

The Effect of Eight Weeks of Aerobic Exercise on Balance Function and Physiological Cost Index in Multiple Sclerosis Patients

Mohammad Reza Sadeh¹ , Reza Sharifatpour^{2*} 

1. Department of Physical Education of University of Najafabad, Branch of Azad University, Isfahan, Iran
2. Department of Sports Sciences, Faculty of Psychology and Educational Sciences, University of Yazd, Yazd, Iran

ARTICLE INFO

Original Article

Received: 15 November 2020

Accepted: 23 December 2020



Corresponding Author:

Reza Sharifatpour

reza.sharifatpour2013@gmail.com

ABSTRACT

Introduction: Muscle weakness and balance problems are limiting factors in Multiple sclerosis patients that can be improved due to physical activity. The purpose of this study was to investigate the effect of 8 weeks of aerobic exercise on balance function and Physiological Cost Index in patients with MS in Yazd city in 1394.

Methods: This quasi-experimental study was conducted in two stages: pretest and post-test. The subjects were selected by targeted and available sampling and randomly divided into training and control groups that included 30 patients (15 in the experimental group and 15 in the control group). The subjects were randomly divided into two groups of experimental and control. Subjects in the experimental group participated in an aerobic exercise program for eight weeks, three days a week, each session of 60-90 minutes with an intensity of 50-70% of maximum heart rate. For statistical analysis we used descriptive statistics such as mean, standard deviation, and the Shapiro-Wilk test used to measure the normality of the data, independent t-test and the covariance (ANCOVA). The significance level of the tests was $p < 0.05$ by using the SPSS-25 software.

Results: ANCOVA results revealed that the selected aerobic training significantly increased both static balance ($p = 0.007$) and dynamic balance ($p = 0.001$). Moreover, aerobic training positively influenced the physiological cost index ($P = 0.001$).

Conclusion: aerobic exercise can improve both static and dynamic balance and increase the Physiological Cost Index in M.S patients. Therefore, these exercises are recommended for patients with MS.

Keywords: Aerobic exercise, Balance, MS patients, Physiological cost index

How to cite this paper:

Sadeh MR, Sharifatpour R. The Effect of Eight Weeks of Aerobic Exercise on Balance Function and Physiological Cost Index in Multiple Sclerosis Patients. J Community Health Research 2020; 9(4): 273-281.

Copyright: ©2020 The Author(s); Published by Shahid Sadoughi University of Medical Sciences. This is an open-access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Introduction

Multiple sclerosis (MS) is a chronic non-inflammatory disease that destroys myelin sheaths in the central nervous system (1). This disease usually affects people of 20-40 years old. However, due to the difficulty of diagnosis, it is usually diagnosed in later stages. Currently, the age of MS occurrence has been decreased to 20 years, and it affects women by 2.5 times more than men (2). The recent reports suggest that about 1000 new cases in Canada and 10000 new cases in America are recorded every year. These statistics suggest that this disease is a global problem (3, 4). In Iran, 15-30 cases occur in every 100 thousand people (5).

The available statistics show the increasing number of this disease that the young population of the country is disabled. The main cause of this disease is still unknown. However, in the case of its occurrence, the white blood cells invade themselves instead of the foreign agents. This process damages the myelin sheaths and leads to dysfunction of nerve signal transmission (6). MS's risk factors include age, family history, genetic susceptibility, geographic condition, and gender (7). The clinical procedure ranges from no-symptom stage to rapidly progressive and disabling. MS symptoms can differ depending on the part of the central nervous system that is affected by the disease (7). In general, the symptoms include fatigue, heat sensitivity, decreased mobility, abnormal gait mechanics, tremor, diplopia, weak movement, poor balance, and muscle stiffness. These disorders can be intensified by a decrease in physical activity (3, 4).

