Eur J Transl Myol 33 (2) 11253, 2023 doi: 10.4081/ejtm.2023.11253

Effects of concurrent training and CoQ10 on neurotrophic factors and physical function in people with Multiple Sclerosis: a pilot study

Amir Hossein Haghighi (1), Amin Ahmadi (1), Antonio Carotenuto (2), Roya Askari (1), Karim Nikkhah (3), Behnam Bagherzadeh-Rahmani (1), Hadi Shahrabadi (1), Daniel Souza (4), Paulo Gentil (4,5)

(1) Department of Exercise Physiology, Faculty of Sport Sciences, Hakim Sabzevari University, Sabzevar, Iran; (2) Department of Neurosciences, Reproductive and Odontostomatological Sciences, Federico II University, Naples, Italy; (3) Department of Neurology, Mashhad University of Medical Sciences, Mashhad, Iran; (4) College of Physical Education and Dance, Federal University of Goias, Goiania, Brazil; (5) Hypertension League, Federal University of Goias, Goiania, Brazil.

Abstract

The present study aimed to investigate the effects of 8-week of coenzyme Q10 (CoQ10) supplementation alone or combined with concurrent training (CT) on functional capacity, serum brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF) in multiple sclerosis (MS) patients. Our hypothesis is that CT promotes improvements in the studied outcomes with higher results for the combination of CT and CoQ10. Randomized placebo-controlled trial. Twenty-eight patients with MS were randomly divided into 4 groups: CT+placebo, CT+CoQ10, CoQ10 and placebo. CT involved two resistance training sessions and one aerobic training session per week. CoQ10 was supplemented with 200 mg daily. Serum levels of BDNF, NGF and functional tests [timed up and go (TUG), 6-min walk (6MW), chest press, lateral pull down, leg extension, and lying leg curls one repetition maximum] were measured before and after the intervention period. CT+placebo and CT+CoQ10 significantly improved performance in TUG, 6MW, chest press, lateral pull down, leg extension, and lying leg curls, with superior results to both CoQ10 and placebo groups. Changes in TUG for CT+placebo were significantly higher than CT+CoQ10 ($p<0.05$). There were no significant differences in NGF and BDNF among the four groups ($p >0.05$). CT improves physical abilities in patient with MS, regardless CoQ10 supplementation. CT should be recommended for MS patients to increase functional capacity, but there seems to be no benefit in supplementing CoQ10.

Key Words: Multiple sclerosis; neurodegenerative disease; exercise therapy; NGF; BDNF; resistance training; interval training; ubiquinone.

Eur J Transl Myol 33 (2) 11253, 2023 doi: 10.4081/ejtm.2023.11253

Multiple sclerosis (MS) is the most common debilitating neurological disease among adults.[1] MS is an autoimmune central nervous system disorder characterised by demyelination and neurodegeneration that leads to physical disability.[2] Previous researches examined nutritional strategies that are potentially effective for MS management.[3,4] Given the important role of inflammation, oxidative stress and mitochondrial dysfunction in MS development, treatments with anti-inflammatory and antioxidant supplements have received growing attention.[5,6] Among them, coenzyme Q10 (CoQ10) is considered a promising therapeutic agent in neurodegenerative diseases. The administration of CoQ10 alone or in combination with other substances in mice with induced-neurodegenerative disease provided neuroprotective effects such as decreased brain oxidative stress and damage, as well as increased neurotrophic factors (e.g., BDNF).[7,8] CoQ10 supplementation might be of potential interest due to its anti-inflammatory and antioxidant effects in MS patients,[9] as well as its positive effects on fatigue and depressive symptoms.[10] Physical exercise is also a potential therapeutic strategy for managing MS, and is considered safe and effective, with positive effects in fitness, functional capacity and quality of life.[11] Exercise exerts its positive therapeutic effects through different pathways. It increases regeneration of sensory neurons after axonal injury, stimulates the

expression of genes associated with axon growth and regeneration, and improves nerve function.[12,13] Physical exercise can also reduce MS symptoms by improving motor coordination, aerobic capacity and muscle strength.[14] Moreover, physical exercise has been shown to increase the expression of neurotrophic factors such as brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF).[15,16] Although many different strategies have been used, the combination of resistance and aerobic training, known as concurrent training (CT), has been shown to be particularly beneficial for people with MS.[17,18] Considering the potential benefits of CoQ10 supplementation in MS, it is plausible to suggest that it might exert additional effects when combined with CT. Therefore, the aim of the present study was to investigate the effects of eight weeks of a CT and CoQ10 supplementation on physical function, serum BDNF and NGF levels in people with MS. Our hypothesis is that CT would promote improvements in the studied outcomes with higher results for the combination of CT and CoQ10.

Materials and Methods

Participants

The study involved 28 MS patients, among 3243 members of the Multiple Sclerosis Association of Mashhad (Iran).

Inclusion criteria were: 1) MS diagnosis according to 2017 McDonald criteria;[19] 2) Expanded Disability Status Scale (EDSS) between 2 and 5; 3) No smoking history; 4) No history of regular exercise; 5) At least 2 years of stable disease modifying treatment; 6) Aged higher than 18 and lower or equal 4. We opted to select younger participants to avoid the confounding effects of age in the studied outcomes.

