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Combined endurance and resistance training in women with multiple sclerosis, strength, fatigue and psychological responses: a randomized controlled trial.

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Multiple Sclerosis is a severe disease of the central nervous system that affects quality of life of the patients. The main aim of this work is to find new strategies to enhance quality of life by the improvement of muscles resistance and endurance in people with Multiple Sclerosis.

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ABSTRACT

COMBINED ENDURANCE AND RESISTANCE TRAINING IN WOMEN WITH MULTIPLE SCLEROSIS, STRENGTH, FATIGUE AND PSYCHOLOGICAL RESPONSES: A RANDOMIZED CONTROLLED TRIAL.

Background and Purpose

Persons with multiple sclerosis (MS) suffer from strength deficit and muscle mass reduction as expression of central motor areas/pathways demyelization lesions that are implicated in motor function. The loss of function and inactivity lead to a reduction of the work and daily activity, which is frequently associated with depression and other psychological diseases leading to a decline of the quality of life.

First aim of this study was to evaluate the effects of a 12-week endurance and strength combined program training on maximal strength, functional capacities and fatigue in women with multiple sclerosis. Therefore, secondary aim was to study the quality of life and psychological outcomes of the participants after the training.

Methods

Sixteen women with MS (mean age 46±7.2; EDSS 2.25±0.85) were randomized to either a combined training (COM) or waitlist group (WTL). All the participants performed 8 physical tests: body composition with bioelectrical impedance analysis, flexibility with Sit and Reach test (S&R), isometric strength with Handgrip test (HG), maximum dynamic strength with 1 Repetition Max test (1RM) for Legs, Chest and Back, Maximal Voluntary Isometric Contraction (MVIC) with Muscle Lab© force sensor for legs and VO_{2peak} with an incremental test on a cycle-ergometer. Fatigue was measured with MFIS-21 questionnaire, Quality of life (QoL) with MSQOL-54, psychological condition with SCL-90 and depression with BDI-2. The tests were performed at baseline (T0), after 12 weeks

(T1), at the end of the combined protocol for WTL and follow-up for COM (T2) and after 12 weeks from the end of intervention for WTL (T3).

The COM group performed 2 times a week for 12 weeks a protocol of supervised combined training. The WTL group began the same combined training intervention, after a 12-week period of habitual lifestyle. Every session lasted 60 minutes and was structured by 3 resistance exercises for body portions (lower, high portion and torso) and 20 minutes of High Intensity Interval Training (HIIT) endurance training.

Results

At the end of the training MVIC improved (+113.4; p=.002; N•m), similarly 1RM increased significantly in Leg Extension and Chest Press (+13.8; p=.001; +6.6; p=.002; Kg). VO_{2peak} increased from 17.5±4.67 to 22±5.93 (p=.02; ml/kg/min). Fatigue decreased significantly in all subscales (Physical -9; p=.003, Cognitive -5; p=.02, Psychosocial -2; p=.005) and depression symptom enhanced from 15.6 to 10.3 points (p<.001) and Quality of life improved significantly in "cognitive function" (p=.01) and "physical health" (p=.005).

Discussion and Conclusion

12 weeks of combined endurance and resistance training increased strength and oxygen consumption in people with MS. The training was also effective to reduce fatigue and depression and to enhance quality of life. A tailored and supervised training should be recommended to people with MS because is safe and effective way of improving fitness in people with MS.

Keywords: *Multiple Sclerosis, Combined Training, Strength, Fatigue, Depression.*

Introduction

Multiple Sclerosis (MS) is an inflammatory and demyelization disease of the central nervous system[1]. MS is characterized by the loss of motor and sensory function such as the consequence of immune-mediated inflammation, demyelination and consequent axonal damages[2,3]. This condition impacts negatively on patients' quality of life[4].

It's common that persons with MS suffer from strength deficit and muscle mass reduction as expression of central motor areas/pathways demyelization lesions that are implicated in motor function[5–11].

Nowadays it's unclear if these modifications are caused by disease pathophysiology, by the muscles' disuse or both. Previous studies on the mankind showed discordant data and the knowledge about translational research still insufficient. The cause could be related to poor evidence on the muscular system of MS animal model.

In the animal model, the muscular modifications are different between the different disease stages: in the initial stage, there is a modification of the mitochondrial function, instead in the advanced stage, we can see a structural modification of the muscular tissue with a neurogenic origin[12].