Physical disabilities, such as fatigue, spasticity, tremor can cause different patients' problems in the long term (8). Reduction in movement caused by lack of balance, weakness, and muscle stiffness has been commonly reported in patients affected by MS (9). These symptoms significantly affect patients' motor function (10). One of the most commonly affected parts of MS is the cerebellum. This condition is accompanied by symptoms such as ataxia, motor control dysfunction, and imbalance.

Additionally, it results in gait dysfunction (11). Furthermore, it has been reported that the vision, depth perception, and vestibular senses that are

necessary for postural stability are disturbed in MS patients (12). Demyelination in sensory pathways is one of the prevalent conditions in MS. Hence, it is useful to focus on the rehabilitation of sensory-motor functions in these patients. One of the main causes of M.S. patients' falling is a balance disorder. Therefore, scientific communities have recently paid special attention to evaluating and treating balance and gait disorders in MS patients (13).

MS patients are prone to a higher risk of sedentariness caused by sedentariness, leading to decreased aerobic capacity in healthy people. Besides, in MS patients, it has been proved that it is not only VO_2 max decreased but also other cardiovascular indicators such as resting heart rate and diastolic blood pressure are increased (3). The change of the steps' length and width is one of the main causes of increased energy expenditure and, consequently, fatigue. Meanwhile, studies suggest that M.S. patients' oxygen consumption during walking is four times more than normal people (14).

As sedentariness is common in MS patients, cardiovascular and muscular endurance are involved in their increased energy expenditure during walking. Thus, the common parameter for calculating the energy expenditure is oxygen consumption (15). Oxygen consumption is an indicator used for calculating energy expenditure. However, the calculation of these indicators should be done by expensive devices that are not available in most treatment centers and clinics (15, 16). McGregor introduced the Physiological Cost Index for calculating the energy expenditure during walking. Physiological Cost Index is defined as the difference between the heart rate while walking and resting, divided by walking speed; it is a simple calculation method without any equipment (18). One of the advantages of using this index in treatment centers is its ease and no need for complex types of equipment. Furthermore, integrating the heart rate changes with physical activity (the average walking speed) provides a reliable index for getting the person's physiological energy consumption (19).

Studies have shown that exercise should be considered a safe and effective tool for rehabilitating MS patients. The evidence suggests that a specific controlled exercise program can improve physical fitness, functional capacity, and quality of life in MS patients without escalating the disease or causing its recurrence (20-24). Mustart et al. performed a systematic review to investigate the effect of physical activity on MS patients. It was concluded that physical activity, and especially aerobic exercises, can effectively improve MS patients' balance without causing recurrence of the disease (25). Newman et al. (2007) reported that aerobic exercises using the treadmill decrease the resting oxygen consumption, increase the comfortable walking speed (C.W.S.), decrease the time of walking a 10-meter distance, increase walking endurance, and create an appropriate gait pattern in MS patients. Also, this program decreases fatigue in some of the patients (26). Investigation of the effect of aerobic exercise on walking in MS patients showed that aerobic exercise improves the gait patterns (19). Due to the positive effect of different exercises, especially the impact of aerobic exercises on the improvement of physical fitness factors, quality of life, and the performance of MS patients, this study aimed to investigate the effect of aerobic exercises on balance performance and Physiological Cost Index in female MS patients.

Methods

The present research is a quasi-experimental study with a pretest-posttest design, experimental, and control group. The subjects consisted of 30 female MS patients (15 patients in the experimental group and 15 patients in the control group) and were the members of the MS Society of Shahid Sadoughi Hospital of Yazd. Some neurologists had diagnosed the disease of the participants.

The inclusion criteria included expanded disability status scale of (EDSS < 4.5), no record of recurrence over the four weeks before the start of the project until the end of the project, no record of other diseases (cardiovascular, respiratory, and skin diseases, arthritis, etc.), and the ability to regularly participate in the training sessions. The exclusion

criteria included heart diseases, high blood pressure, orthopedic disorders, and diabetes, using other drugs in addition to MS medicines that could affect the subjects' responses to the tests, failing to regularly participate in the training sessions and test sessions, and recurrence of the disease during the research period. After providing the subjects with explanations about the research procedure and filling in the written consent form, the subjects voluntarily joined the study.