Exclusion criteria: 1) MS relapse within 30 days from patient enrolment; 2) Moderate to severe cardiovascular disease (Stage III or IV, according to the New York Heart Association); 3) Any other condition that could be aggravated by the study protocol.

This study was approved by relevant Ethics Committee and registered at Clinical Trials records (2019-08-11, 1398/05/20). All subjects or their parents provided a written informed consent prior to study participation. The study was performed in accordance with good clinical practices and Declarations of Helsinki.

Study procedures

Participants were divided into four groups: CT+placebo, CT+CoQ10, CoQ10, and placebo using a simple random method (lottery). Participants in the CoQ10 and placebo groups did not engage in any form of physical exercise during the study. CoQ10 was manufactured by Nutri Century (Canada) and ingested as one 200 mg capsule daily. Starch powder was used as placebo and its

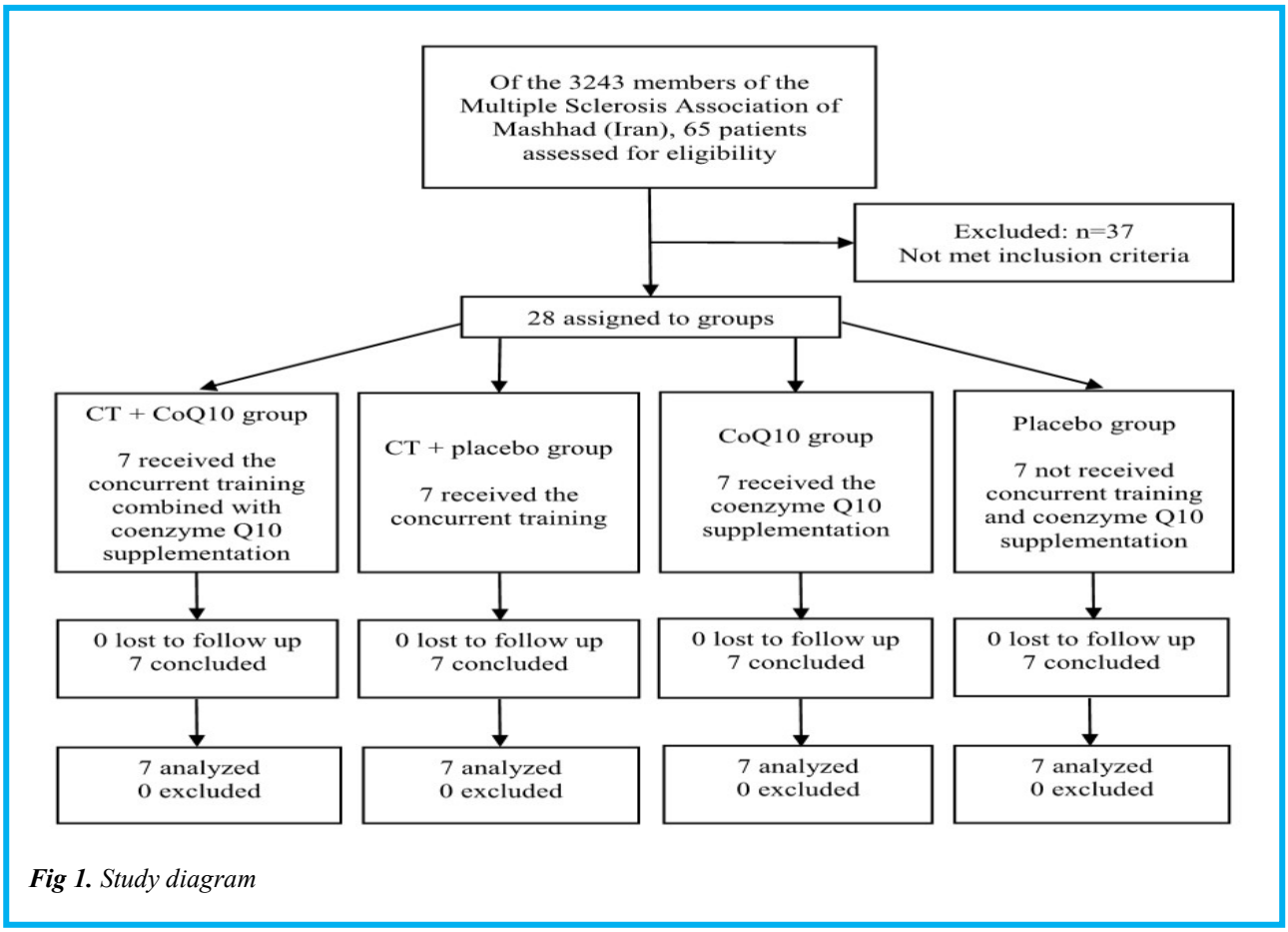

Fig 1. *Study diagram*

Table 1. *Demographic and clinical features for enrolled subjects according to treatment group.*