A lot of scientific evidence confirm that the modifications in the patients with MS are both central and peripheral (muscular), during and at the end of the physical activity. Examples of these alterations are: incomplete recruitment of the motor unit[11,13], asymmetric recruitment[14], muscular contraction slowness[7], reduction of the oxidative capacity[13]; stimulation-contraction response and muscular cell metabolism alteration[11,13]. Therefore, patients with MS develop an atrophy of the muscular cross sectional area (CSA)[5,8,15]. Accordingly, the recovery of the muscular function could be affected by the alterations of the normal muscular structure. Moreover, physical activity habits differ between patients with MS and healthy subjects. A possible explanation could be the feeling of fatigue that persons with MS refer as increased weakness with exercise and an abnormal sense of tiredness[16–18]. This condition could be the reason for a low physical activity level. Actually, only 20% of patients reach the daily physical activity levels of moderate intensity, instead of 40% of the healthy subjects[19–21]. Then, the recovery of muscular function could be compromised also by the muscular disuse. A study of Mostert and Kesselring (2002) shows that the muscular disuse is caused by the strength and endurance reduction[22], with a decrease of the muscular mass[10].

The loss of function and inactivity lead to a reduction of the work and daily activity. The main problem in this framework is the decline of the quality of life of the patients, frequently, it's associated with depression and other psychological diseases[23,24].

The compromising of muscular function is both related to the disease and to the lack of physical activity. For this reason, strength training could be useful to partially recover muscular function, to enhance resistance, endurance and physical activity level. In particular strength training has been proven effective to improve also flexibility and electromyographic activity with an increase of the fiber volume and a reduction of fatigue perception[25–28]. In adjunction there are evidences of endurance training and improvement of maximal oxygen consumption and strength[24].

Exercise evidence in MS

Resistance Training

A consequence of MS demyelination of the central motor system is also the reduction of muscle mechanical function as isometric strength, dynamic strength, explosive strength and muscle power[29–32]. Previous studies show that a reduction of strength in lower extremity muscles negatively influences balance, walking performance, stair climbing and sit-to-stand ability[32–36]. This could be the main reason to lower physical activity levels observed in persons with MS compared to healthy controls[37,38]. A possible solution to increase muscle mechanical function could be the progressive resistance training (PRT). Latest reviews show a positive effect of PRT on muscle function as isometric and dynamic strength[39,40]. Moreover, a review of Jørgensen MLK et al. (2017), showed that PRT program is well tolerated in person with MS and improves Maximal voluntary isometric contraction (MVIC) and Maximal voluntary dynamic contraction (MVDC) with dropout rates generally below 20% and an adherence above 90% [41]. As reported in a study of Dalgas U et al. (2010), after 12 weeks of PRT, muscle cross-sectional area (CSA) increased at the fiber level (for all types of fiber)[42], while a study of Fimland M et al. (2010), showed that 3 weeks of PRT are effective to enhance EMG activity and V-wave amplitude in the muscle, indicating an improve in neural efferent output and an increases in motor unit recruitment frequency and excitability[43].

High intensity interval training (HIIT)

In people with multiple sclerosis (pwMS) the cardiovascular fitness is lower compared to healthy subjects and it's inversely correlated with disease severity[44,45]. Moreover, a high level of aerobic capacity could prevent MS comorbidity like cardiovascular and metabolic diseases and helps to reduce fatigue perception and to improve daily activity level and walking autonomy[4,21,22,34,46]. For this reason, an efficient aerobic training in MS is crucial. HIIT is an aerobic training that is structured by alternating bursts of exercise at high intensity with working rests at low intensity[47].

Previous studies demonstrated that HIIT is safe in healthy subjects as in people with different diseases, as coronary artery disease, heart failure, Parkinson and Multiple Sclerosis[48–50].

Compared to continuous aerobic training, HIIT is more efficient in improving VO_{2max} and more enjoyable[47,49,51].

Additionally, HIIT is more suitable for pwMS because is required less time to achieve similar energy expenditure and comparable benefits of continuous training[52]. A study of Dalgas et al. (2008)

recommends HIIT as a feasible and effective intervention for pwMS because it allows people to exercise at higher intensities avoiding thermosensitive reactions[53].