The subjects were selected by targeted and available sampling and randomly divided into training and control groups that included 30 patients (15 in the experimental group and 15 in the control group). The subjects of the training group participated in an aerobic exercise program for eight weeks, while the control group did not take part in any exercise program. The training group participated in an aerobic exercise program for eight weeks and three days a week; each session lasting for 60-90 minutes with an intensity of 50-70% of the maximum heart rate. After warming up for 10 minutes at the beginning of the training sessions, the participants performed the designed exercise for 40 minutes, and at the end, 10 minutes were allocated for cooling down.

Static balance was evaluated by the Sharpened Romberg test. The reliability of this test was obtained as 0.90-0.91 with open eyes and 0.76-0.77 with closed eyes (8). For the present study, the participants were first asked to warm up and later stand in a barefoot manner so that one foot (dominant leg) was ahead of the other foot, and the arms were kept on the chest in a crosswise manner. The period for which the participants could keep this posture was considered as their score. When the participants' posture started to sway, the tester stopped the timer.

Dynamic balance was evaluated by the Timed Up and Go test. In this test, initially, the subjects sat on an armchair with their feet on the ground behind the specified line. Next, with the tester's indication, the participants were asked to stand up and walk a 3-meter distance with their potential speed and their usual steps in a safe manner until they reach the marked point. Then, they return and walk to the

chair and sit in their primary posture. The test time was recorded from when the participants got up from the chair and got back to sit down and lean on the chair. The test time was recorded in seconds for the individuals.

The patients' Physiological Cost Index was determined by physiological cost test. For this purpose, this test was done after the subjects became familiar with walking on a treadmill. After placing the Polar pulse meter made in Finland (Electro O.Y. type PE-3000) on the body, the patient's resting heart rate was measured and recorded every ten seconds for two minutes, after five minutes of resting. Then, the patients started walking slowly on the treadmill (with the intensity of 45-65% of the maximum heart rate). The examiner gradually increased the patient's walking speed until the participant declared that she had reached the usual speed of walking. From this moment, the individual walked on the treadmill at the same speed for 2 minutes, and the heart rate was recorded every 10 seconds. Finally, the Physiological Cost Index was calculated using the information, namely the resting heart rate measured during walking, the average walking speed, and applying the following formula(1).

Physiological Cost Index (PCI), Walking Heart Rate (W.H.R.), Resting Heart Rate (R.H.R.), the average Walking Speed (W.S.)

Formula 1.

$$PCI (\text{beats}/\text{min}) = \frac{WHR - RHR(\text{beats} / \text{min})}{WS(m / \text{min})}$$

The participants' walking heart rate and resting heart rate were calculated by the average of the recorded heart rates.

Aerobic exercise program: The individuals participated in aerobic walking exercises on a treadmill for three weeks and three sessions per week. For further monitoring and control, the exercise was performed individually, and each person arrived at the training site at a predetermined time and performed the exercise for about 40 to 60 minutes. In all training sessions, the first 10 minutes of training and the last 10 minutes of training were dedicated to warming up and cooling down, respectively. The intensity of training for walking

on a treadmill was 40 to 75% of the maximum heart rate. The participants' heart rate was monitored in all training sessions using a Polar pacemaker made in Finland (Electro O.Y. type PE-3000) (19, 26, 43).

The participants were asked to rest for 5 minutes at each stage of the exercise whenever they felt tired and then resume training. Due to the importance of the effects of temperature for MS patients, the temperature of the continuous training environment was controlled by a thermometer (the training site's temperature was 25 to 27 ° C) (19, 26, 43).