	CT + CoQ10 (n=7)	CT + placebo (n=7)	CoQ10 (n=7)	Placebo (n=7)	p-value
Gender					
Men (%)	4 (57.14)	4 (57.14)	4 (57.14)	4 (57.14)	1.000
Women (%)	3 (42.86)	3 (42.86)	3 (42.86)	3 (42.86)	
Age, years median (Q1-Q3)	41.00 (40.00-45.00)	32.00 (28.00-45.00)	35.00 (32.00-44.00)	36.00 (31.00-44.00)	0.448
Weight, kg mean ± standard deviation	68.64 ± 3.70	66.50 ± 3.01	67.94 ± 2.21	68.50 ± 1.21	0.445
Height, cm mean ± standard deviation	167.00 ±3.83	162.14 ± 4.63	163.71 ± 5.68	165.43 ± 4.54	0.270
History of MS, years mean ± standard deviation	5.86 ± 1.35	4.86 ± 1.07	4.86 ± 2.03	4.86 ± 1.57	0.543
EDSS, score mean ± standard deviation	3.69 ± .052	3.79 ± 0.39	3.64 ± 0.75	3.64 ± 0.69	0.967
Vo_{2Peak} (ml/kg/min) mean ± standard deviation	25.27±1.00	24.93±0.89	24.29±1.74	24.26±0.50	0.278

MS = Multiple sclerosis; EDSS = Expanded disability status scale

consumption was similar to the consumption of CoQ10 supplements. The study diagram is presented in Figure 1.

Exercise protocol

CT was performed three sessions per week (two resistance training sessions and one aerobic training session) for eight weeks. Every session started with a 5-10 minutes warm-up and ended with 5-10 minutes cool down. Resistance training involved chest press, lateral pull down, leg extensions, and lying leg curls using a minimal dose approach. Exercises were performed in three sets of eight to 10 repetitions at 50-60% of one repetition maximum (1RM), 2-3 minutes rest between sets and 3-4 minutes between exercises.

Aerobic exercises included moderate intensity interval training on a cycle ergometer. Training involved 5 to 12 bouts of 3 minutes interspersed by 1 minute of passive recovery. For exercise prescription, VO2peak was estimated through the Astrand bicycle aerobic test.[20] Aerobic training started with 5 bouts at 50% of the peak oxygen consumption (VO2peak) in the first week and ended with 12 bouts at 60% VO2peak.

Blood analysis

Blood samples (5 cc) were collected 24 hours before the beginning of the study and 24 hours after the last training session, after 10 hours overnight fasting. Women were evaluated in the follicular stage (first 3 to 5 days of the cycle). BDNF (Human BDNF Elisa kit, Boster Biological Technology Co) and NGF concentration (Human NGF Elisa kit, Boster Biological Technology Co) were measured with ELISA method using specific kits.

Functional tests

Timed up and go (TUG) and 6-min walk (6MW) tests were used to evaluate physical functioning. Muscle strength was evaluated by estimated 1RM on chest press, lateral pull down, leg extension, and lying leg curls. Tests were performed in the beginning (24 hours before the first training session) and in the end of study period (48 hours after the last training session). All tests were performed using the same procedures and supervised by the same investigator, that was blind to group allocation. For TUG, participants stand up from a standard armchair,

Table 2. *Outcome measures pre- and post- treatment.*

	Groups	Baseline	Follow-up	F	p-value	ES
Daily calorie intake (kcal) mean± standard deviation	CT + CoQ10	1977.90±181.97	2068.30±146.99	0.175	0.912	0.022
	CT + placebo	2029.30±217.56	2009.00±242.11			
	CoQ10	2063.40±119.47	2056.90±189.65			
	Placebo	2080.30±151.63	1996.40±168.59			
BDNF (ng/ml) mean± standard deviation	CT + CoQ10	2.94±0.27	2.92±0.15	0.345	0.793	0.041
	CT + placebo	2.81±0.42	2.81±0.47			
	CoQ10	2.89±0.13	3.04±0.16			
	Placebo	2.98±0.10	2.98±0.25			
NGF (pg/ml) mean± standard deviation	CT + CoQ10	376.14±41.38	399.00±54.02	0.267	0.849	0.034
	CT + placebo	394.80±38.55	385.17±76.82			
	CoQ10	399.23±22.38	413.17±61.81			
	Placebo	428.23±105.56	407.46±34.79			
Time up and go (s) mean±standard deviation	CT + CoQ10	7.70±0.71	**6.79±0.51	23.262	‡<0.001	0.752
	CT + placebo	8.15±0.74	***6.55±0.47			
	CoQ10	7.70±0.52	7.66±0.61			
	Placebo	7.61±0.71	7.72±0.92			
6-min walk (m) mean±standard deviation	CT + CoQ10	272.14±6.26	***303.29±11.34	19.110	‡<0.001	0.714
	CT + placebo	269.57±18.68	**294.71±27.18			
	CoQ10	271.00±16.71	270.14±16.49			
	Placebo	266.14±13.26	267.76±10.17			
Chest press (kg) mean±standard deviation	CT + CoQ10	23.78±1.70	**31.38±2.98	26.933	‡<0.001	0.788
	CT + placebo	23.51±3.43	***31.73±3.05			
	CoQ10	24.65±2.05	24.87±2.01			
	Placebo	24.52±2.17	24.66±2.79			
Lateral pull down (kg) mean±standard deviation	CT + CoQ10	22.70±1.78	***26.01±1.43	17.111	‡<0.001	0.691
	CT + placebo	22.27±2.55	***25.92±1.76			
	CoQ10	21.76±2.31	22.29±2.97			
	Placebo	20.91±2.40	21.47±2.19			
	Groups	Baseline	Follow-up	Chi-Square	p-value	ES
Leg extension (kg) median (Q1-Q3)	CT + CoQ10	12.00(11.61-13.36)	*16.87(15.88-17.42)	16.869	†0.001	0.578
	CT + placebo	12.41(10.90-13.33)	*16.87(15.88-18.62)			
	CoQ10	12.86(12.41-13.33)	*12.86(12.86-16.87)			
	Placebo	12.41(11.61-13.33)	12.00(12.00-13.33)			
Lying leg curls (kg) median (Q1-Q3)	CT + CoQ10	12.00(11.61-12.86)	*16.36(16.36-17.42)	21.395	‡<0.001	0.766
	CT + placebo	12.41(10.90-13.33)	*17.42(16.87-18.62)			
	CoQ10	12.00(11.61-13.33)	12.00(12.00-13.33)			
	Placebo	12.00(11.25-13.33)	12.00(11.61-12.86)			