Endurance and resistance combined training

Endurance and resistance combined training (ERCT) was previously investigated in MS by Kerling A et al. (2015) with a randomized controlled trial. After 3 months of ERCT program with two 40-min-session per week, participants increased their aerobic capacity, strength and quality of life. Moreover, their total fatigue score decreased significantly[54]. A study of Deckx N et al. (2016) showed potential benefits of ERCT on inflammation markers in person with MS. After a 12-week ERCT program, it was reported a reduction in secretion of inflammatory mediators and an increase in immunoregulatory function[55].

Despite previous studies showed a positive effect of the combination of these two kinds of training together on strength and aerobic capacity[5,56], little is known about the positive effects of psychological outcomes as depression, cognitive function, fatigue, mental health and quality of life [21,24,54].

Aim

First aim of this study was to evaluate the effects of a 12-week endurance and strength combined program training (ERCT) on maximal strength, functional capacities and fatigue in women with MS. Therefore, secondary aim was to study the quality of life and psychological outcomes of the participants after the training.

A follow up three months after the end of the training verified long-term effects of the protocol.

Methods

Participants

Women with MS were recruited from the MS Centre of the IRCCS C. Mondino in Pavia during the period from September 2017 to February 2018.

Inclusion criteria were:

• female gender;

• 18–50 years;

• definite MS diagnosis according to the McDonald criteria[57];

• mild to moderate neurological disability due to MS, that is Expanded Disability Status Scale (EDSS) score of <4 with a 'pyramidal functions' sub-score of 1 to 3[58];

• being able to train twice a week.

Exclusion criteria were:

• co-morbidities preventing participation (i.e. cardiovascular-, respiratory-, orthopedic or metabolic diseases);

• pacemaker (or another metallic implant);

• pregnancy;

• clinical MS relapse within an eight-week period prior to inclusion;

• participation in systematic physical activity three months prior to inclusion.

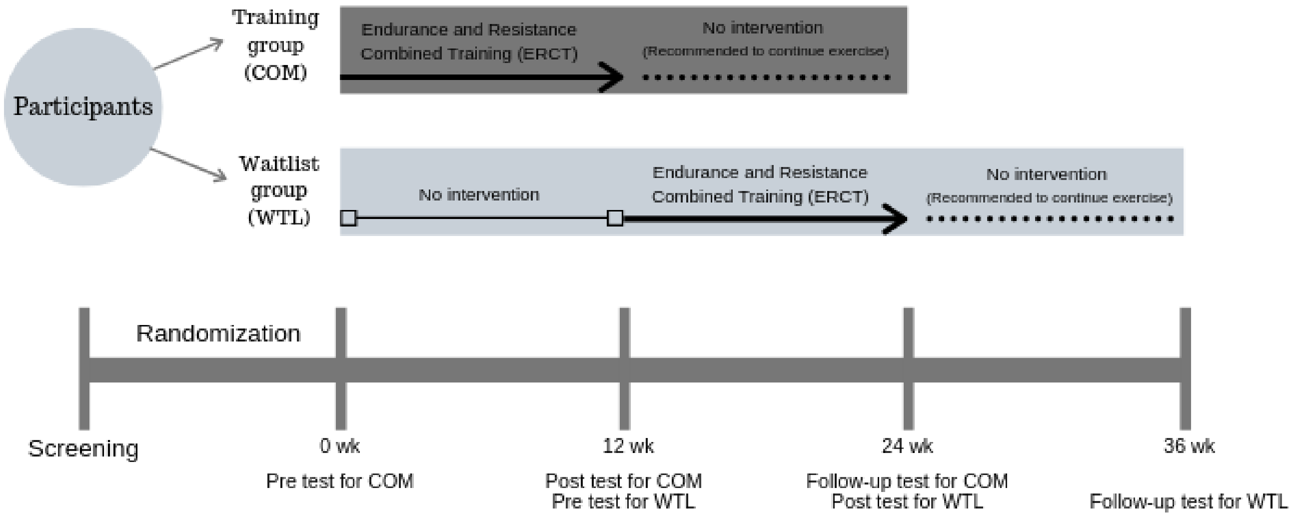
Study design

Following inclusion and baseline testing, MS patients were randomized to either a combined training (COM) or waitlist group (WTL). Randomization was assessed using a random number generation procedure by an independent biostatistician. The training intervention consisted of 12 weeks of 2 times/week supervised training program aimed to increase the strength of major muscle groups and to improve cardiorespiratory fitness. Every session lasted 60 minutes of ERCT. Training sessions were interspersed by at least one day of rest, to ensure adequate recovery.