Work on the treadmill had been lighter or stopped if A) The training session time was over (according to previous planning). B) The patient's heart rate exceeded 75% of the maximum heart rate. C) Due to the significant effect of fatigue on MS patients, the subject announced before the end of the training time that she cannot continue the training due to fatigue (19, 26, 43).

During the exercise, the intensity of the work was also controlled using the 20-point Berg Balance Scale. Samples were advised to empty the bladder before attending training sessions and to take a cold shower if possible (19, 26, 43).

For statistical analysis we used descriptive statistics such as mean, standard deviation, and the shapiro-Wilk test was used to measure the normality of the data, independent t-test to determine the difference between the two groups in variables and data analysis was done by the analysis of covariance (ANCOVA) to control the effect of covariate variable, not only the changes in the variance of the dependent variable are examined (ANOVA), but also the relationship between the dependent variable and covariate in different levels of a qualitative variable is analyzed (Regression) (45). The significance level of the tests was $P < 0.05$ by using the SPSS-25.

Results

Table 1 presents the descriptive information of the participants. Data distribution was normal in both groups. The independent t-test showed no significant difference between the two groups in terms of age, height, weight, disease, and EDSS ($P > 0.05$).

The modified means of variables in pretest and post-test separately in different groups are shown in Table 2.

Table 1. The subjects' descriptive statistics in the two groups

Variable	Group	Mean \pm SD
Height (cm)	Experimental	164.00 \pm 6.89
	Control	163.27 \pm 4.87
Weight (kg)	Experimental	65.40 \pm 9.60
	Control	61.80 \pm 6.34
Age (year)	Experimental	34.13 \pm 5.18
	Control	35.13 \pm 4.95

Table 2. Modified means of variables before and after intervention in groups

Variable	Group	Time	Mean \pm SD
Static balance	Experimental	Pre-Test	16.14 \pm 4.56
		Post-Test	19.35 \pm 5.45
	Control	Pre-Test	17.86 \pm 7.88
		Post-Test	18.53 \pm 7.99
Dynamic balance	Experimental	Pre-Test	16.09 \pm 5.29
		Post-Test	13.50 \pm 4.83
	Control	Pre-Test	14.61 \pm 3.65
		Post-Test	15.01 \pm 4.23
Physiological cost index	Experimental	Pre-Test	0.566 \pm 0.7
		Post-Test	0.503 \pm 0.3
	Control	Pre-Test	0.545 \pm 0.5
		Post-Test	0.534 \pm 0.8

Table 3. The results of ANCOVA for the variables studied in the experimental and control groups

Variable	Sum of squares	df	Mean square	F	Sig	Eta squared
Static balance	18.89	1	18.89	8.44	0.007	0.23
Dynamic balance	49.71	1	49.71	13.91	0.001	0.34
Physiological cost index	0.012	1	0.012	11.99	0.002	0.30

As seen in Table 3, after modifying the pretest scores, the results of ANCOVA was significant for static balance ($F = 8.44$, $P = 0.007$), dynamic balance ($F = 13.91$, $P < 0.001$), and Physiological Cost Index ($F = 11.99$, $P = 0.02$). As a result, there was a significant difference between the modified means of the experimental and control group. Therefore, the results revealed that aerobic exercises cause a significant improvement in static balance and dynamic balance in the experimental group (MS patients). Considering that there was no significant difference between the average walking speed, resting heart rate, walking heart rate, and Physiological Cost Index of patients in the pretest in the

study groups, a significant difference can be noticed in the post-test relating to the effect of the training intervention in the experimental group. (Table 3).

Discussion

The results of the present study showed that a program of 8-week aerobic exercise has improved both static and dynamic balance in addition to the Physiological Cost Index in MS patients.