** p-value<0.05, ** p-value < 0.01, *** p-value<0.001, by paired-samples t test and Wilcoxon; † p-value < 0.01, ‡ p-value<0.001, by analysis of variance, Kruskal-Wallis, analysis of covariance tests*

walked three meters as fast is possible, turned back, walked back to the chair, and sited down again. The test was performed twice, and the best result was used in the analysis. The 6MW test consisted in walking continuously as fast is possible around a 30 meters track for six minutes and the final distance achieved was recorded in meters. To calculate 1RM, participants performed each exercise to momentary muscle failure,

then 1RM was estimated using the Brzycki formula (21). During all tests participants were verbally encouraged to give their maximum effort.

Dietary analysis

Dietary information was collected during the first and last study week using a 24-hour food recall questionnaire for three days. Data was analysed using Nutrition 4 software (First Databank, San Bruno, CA, USA).

Statistical analysis

Sample size (n=28) was estimated using G*Power software v3.1.9.4, with alpha coefficient of 0.05, statistical power of 0.80, and effect size of 0.5, based on previous research. All analyses were conducted using SPSS software (Statistical Package for Social Sciences Chicago, IL, USA) version 20.0. Normal distribution for continuous variables was explored through Shapiro-Wilk test. Changes for BDNF, NGF, timed up and go, 6-min walk, chest press, lateral pull down, leg extension, and lying leg curls between baseline and follow-up were analysed through paired-samples t test and Wilcoxon. The analysis of variance (ANOVA), Kruskal-Wallis, analysis of covariance (ANCOVA) tests were used to compare groups. The LSD and Gamese-Howell tests were used for post hoc comparisons were necessary. Results were considered statistically significant when $p < 0.05$.

Results

Participants' demographic and clinical characteristics are shown in Table 1. There was no significant difference within or between groups for daily calorie intake (Table 2). CT+CoQ10 and CT+placebo groups showed significant improvements in TUG ($p<0.01$), 6MW ($p<0.01$) and on 1RM loads for chest press ($p<0.01$), lateral pull down ($p<0.01$), leg extension ($p<0.01$), and lying leg curls ($p<0.01$). CoQ10 group showed a significant improvement only in 1RM leg extension ($p<0.05$). NGF and BDNF levels did not change for any group (Table 2). All indicators of functional capacities improved at post intervention for CT+CoQ10 and CT+placebo groups compared to CoQ10 and placebo groups. There was a significant difference ($p=0.011$) in TUG between CT+CoQ10 and CT+placebo, with greater changes for CT+placebo than CT+CoQ10 (Figure 2).

Discussion

The present study aimed to investigate the effects of eight weeks of CT and CoQ10 supplementation, alone or combined, on physical function, serum BDNF and NGF levels in people with MS. As our main result, CT with or without CoQ10 supplementation, significantly improved physical capacity in MS patients, without changes in NGF and BDNF. Our results are in agreement with previous studies showing that CT improves physical function in patients with MS and might help to manage the negative effects of MS on physical disability and quality of life.[22,23] Similarly to our study, Grazioli et al.[17] reported that 12 weeks of CT significantly improved TUG and 6MW test in patients with MS. Moreover, Bahari et al.[24] reported that eight weeks of CT increased strength and balance in patients with MS. Resistance training has been introduced to improve muscle function, specially for its effects on neural adaptations.[25] Increasing lower limbs strength might help to counteract motor fatigue and affects sensory and peripheral nerve pathways or both, leading to improvements in walking speed, endurance and economy.[26] Another important effect of resistance training in MS is the increase in maximal neural drive and neural plasticity.[27] The combination of increased motor units recruitment, movement economy, reductions on inhibitory inputs from alpha motor neurons can be among the factors responsible for increasing muscle adaptations observed in the present study.[25] One factor that might have mediated functional improvements was balance. There is a direct and significant relationship between lower body muscle strength and balance, such that muscle weakness leads to reduced balance and increased risk of falling.[28]

