An increase in the concentration of

extracellular glutamate, for any reason, leads to over-activation of glutamate receptors (29), which can transfer large amounts of calcium ions into the cell, which in turn might increase NFL phosphorylation (30). On the other hand, an increase in BDNF leads to a decrease in the NFL (19). Given the role of resistance training in increasing the levels of neurotrophic factors and decreasing the glutamate level, this type of exercise may reduce the rate of NFL phosphorylation. Given that the biological changes caused by resistance training depend on the duration, intensity and type of training (18), changing these parameters may affect the exercise-related reduction of this biomarker.

## CONCLUSION

Our findings indicate that resistance training can significantly reduce tau protein but has no favorable effect on NFL in women with MS. However, further studies are required to confirm our findings.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## REFERENCES

1. Negaresh R, MotlRW, Zimmer P, Mokhtazade M, Baker JS. *Effects of exercise training on multiple sclerosis biomarkers of central nervous system and disease status: a systematic review of intervention studies*. European Journal of Neurology. 2019; 26(5): 711-21. [View at Publisher] [DOI:10.1111/ene.13929] [PubMed] [Google Scholar]
2. Olsson T, Barcellos LF, Alfredsson L. *Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis*. Nature Reviews Neurology. 2017 Jan;13(1):25. [View at Publisher] [DOI:10.1038/nrneuro.2016.187] [PubMed] [Google Scholar]
3. KamalianLari S, Haghgoo HA, Farzad M, Hosseinzadeh S. *Investigation of the validity and reliability of Balance Evaluation Systems Test (BESTest) in assessment of balance disorders in people with multiple sclerosis*. Archives of Rehabilitation. 2018;18(4):288-295. [Persian]. [View at Publisher] [DOI:10.21859/jrehab.18.4.3] [Google Scholar]
4. Petrova N, Carassiti D, AltmannDR, Baker D, Schmierer K. *Axonal loss in the multiple sclerosis spinal cord revisited*. Brain Pathology. 2018 May;28(3):334-48. [View at Publisher] [DOI:10.1111/bpa.12516] [PubMed] [Google Scholar]