Balance and posture control are inseparable in independent activities such as sitting, standing, and walking and turn out to be undeniably important. Performing and maintaining balance in a standing position or during motor activity requires the production of sufficient force in the muscles and the

application of this force to the levers (bones), which requires a complex interaction between the musculoskeletal and nervous systems. In patients with MS, as the disease progresses, their balance function gradually declines, and they experience a variety of balance disorders (4). Many studies have reported that exercise is significantly effective in decreasing fatigue in MS patients (27, 28). Other studies have also proved the significant effects of exercise on improving balance (29, 30). The results of the present study are consistent with the findings reported by some of the previous studies (31-34) that emphasize the improvement of balance in MS patients as a result of physical activity and exercise. Carpathkin et al. (2016) reported that an 8-week program of extreme strength training can improve walking and functional balance in MS patients (35). Rietberg et al. (2005) indicated that physical activity and especially aerobic exercises can improve balance in MS patients with an absence of the recurrence of the disease (37). Kargarfard et al. indicated that rehabilitation by the selected aerobic and anaerobic exercises can improve balance in MS patients with EDSS<4.5. According to an investigation of the effect of a hydrotherapy (aerobic) program, a program of 4 to 8 weeks of aerobic exercise led to improved balance performance, endurance, and walking speed in female MS patients (37).

The risk of bone fractures as an outcome of falling is 3.5 times more in M.S. patients than in healthy people. Physical activities, especially walking on a treadmill, decrease the risk of falling in such patients, and increase neuromuscular coordination and muscle power. It is obvious that continuous physical activities, especially aerobic exercises that are more possible for these patients to perform, can increase the efficiency of motor functions in them. These factors help to explain the effectiveness of physical activities as suggested by the research findings (38).

The findings of the present study suggested that eight weeks of aerobic exercise changes the patients' Physiological Cost Index. Measurement of average walking speed as an indicator of physical efficiency and measurement of Physiological Cost Index as

physiological energy expenditure of the participants in this study show the aerobic exercise intervention program before and after eight weeks in the experimental group and compare them with the control group. Farrell et al. (39), Fragoso et al. (40), Douglas et al. (3), and Arastou et al. (41) have reported consistent findings, while the findings of Mustart and Kesselring (42) are inconsistent. According to Newman et al. (2007), the increased walking speed as a result of aerobic exercise is probably due to the specificity of the training methods in the present research (26). One of the studies reporting similar findings to the present study is Pariser et al. (2006) research titled "The Effect of Aerobic Exercise in Water on Aerobic Capacity (as an indicator of Physiological Cost Index), Lactate Threshold, and Fatigue." They studied two MS patients and observed that although both had a poor cardiovascular system and low lactate threshold and oxygen consumption, following a period of hydrotherapy, the patients achieved a higher maximum workload due to the increased Vo_2 peak. Due to the increased lactate threshold, the patients could bear a higher sub-maximum workload without lactic acid accumulation. One of the patients reported a decrease in fatigue, while the other did not report any change (43).

Arastu et al. (2011) compared the effects of eight weeks of aerobic exercise and yoga on the Physiological Cost Index in MS patients. The results revealed that the Physiological Cost Index of patients in the selected aerobic exercise group and also patients in the selected yoga group had a significant decrease and that it was significantly more evident in the aerobic exercise group than the selected yoga exercise group (41). Ahmadi et al. (2010) indicated that aerobic exercises have a significant positive effect on the average walking speed and Physiological Cost Index in MS patients (44). On the other hand, Mustart and Kesselring (2002) did not observe any significant changes in the MS patients' Vo_2 max after four weeks of aerobic exercises (42). These findings can probably be attributed to the short period of the exercise program and the individual differences.