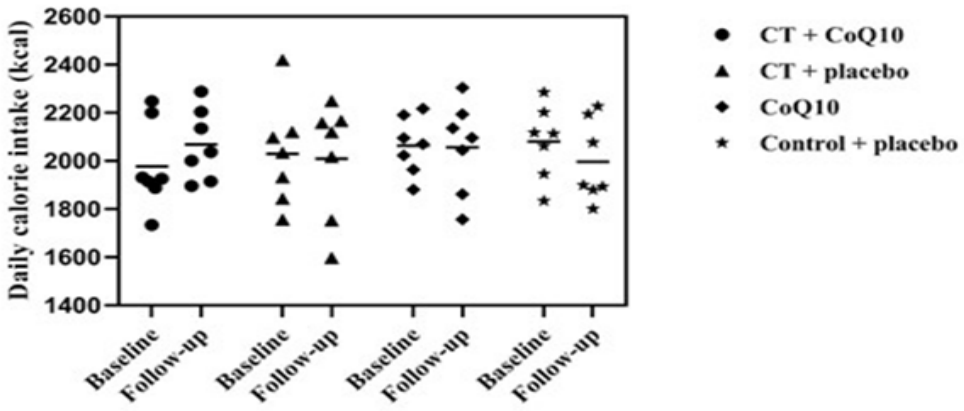

Fig 2. *Indicators of functional capacities*

In the present study muscles strengthening due to both resistance training and cycling,[29] might have impact balance in these patients. Specifically, resistance exercises might improve balance in MS patients by reducing muscle spasms and sensory disturbances.[30] While previous authors found positive effects of cycling in MS,[31–34] the mechanism are not fully understood, but might be associated with general improvements in muscle function and physical fitness.[32–34] Lower limb muscle strength is related to walking speed and is an important predictor of motor performance in MS patients.[35] Resistance exercises has been shown to improve walking kinematics in persons with MS,[36] leading to improvement in the performance of 6-min walk test. Moreover, exercise has been shown to increase endorphin levels and improvement psychological factors, which could influence fatigue and improve motor performance.[37] Regarding neurotrophic factors, Abbaspoor et al.[38] showed that BDNF levels did not change after eight weeks of exercise training. Similarly, Khademosharie et al.[39] showed that CT did not cause significant differences in NGF and BDNF levels of patient with MS. However, different from the present findings, previous studies demonstrated that CT increased BDNF levels in patient with MS.[40,41] It is difficult to explain this divergence, since the mechanism involved in exercise-induced BDNF concentration is not well known. These differences and inconsistencies might be due to the type and intensity of exercise, the length of the training period, differences in research samples, supplementation dose and duration. Although the benefits of CT are of clinical importance and reinforce previous findings, a major novelty of the present study is the combined supplementation of CoQ10, which has been hypothesized to reduce inflammation and oxidative stress in MS patients.[42] Contrary to our hypothesis, there was no benefit in supplementing CoQ10 in the present study, alone or combined with CT, in physical function and NGF and BDNF levels. Based on these findings, CT should be recommended to help in MS management specially for its potential benefits for improving physical function, but this was not the case for CoQ10 supplementation. Low dose CoQ10 supplementation (200 mg daily) or short duration of CoQ10 supplementation period (eight weeks) may have limited the possibility of observing CoQ10 effects on motor abilities and neurotrophic factors. Therefore, longer intervention periods and higher CoQ10 doses should be further investigated in future research. The absence of changes in NGF and BDNF levels may be due to the small sample size. Although we conducted an a priori analysis for samples size, we could not exclude the possibility of type II error in the present study. Consequently, studies with larger samples might be needed to corroborate our findings. Other limitations that can be mentioned in this research are: the lack of precise control of activities outside the training protocol and drugs used by these patients.

List of acronyms

1RM – one repetition maximum
6MW - 6-min walk
ANCOVA – analysis of covariance
BDNF – brain derived neurotrophic factor
CoQ10 – Coenzime Q19
CT - concurrent training
MS – multiple sclerosis
NGF – nerve growth factor
TUG - timed up and go

Contributions of Authors

Conceptualization, AHH and AA; methodology, AHH, AA, RA, KN, BBR, HS; formal analysis, AHH, AA, RA, KN, BBR, HS; writing—original draft preparation, AHH, AA, AC, RA, KN, BBR, HS, DS and PG —review and editing, AHH, AA, AC, RA, KN, BBR, HS, DS and PG; visualization, AHH, AA, AC, RA, KN, BBR, HS, DS and PG. Authors approved the final typescript.

Acknowledgments

We thanks all the participants of the study.

Funding

The authors received no specific funding for this work.