5. Petzold A, Gveric D, Groves M, Schmierer K, Grant D, Chapman M, et al. *Phosphorylation and compactness of neurofilaments in multiple sclerosis: indicators of axonal pathology*. *Experimental neurology*. 2008; 213(2): 326-35. [[View at Publisher](#)] [[DOI:10.1016/j.expneurol.2008.06.008](#)] [[PubMed](#)] [[Google Scholar](#)]
6. Dujmovic I. *Cerebrospinal fluid and blood biomarkers of neuroaxonal damage in multiple sclerosis*. *Multiple sclerosis international*. 2011;2011:767083. [[DOI:10.1155/2011/767083](#)] [[PubMed](#)] [[Google Scholar](#)]
7. Yuan A, Rao MV, Veeranna, Nixon RA. *Neurofilaments at a glance*. *Journal of Cell Science*. 2012; 125(Pt 14): 3257-3263. [[View at Publisher](#)] [[DOI:10.1242/jcs.104729](#)]
8. Siller N, Kuhle J, Muthuraman M, Barro C, Uphaus T, Groppa S, et al. *Serum neurofilament light chain is a biomarker of acute and chronic neuronal damage in early multiple sclerosis*. *Mult Scler*. 2019; 25(5): 678-686. [[DOI:10.1177/1352458518765666](#)] [[PubMed](#)] [[Google Scholar](#)]
9. Niklas N. *Neurofilament light as a marker for neurodegenerative diseases*. *Diss. Kliniskmikrobiologi*, 2004. [[Google Scholar](#)]
10. VarhaugKN, Torkildsen Ø, Myhr KM, Vedeler CA. *Neurofilament light chain as a biomarker in multiple sclerosis*. *Frontiers in neurology*. 2019; 10: 338. [[DOI:10.3389/fneur.2019.00338](#)] [[PubMed](#)] [[Google Scholar](#)]
11. Dubuisson N, Puentes F, Giovannoni G, Gnanapavan S. *Science is 1% inspiration and 99% biomarkers*. *Mult Scler*. 2017; 23(11): 1442-1452. [[DOI:10.1177/1352458517709362](#)] [[PubMed](#)] [[Google Scholar](#)]
12. Derisbourg M, Leghay C, Chiappetta G, Fernandez-Gomez FJ, Laurent C, Demeyer D, et al. *Role of the Tau N-terminal region in microtubule stabilization revealed by new endogenous truncated forms*. *Sci Rep*. 2015 May 14;5:9659. [[DOI:10.1038/srep09659](#)] [[PubMed](#)] [[Google Scholar](#)]
13. Peric A, Annaert W. *Early etiology of Alzheimer's disease: tipping the balance toward autophagy or endosomal dysfunction?* *Acta Neuropathol*. 2015 ;129(3):363-81. [[DOI:10.1007/s00401-014-1379-7](#)] [[PubMed](#)] [[Google Scholar](#)]
14. Kim DH, Yeo SH, Park JM, Choi JY, Lee TH, Park SY, et al. *Genetic markers for diagnosis and pathogenesis of Alzheimer's disease*. *Gene*. 2014 25;545(2):185-93. [[View at Publisher](#)] [[DOI:10.1016/j.gene.2014.05.031](#)] [[PubMed](#)] [[Google Scholar](#)]
15. MohammadiZF, Khezri A, Ebrahimzadeh M. *The Effects of Voluntary Exercise on a Running Wheel and Allium Paradoxum on Tau Protein in the Cerebellum of Diabetic Rats*. *Journal of Isfahan Medical School*. 2012 Jun 18;30(185).[ persian]. [[Google Scholar](#)]
16. Thompson AJ, Baranzini SE, Geurts J, Hemmer B, Ciccarelli O. *Multiple sclerosis*. *Lancet Lond*. Engl. 391, 1622-1636.2018. [[DOI:10.1016/S0140-6736\(18\)30481-1](#)]
17. Kjølhede T, Siemonsen S, Wenzel D, Stellmann JP, Ringgaard S, Pedersen BG, et al. *Can resistance training impact MRI outcomes in relapsing-remitting multiple sclerosis?* *Mult Scler*. 2018 ;24(10):1356-1365. [[DOI:10.1177/1352458517722645](#)] [[PubMed](#)] [[Google Scholar](#)]
18. Pinho RA, Aguiar AS Jr, Radák Z. *Effects of Resistance Exercise on Cerebral Redox Regulation and Cognition: An Interplay Between Muscle and Brain*. *Antioxidants (Basel)*. 2019 6;8(11):529. [[DOI:10.3390/antiox8110529](#)] [[PubMed](#)] [[Google Scholar](#)]
19. Gordon J. *Long-term Aerobic Exercise Can Enhance Cognition and Delay the Onset of Alzheimer's Disease*. 2019. [[Google Scholar](#)]
20. Ohia-Nwoko O, Montazari S, Lau YS, Eriksen JL. *Long-term treadmill exercise attenuates tau pathology in P301S tau transgenic mice*. *Mol Neurodegener*. 2014 28;9:54. [[DOI:10.1186/1750-1326-9-54](#)] [[PubMed](#)] [[Google Scholar](#)]
21. Conceição MS, Bonganha V, Vechin FC, de Barros Berton RP, Lixandrão ME, NogueiraFR, et al. *Long-term treadmill exercise attenuates tau pathology in P301S tau transgenic mice*. *Mol Neurodegener*. 2014; 9: 54.2013;8:1221. [[DOI:10.12965/jer.1734896.448](#)] [[PubMed](#)] [[Google Scholar](#)]
22. Daniele S, Pietrobono D, Fusi J, Lo Gerfo A, Cerri E, Chico L, et al.  *$\alpha$ -Synuclein Aggregated with Tau and  $\beta$ -Amyloid in Human Platelets from Healthy Subjects: Correlation with Physical Exercise*. *Front Aging Neurosci*. 2018 30;10:17. [[DOI:10.3389/fnagi.2018.00017](#)] [[PubMed](#)] [[Google Scholar](#)]
23. GharariArefi. R, Saghebjoos. M, Hedayati. M, Fathi R. *The Role of Aerobic Training and Omega-3 Supplement Intake on Phosphorylated Tau Protein in the Hippocampus of Alzheimer Induced Rats with Homocysteine*. *Sport Physiology*. Fall 2016; 8 (31): 171-88. [Persian]. [[DOI:10.22089/spj.2016.814](#)] [[Google Scholar](#)]
24. Leem YH, Lim HJ, Shim SB, Cho JY, Kim BS, Han PL. *Repression of tau hyperphosphorylation by chronic endurance exercise in aged transgenic mouse model of tauopathies*. *J Neurosci Res*. 2009 15;87(11):2561-70. [[View at Publisher](#)] [[DOI:10.1002/jnr.22075](#)] [[PubMed](#)] [[Google Scholar](#)]
25. Liang KY, Mintun MA, Fagan AM, Goate AM, Bugg JM, Holtzman DM, et al. *Exercise and Alzheimer's disease biomarkers in cognitively normal older adults*. *Ann Neurol*. 2010 ;68(3):311-8. [[View at Publisher](#)] [[DOI:10.1002/ana.22096](#)] [[PubMed](#)] [[Google Scholar](#)]
26. Jensen CS, Portelius E, Høgh P, Wermuth L, Blennow K, Zetterberg H, et al. *Effect of physical exercise on markers of neuronal dysfunction in cerebrospinal fluid in patients with Alzheimer's disease*. *Alzheimers Dement (N Y)*. 2017 17;3(2):284-290. [[View at Publisher](#)] [[DOI:10.1016/j.trci.2017.03.007](#)] [[PubMed](#)] [[Google Scholar](#)]



27. Garcia PC, Real CC, Ferreira AF, Alouche SR, Britto LR, Pires RS. *Different protocols of physical exercise produce different effects on synaptic and structural proteins in motor areas of the rat brain*. Brain Res. 2012 25;1456:36-48. [[View at Publisher](#)] [[DOI:10.1016/j.brainres.2012.03.059](#)] [[PubMed](#)] [[Google Scholar](#)]
28. Kostic M, Zivkovic N, Stojanovic I. *Multiple sclerosis and glutamate excitotoxicity*. Reviews in the neurosciences. 2013; 24(1): 71-88. [[DOI:10.1515/revneuro-2012-0062](#)] [[PubMed](#)] [[Google Scholar](#)]
29. Malekzadeh Shafaroudi M, Zarei H, Malekzadeh Shafaroudi A, Karimi N, Abedini M. *The Relationship between Glutamate and Multiple Sclerosis*. International Biological and Biomedical Journal. 2018 Jan 15;4(1):1-3. ). [persian]. [[View at Publisher](#)] [[Google Scholar](#)]
30. Loureiro SO, Heimfarth L, Pelaez Pde L, Vanzin CS, Viana L, Wyse AT, et al. *Homocysteine activates calcium-mediated cell signaling mechanisms targeting the cytoskeleton in rat hippocampus*. Int J Dev Neurosci. 2008 ;26(5):447-55. [[DOI:10.5772/66926](#)] [[PubMed](#)] [[Google Scholar](#)]

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