Studies have suggested that oxygen consumption in MS patients during walking is 4 times more than in healthy people. As sedentariness is common among MS patients, the low levels of cardiovascular and muscular endurance are also involved in their increased energy expenditure during walking (41). Consequently, the results can be explained by the fact that the improvement of this indicator in the aerobic exercise group is due to the improvement of the average walking speed and heart rate in these people resulting in the significant difference of Physiological Cost Index in the training group. One of the limitations of this study was the lack of control over the psychological state of patients (in terms of personal life). Other limitations include the lack of control over the dose of drugs used and the nutrition of these patients

Conclusion

According to the results of the present study, participation in aerobic exercise can affect the bio-

motor abilities of MS patients such as balance (static and dynamic) and Physiological Cost Index, thus recommending the use of these exercises as a part of an effective rehabilitation program or exercise programs for MS patients.

Acknowledgment

This article is taken from part of the MSc thesis related to exercises physiology of University of Shiraz International Campus and holds a code 909383.

Author Contribution

R.Sh. and M.R.S. performed the measurements, M.R.S. and R.Sh. were involved in planning and supervising the work. M.R.S. and R.Sh. processed the experimental data, performed the analysis, drafted the manuscript, and designed the figures. All authors aided in interpreting the results, working on the manuscript, discussing the results, and commenting on the manuscript.

References

1. Nilsagård Y. Walking Ability, Balance and Accidental Falls in Persons with Multiple Sclerosis. 2008.
2. Freeman J, Fox E, Gear M, et al. Pilates Based Core Stability Training in Ambulant Individuals with Multiple Sclerosis: Protocol for A Multi-Centre Randomised Controlled Trial. *BMC Neurology*. 2012; 12(1):19.
3. Dalgas U, Stenager E, Ingemann-Hansen T. Multiple Sclerosis and Physical Exercise: Recommendations for The Application of Resistance-, Endurance-and Combined Training. *Multiple Sclerosis Journal*. 2008; 14(1):35-53.
4. Horton S, MacDonald DJ, Erickson KMS. Exercise, and the Potential for Older Adults. *European Review of Aging and Physical Activity*. 2010; 7(1): 49-57.
5. Taraghi Z, Eleiae M. Quality of Life of Patient Member of MS Society of Mazandaran. *Iranian Journal of Neurology*. 2007; 20(55):51-60.
6. Sarvari F, Ebrahimi Atri A, Khorshid Sokhangooy M. The Comparison of Resistance and Endurance Exercises on Fatigue Severity and Balance in Women with Multiple Sclerosis. *Sport medicine*. 2013; 5(10):89-102. [Persian]
7. Doucett A, Seminary J. Pilates Adapted for Parkinson's disease and Multiple Sclerosis. 2013.
8. Salavati M, Negahban H, Soleimanifar M, et al. The Persian Version of the Berg Balance Scale: Inter and Intra Rater Reliability and Construction Validity in Elderly Adults. *Disability and Rehabilitation*. 2012; 34(20):34-48.
9. Annovazzi P, Tomassini V, Bodini B, et al. A Cross-Sectional, Multicentre Study of the Therapeutic Management of Multiple Sclerosis Relapses in Italy. *Neurological Sciences*. 2013; 34(2):197-203.
10. Coote S, Hogan N, Franklin S. Falls in People with Multiple Sclerosis who Use A Walking Aid: Prevalence, Factors, and Effect of Strength and Balance Interventions. *Archives of Physical Medicine and Rehabilitation*. 2013; 94(4):616-21.
11. Mariotti C, Fancellu R, Di Donato S. An overview of the patient with ataxia. *Journal of neurology*. 2005; 252(5):511-8.
12. Silkwood-Sherer D, Warmbier H. Effects of Hippotherapy on Postural Stability, In Persons with Multiple Sclerosis: A Pilot Study. *Journal of Neurologic Physical Therapy*. 2007; 31(2):77-84.
13. Cattaneo D, Jonsdottir J, Zocchi M, et al. Effects of Balance Exercises on People with Multiple Sclerosis: A Pilot Study. *Clinical Rehabilitation*. 2007; 21(9):771-81.
14. Olgiati R, Burgunder JM, Mumenthaler M. Increased Energy Cost of Walking in Multiple Sclerosis: Effect of Spasticity, Ataxia, and Weakness. *Archives of Physical Medicine and Rehabilitation*. 1988; 69(10): 846-9.