Conflict of Interest

The authors declare no financial, personal, or other conflicts of interest.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Corresponding Author

Paulo Gentil, Av. Esperança, s/n - Chácaras de Recreio Samambaia, Goiânia - GO, 74690-900 – Brasil.
Phone/Fax: +55 62 3521-1141
ORCHID iD: 0000-0003-2459-4977
E-mail: paulogentil@hotmail.com

E-mails and ORCID iD of co-authors

Amir Hossein Haghighi: ah.haghighi@hsu.ac.ir
ORCID iD: 0000-0002-7258-9737
Amin Ahmadi: amin.ahmadi83@gmail.com
Antonio Carotenuto: carotenuto.antonio87@gmail.com
ORCID iD: 0000-0002-1574-9693
Roya Askari: r.askari@hsu.ac.ir
ORCID iD: 0000-0003-4331-2293
Karim Nikkhah: nikkhahk@mums.ac.ir
Behnam Bagherzadeh-Rahmani: b.bagherzadehrahmani@hsu.ac.ir
ORCID iD: 0000-0001-9900-0833
Hadi Shahrabadi: h.shahrabadi@gmail.com
ORCID iD: 0000-0001-8404-6927
Daniel Costa Souza: daniel_souza86@hotmail.com
ORCID iD: 0000-0003-0626-1466

References

1. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. N Engl J Med. 2000 Sep 28;343(13):938-52. doi: 10.1056/NEJM200009283431307. PMID: 11006371.
2. Filippi M, Bar-Or A, Piehl F, Preziosa P, Solari A, Vukusic S, Rocca MA. Multiple sclerosis. Nat Rev Dis Primers. 2018 Nov 8;4(1):43. doi: 10.1038/s41572-018-0041-4. Erratum in: Nat Rev Dis Primers. 2018 Nov 22;4(1):49. PMID: 30410033.
3. Riccio P, Rossano R. Nutrition facts in multiple sclerosis. ASN Neuro. 2015 Feb 18;7(1):1759091414568185. doi: 10.1177/1759091414568185. PMID: 25694551; PMCID: PMC4342365.
4. Bagur MJ, Murcia MA, Jiménez-Monreal AM, Tur JA, Bibiloni MM, Alonso GL, Martínez-Tomé M. Influence of Diet in Multiple Sclerosis: A Systematic Review. Adv Nutr. 2017 May 15;8(3):463-472. doi: 10.3945/an.116.014191. PMID: 28507011; PMCID: PMC5421121.
5. Marx W, Hockey M, McGuinness AJ, Lane M, Christodoulou J, van der Mei I, Berk M, Dean OM, Taylor B, Broadley S, Lechner-Scott J, Jacka FN, Lucas RM, Ponsonby AL; RELIEF Trial team. The effect of emerging nutraceutical interventions for clinical and biological outcomes in multiple sclerosis: A systematic review. Mult Scler Relat Disord. 2020 Jan;37:101486. doi: 10.1016/j.msard.2019.101486. Epub 2019 Nov 2. PMID: 31707234.
6. Riccio P, Rossano R. Nutrition facts in multiple sclerosis. ASN Neuro. 2015 Feb 18;7(1):1759091414568185. doi: 10.1177/1759091414568185. PMID: 25694551; PMCID: PMC4342365.
7. El-Laithy NA, Mahdy EME, Youness ER, Shafee N, Mowafy MSS, Mabrouk MM. Effect of co enzyme Q10 alone or in combination with vitamin C on Lipopolysaccharide-induced brain injury in rats. Biomedical and Pharmacology Journal. 2018;11(3):1215–26.
8. Yang L, Calingasan NY, Wille EJ, Cormier K, Smith K, Ferrante RJ, Beal MF. Combination therapy with coenzyme Q10 and creatine produces additive neuroprotective effects in models of Parkinson's and Huntington's diseases. J Neurochem. 2009 Jun;109(5):1427-39. doi: 10.1111/j.1471-4159.2009.06074.x. Epub 2009 Mar 28. PMID: 19476553; PMCID: PMC2866530.
9. Sanoobar M, Eghtesadi S, Azimi A, Khalili M, Jazayeri S, Reza Gohari M. Coenzyme Q10 supplementation reduces oxidative stress and increases antioxidant enzyme activity in patients with relapsing-remitting multiple sclerosis. Int J Neurosci. 2013 Nov;123(11):776-82. doi: 10.3109/00207454.2013.801844. Epub 2013 Jun 17. PMID: 23659338.
10. Moccia M, Capacchione A, Lanzillo R, Carbone F, Micillo T, Perna F, De Rosa A, Carotenuto A, Albero R, Matarese G, Palladino R, Brescia Morra V. Coenzyme Q10 supplementation reduces peripheral oxidative stress and inflammation in interferon-β1a-treated multiple sclerosis. Ther Adv Neurol Disord. 2019 Feb 18;12: 1756286418819074. doi: 10.1177/1756286418819074. PMID: 30815035; PMCID: PMC6381428.
11. Halabchi F, Alizadeh Z, Sahraian MA, Abolhasani M. Exercise prescription for patients with multiple sclerosis; potential benefits and practical recommendations. BMC Neurol. 2017 Sep 16;17(1):185. doi: 10.1186/s12883-017-0960-9. PMID: 28915856; PMCID: PMC5602953.
12. Oken BS, Kishiyama S, Zajdel D, Bourdette D, Carlsen J, Haas M, Hugos C, Kraemer DF, Lawrence J, Mass M. Randomized controlled trial of yoga and exercise in multiple sclerosis. Neurology. 2004 Jun 8;62(11):2058-64. doi: 10.1212/01.wnl.0000129534.88602.5c. PMID: 15184614.
13. Dalgas U, Stenager E, Jakobsen J, Petersen T, Hansen HJ, Knudsen C, Overgaard K, Ingemann-Hansen T. Resistance training improves muscle strength and functional capacity in multiple sclerosis. Neurology. 2009 Nov 3;73(18):1478-84. doi: 10.1212/WNL.0b013e3181bf98b4. PMID: 19884575.
14. Molteni R, Zheng JQ, Ying Z, Gómez-Pinilla F, Twiss JL. Voluntary exercise increases axonal regeneration from sensory neurons. Proc Natl Acad Sci U S A. 2004 Jun 1;101(22):8473-8. doi: 10.1073/pnas.0401443101. Epub 2004 May 24. PMID: 15159540; PMCID: PMC420418.
15. Briken S, Rosenkranz SC, Keminer O, Patra S, Ketels G, Heesen C, Hellweg R, Pless O, Schulz KH, Gold SM. Effects of exercise on Irisin, BDNF and IL-6 serum levels in patients with progressive multiple sclerosis. J Neuroimmunol. 2016 Oct 15;299:53-58. doi: 10.1016/j.jneuroim.2016.08.007. Epub 2016 Aug 5. PMID: 27725121.
16. Abbaspoor E, Zolfaghari M, Ahmadi B, Khodaei K. The effect of combined functional training on BDNF, IGF-1, and their association with health-related fitness in the multiple sclerosis women. Growth Horm IGF Res. 2020 Jun;52:101320. doi: 10.1016/j.ghir.2020.101320. Epub 2020 Apr 2. PMID: 32305012.
17. Grazioli E, Tranchita E, Borriello G, Cerulli C, Minganti C, Parisi A. The Effects of Concurrent Resistance and Aerobic Exercise Training on Functional Status in Patients with Multiple Sclerosis. Curr Sports Med Rep. 2019