15. Waters RL, Mulroy S. The Energy Expenditure of Normal and Pathologic Gait. *Gait Posture*. 1999; 9(3): 207-31.
16. Nene AV, Jennings SJ. Physiological Cost Index of Paraplegic Locomotion Using the ORLAU ParaWalker. *Spinal Cord*. 1992; 30(4): 264-52.
17. Rose J, Gamble JG, Medeiros J, et al. Energy cost of walking in normal children and in those with cerebral palsy. Comparison of heart rate and oxygen uptake. *Journal of Pediatric Orthopaedics*. 1989; 9(3): 2769.
18. MacGregor J. *Rehabilitation ambulatory monitoring*. Palgrave Macmillan, London .1979: 159-72.
19. Rampello A, Franceschini M, Piepoli M, et al. Effect of Aerobic Training on Walking Capacity and Maximal Exercise Tolerance in Patients with Multiple Sclerosis: A Randomized Crossover Controlled Study. *Physical therapy*. 2007; 87(5):545-55.
20. Halabchi F, Alizadeh Z, Sahraian MA, et al. Exercise Prescription for Patients with Multiple Sclerosis Potential Benefits and Practical Recommendations. *BMC Neurology*. 2017; 17(1):185.
21. Dalgas U, Stenager E, Jakobsen J, et al. Resistance Training Improves Muscle Strength and Functional Capacity in Multiple Sclerosis. *Neurology*. 2009; 73(3):1478-84.
22. Dalgas U, Stenager E, Jakobsen J, et al. Fatigue, Mood and Quality of Life Improve in MS Patients after Progressive Resistance Training. *Multiple Sclerosis Journal*. 2010; 16(4):480-90.
23. Dalgas U, Stenager E, Jakobsen J, et al. Muscle Fiber Size Increases Following Resistance Training in Multiple Sclerosis. *Multiple Sclerosis Journal*. 2010; 16(11): 1367-76.
24. Dalgas U, Stenager E, Lund C, et al. Neural Drive Increases Following Resistance Training in Patients with Multiple Sclerosis. *Journal of Neurology*. 2013; 260(7): 1822-32.
25. Mostert S, Kesselring J. Effect of A Short-Term Exercise Training Program on Aerobic Fitness, Fatigue, Health Perception and Activity Level of Subjects with Multiple Sclerosis. *Multiple Sclerosis Journal*. 2002; 8(2): 61–168.
26. Newman MA, Dawes H, van den Berg M, et al. Can Aerobic Treadmill Training Reduce The Effort of Walking and Fatigue in People with Multiple Sclerosis: A Pilot Study. *Multiple Sclerosis Journal*. 2007; 13(1):113-9.
27. Pazokian M, Shabani M, Zakerimoghdam M, et al. The Effect of Stretching Together Aerobic Exercise on Fatigue Level in Multiple Sclerosis Patients Refer to MS Society of Iran Those Suffer From Fatigue. *Journal of Holistic Nursing and Midwifery*. 2012; 22(2):18-24. [Persian]
28. Shanazari Z, Marandi M, Minasian V. Effect of 12 Week Pilates and Aquatic Traianing on Fatigue in Women with Multiple Sclerosis. *Journal of Mazandaran University of Medical Sciences*. 2013; 23(98): 257-64. [Persian]
29. Bolouchi R, Ghyasi A, Naderi A, et al. The Survey of Cawthorne and Cooksey Exercise on the Quality of Life, Balance and Fatigue in Patients with Multiple Sclerosis. *Journal of Ilam University of Medical Sciences*. 2014; 21(7): 43-53. [Persian]
30. Taheri Torbati H, Mahjor M, Enferadi A. Comparison of Single and Dual Task Balance Training on Balance in the Women with Multiple Sclerosis. *Journal of Kurdistan University of Medical Sciences*. 2016; 20(6): 34-43. [Persian]
31. Farsi A, Akbar PS, Mosavi MK.V, et al. Effect of Pilates Training Based on Core Stability on Balance and Electromyography of Women with Multiple Sclerosis. *The Scientific Journal of Rehabilitation Medicine*. 2017; 6(3): 165-173. [Persian]
32. Sarvari, Fatemeh, Ebrahimi Atri, Ahmad, Saeedi, Morteza, Khorshid Sokhangooy, Maryam. The relationship between lower extremity strength and dynamic balance in patients with multiple sclerosis. *Eighth International Conference on MS*. 2011: 1-17.
33. Kurdi M, Anoosheh L, Khodadadh S, et al. The Effect of Selected Combined Training on Strength, Balance and Life Quality of Patients Multiple Sclerosis. *Journal of Sport Medicine*. 2011; 2(5): 46-59. [Persian]
34. Cattaneo D, Jonsdottir J, Zocchi M, et al. Effect of balance exercise on people with multiple sclerosis, a pilot study. *Clinical rehabilitation*. 2007; 21(9): 771-81.
35. Karpatkin HI, Cohen ET, Klein S, et al. The effect of maximal strength training on strength, walking, and balance in people with multiple sclerosis: a pilot study. *Multiple sclerosis international*. 2016: 5235971.
36. Rietberg MB, Brooks D, Uitdehaag BM, et al. Exercise Therapy for Multiple Sclerosis. *Cochrane Database of Systematic Reviews*. 2005; (1).
37. Kargarfard M, Mehrabi M, Hamidi-Tehrani J, et al. Changes in speed, Endurance and Balance in Women with Multiple Sclerosis after 4 and 8 weeks of Aquatic Exercise Training. *Journal of Isfahan Medical School*. 2013; 31(256): 1628-1639. [Persian]
38. White LJ, Dressendorfer RH. Exercise and Multiple Sclerosis. *Sports Medicine*. 2004; 34(15):1077-100.
39. Freal JE, Kraft GH, Coryell JK. Symptomatic Fatigue in Multiple Sclerosis. *Archives of Physical Medicine and Rehabilitation*. 1984; 65(3): 135-8.