Dec;18(12):452-457. doi: 10.1249/JSR.0000000 000000661. PMID: 31834177.
18. Keytsman C, Hansen D, Wens I, Eijnde BO. Impact of high-intensity concurrent training on cardiovascular risk factors in persons with multiple sclerosis - pilot study. Disabil Rehabil. 2019 Feb;41(4):430-435. doi: 10.1080/09638288.2017.1395086. Epub 2017 Oct 27. PMID: 29076386.
19. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, Correale J, Fazekas F, Filippi M, Freedman MS, Fujihara K, Galetta SL, Hartung HP, Kappos L, Lublin FD, Marrie RA, Miller AE, Miller DH, Montalban X, Mowry EM, Sorensen PS, Tintoré M, Traboulsee AL, Trojano M, Uitdehaag BMJ, Vukusic S, Waubant E, Weinshenker BG, Reingold SC, Cohen JA. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018 Feb;17(2):162-173. doi: 10.1016/S1474-4422(17)30470-2. Epub 2017 Dec 21. PMID: 29275977.
20. Astrand I, Astrand PO, Christensen EH, Hedman R. Intermittent muscular work. Acta Physiol Scand. 1960 Apr 25;48:448-53. doi: 10.1111/j.1748-1716.1960.tb01879.x. PMID: 13794890.
21. Brzycki M. Strength Testing—Predicting a One-Rep Max from Reps-to-Fatigue. J Phys Educ Recreat Dance. 1993;64(1):88–90.
22. Kjølhede T, Vissing K, Dalgas U. Multiple sclerosis and progressive resistance training: a systematic review. Mult Scler. 2012 Sep;18(9):1215-28. doi: 10.1177/1352458512437418. Epub 2012 Apr 24. PMID: 22760230.
23. Petajan JH, Gappmaier E, White AT, Spencer MK, Mino L, Hicks RW. Impact of aerobic training on fitness and quality of life in multiple sclerosis. Ann Neurol. 1996 Apr;39(4):432-41. doi: 10.1002/ana.410390405. PMID: 8619521.
24. Bahari F, Naghdi N, Sheikh M, Shaw BS. Effect of physical exercise on muscle strength, static and dynamic balance and resiliency in women with multiple sclerosis. South African Journal for Research in Sport, Physical Education & Recreation. 2021;43(1):1–11.
25. Medina-Perez C, de Souza-Teixeira F, Fernandez-Gonzalo R, de Paz-Fernandez JA. Effects of a resistance training program and subsequent detraining on muscle strength and muscle power in multiple sclerosis patients. NeuroRehabilitation. 2014;34(3):523-30. doi: 10.3233/NRE-141062. PMID: 24463236.
26. Kalron A, Achiron A, Dvir Z. Muscular and gait abnormalities in persons with early onset multiple sclerosis. J Neurol Phys Ther. 2011 Dec;35(4):164-9. doi: 10.1097/NPT.0b013e31823801f4. PMID: 22052130.
27. Dalgas U, Stenager E, Lund C, Rasmussen C, Petersen T, Sørensen H, Ingemann-Hansen T, Overgaard K. Neural drive increases following resistance training in patients with multiple sclerosis. J Neurol. 2013 Jul;260(7):1822-32. doi: 10.1007/s00415-013-6884-4. Epub 2013 Mar 13. PMID: 23483214.
28. Filipi ML, Leuschen MP, Huisinga J, Schmaderer L, Vogel J, Kucera D, et al. Impact of Resistance Training on Balance and Gait in Multiple Sclerosis. Int J MS Care. 2010 Apr;12(1):6–12.
29. Silva MH, Andre Barbosa De Lira C, Steele J, Fisher JP, Mota JF, Gomes AC, Gentil P. Cycle ergometer training and resistance training similarly increase muscle strength in trained men. J Sports Sci. 2022 Mar;40(5):583-590. doi: 10.1080/02640414.2021.2005282. Epub 2021 Nov 18. PMID: 34789054.
30. DeBolt LS, McCubbin JA. The effects of home-based resistance exercise on balance, power, and mobility in adults with multiple sclerosis. Arch Phys Med Rehabil. 2004 Feb;85(2):290-7. doi: 10.1016/j.apmr.2003.06.003. PMID: 14966716.
31. Hortobágyi T, Ács P, Baumann P, Borbély G, Áfra G, Reichardt-Varga E, Sántha G, Tollár J. Comparative Effectiveness of 4 Exercise Interventions Followed by 2 Years of Exercise Maintenance in Multiple Sclerosis: A Randomized Controlled Trial. Arch Phys Med Rehabil. 2022 Oct;103(10):1908-1916. doi: 10.1016/j.apmr.2022.04.012. Epub 2022 May 16. PMID: 35584738.
32. Kasser SL, Jacobs JV, Sibold J, Marcus A, Cole L. Using Body-Worn Sensors to Detect Changes in Balance and Mobility After Acute Aerobic Exercise in Adults with Multiple Sclerosis. Int J MS Care. 2020 Jan-Feb;22(1):1-6. doi: 10.7224/1537-2073.2018-073. PMID: 32123522; PMCID: PMC7041613.
33. Wong VL, Holahan MR. A systematic review of aerobic and resistance exercise and inflammatory markers in people with multiple sclerosis. Behav Pharmacol. 2019 Dec;30(8):653-660. doi: 10.1097/FBP.0000000000000514. PMID: 31703029.
34. Tollár J, Nagy F, Tóth BE, Török K, Szita K, Csutorás B, Moizs M, Hortobágyi T. Exercise Effects on Multiple Sclerosis Quality of Life and Clinical-Motor Symptoms. Med Sci Sports Exerc. 2020 May;52(5):1007-1014. doi: 10.1249/MSS.0000000000002228. PMID: 31876670.
35. Cakt BD, Nacir B, Genç H, Saraçoğlu M, Karagöz A, Erdem HR, Ergün U. Cycling progressive resistance training for people with multiple sclerosis: a randomized controlled study. Am J Phys Med Rehabil. 2010 Jun;89(6):446-57. doi:

10.1097/PHM.0b013e3181d3e71f. PMID: 20216060.
36. Gutierrez GM, Chow JW, Tillman MD, McCoy SC, Castellano V, White LJ. Resistance training improves gait kinematics in persons with multiple sclerosis. Arch Phys Med Rehabil. 2005 Sep;86(9):1824-9. doi: 10.1016/j.apmr.2005.04.008. PMID: 16181949.
37. Filipi ML, Leuschen MP, Huisinga J, Schmaderer L, Vogel J, Kucera D, et al. Impact of Resistance Training on Balance and Gait in Multiple Sclerosis. Int J MS Care. 2010;15(SUPPL.1):24–33.
38. Abbaspoor E, Zolfaghari M, Ahmadi B, Khodaei K. The effect of combined functional training on BDNF, IGF-1, and their association with health-related fitness in the multiple sclerosis women. Growth Horm IGF Res. 2020 Jun;52:101320. doi: 10.1016/j.ghir.2020.101320. Epub 2020 Apr 2. PMID: 32305012.
39. Khademosharie M, Tadibi V, Behpoor N, Hamedinia MR. The effect of 12-weeks concurent training on the serum levels NGF, BDNF, and VDBP in women with multiple sclerosis. International journal of applied exercise physiology. 2018;7(1):77–86.
40. Ozkul C, Guclu-Gunduz A, Irkec C, Fidan I, Aydin Y, Ozkan T, Yazici G. Effect of combined exercise training on serum brain-derived neurotrophic factor, suppressors of cytokine signaling 1 and 3 in patients with multiple sclerosis. J Neuroimmunol. 2018 Mar 15;316:121-129. doi: 10.1016/j.jneuroim.2018.01.002. Epub 2018 Jan 3. PMID: 29329698.
41. Wens I, Keytsman C, Deckx N, Cools N, Dalgas U, Eijnde BO. Brain derived neurotrophic factor in multiple sclerosis: effect of 24 weeks endurance and resistance training. Eur J Neurol. 2016 Jun;23(6):1028-35. doi: 10.1111/ene.12976. Epub 2016 Mar 16. PMID: 26992038.
42. Moccia M, Capacchione A, Lanzillo R, Carbone F, Micillo T, Perna F, De Rosa A, Carotenuto A, Albero R, Matarese G, Palladino R, Brescia Morra V. Coenzyme Q10 supplementation reduces peripheral oxidative stress and inflammation in interferon-β1a-treated multiple sclerosis. Ther Adv Neurol Disord. 2019 Feb 18;12:1756286418819074. doi: 10.1177/1756286418819074. PMID: 30815035; PMCID: PMC6381428.

Disclaimer

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

Submission: February 12, 2023
Revision received: March 7, 2023
Accepted for publication: March 7, 2023