40. Fragoso YD, Santana DL, Pinto RC. The Positive Effects of A Physical Activity Program for Multiple Sclerosis Patients with Fatigue. *NeuroRehabilitation*. 2008; 23(2):153-7.
41. Arastu A.A, Ahmadi A, Zahednejad Sh. The Comparison of Effect of 8 Weeks Aerobic and Yoga Training on Physiological Cost Index in Multiple Sclerosis Patients. *Jundishapur Scientific Medical Journal*. 2011; 10(2): 153-162. [Persian]
42. Mostert S, Kesselring J. Effects of a Short-Term Exercise Training Program on Aerobic Fitness, Fatigue, Health Perception and Activity Level of Subjects with Multiple Sclerosis. *Multiple Sclerosis Journal*. 2002; 8(2): 161-8.
43. Pariser G, Madras D, Weiss E. Outcomes of An Aquatic Exercise Program Including Aerobic Capacity, Lactate Threshold, and Fatigue in Two Individuals with Multiple Sclerosis. *Journal of Neurologic Physical Therapy*. 2006; 30(2): 82-90.
44. Ahmadi A, Nikbakht M, Arastoo AA. The Effects of A Yoga Intervention on Balance, Speed and Endurance of Walking, Fatigue and Quality of Life in People with Multiple Sclerosis. *Journal of Human Kinetics*. 2010; 23(1): 71-8.
45. Khammar A, Yarahmadi M, Madadzadeh F. What Is Analysis of Covariance (ANCOVA) and How to Correctly Report Its Results in Medical Research? *Iran Journal Public Health*. 2020; 49(5): 1016-1017.