This study was designed to ensure the largest participation from pwMS allowing each group to attend the training (fig. 1). The COM group performed 2 times a week for 12 weeks a protocol of supervised combined training. The WTL group began the same combined training intervention, after a 12-week period of habitual lifestyle. All the participants performed 8 physical tests: body composition with bioelectrical impedance analysis , flexibility with Sit and Reach test (S&R), isometric strength with Handgrip test (HG), maximum dynamic strength with 1 Repetition Max test (1RM) for Legs, Chest and Back, Maximal Voluntary Isometric Contraction with Muscle Lab© force sensor (MVIC) for legs and VO_{2peak} with an incremental test on a cycle-ergometer. Fatigue was measured with MFIS-21 questionnaire, Quality of life (QoL) with MSQOL-54, psychological condition with SCL-90 and depression with BDI-2. The tests were performed at baseline (T0), after 12 weeks (T1), at the end of the combined protocol for WTL and follow-up for COM (T2) and after 12 weeks from the end of intervention for WTL (T3).

The COM group performed 2 times a week for 12 weeks a protocol of supervised combined training. The WTL group began the same combined training intervention, after a 12-week period of habitual lifestyle. Every session lasted 60 minutes and was structured by 3 resistance exercises for body portions (lower, high portion and torso) and 20 minutes of High Intensity Interval Training (HIIT) endurance training.

Figure 1. Study design.



Intervention

Exercise protocol

Every session started with a 5-minutes warm-up at 50% of heart resting rate (HRR) followed by 25 minutes of steady state at 70% of HRR or High Intensity Interval Training (HIIT) alternating low (50%HRR) and high (70%HRR) intensity every minute both performed on treadmill or cycle-ergometer (fig. 2) depending on participants' aptitudes. The session continued with 30 minutes of resistance training composed by calisthenics, lightweights and elastic band exercises of both peripheral and main muscle groups (fig. 2). Each resistance training was structured by 3 exercises for body portions (lower body, upper body and trunk) with 8-10 repetitions and 3 sets. Loads were determined with the number of repetitions for calisthenics, weight for lightweight and resistance of elastic band exercises. Once patients were able to easily complete 12 consecutive repetitions of an exercise, the load or resistance were increased with the purpose to keep the training intensity on a target level.

In order to ensure an optimal condition and to avoid injuries, mobility was performed at the beginning of the session and stretching at the end. Every 3 weeks the endurance session was alternatively upgraded with an increase of 5% of intensity or 10 minutes length.

Characteristics of exercise protocol are shown in table 1.

Table 1. Exercise protocol.

Combined	Exercise	Duration	Intensity	Repetitions
Endurance Training	Steady State or HIIT	25 min.	50% to 70% HRR	
Resistance Training	Circuit Training	30 min.	8-10 RM	8-10 for each exercise

Circuit Training exercises (3 exercises for portion per 2 sets; 30 sec. rest between sets)		
Lower body	**Upper body**	**Trunk**
Squats; Isometric Wall Squat (30 sec.) and Lounges	Horizontal Adduction with elastic bands; Push-up and Triceps push-down	Rowing with elastic bands; Tractions with rigid bands and Curl Biceps with elastic bands

Figure 2. Examples of endurance and resistance exercises of the protocol.

Outcome Measures

Primary outcome

Maximal Voluntary Isometric Contraction (MVIC): MVIC was performed using Muscle Lab© force sensor. The knee extension isometric test was performed using knee extension weight training machine locked at the knee angle of 90° (Leg extension G7-S71; Matrix fitness, Ascoli Piceno, Italy). The test was performed in each single leg and both together. On a given signal, the subject extended knee as quickly and forcefully as possible.

Secondary outcomes

Maximal muscle strength: According to the procedure described by ACSM[59] (American College of Sport and Medicine) were performed 3 tests to assess 1 repetition maximum (1RM) of the major muscular groups (femoral quadriceps, pectoral and dorsal). To perform these tests, we used isotonic machines: Leg extension, Pectoral and Rowing machine (Matrix fitness, Ascoli Piceno, Italy) and we used prediction formula by Baechle et al. (2000)[60,61] to calculate the exact maximum load.

Aerobic capacity: A maximal incremental test was performed to test the aerobic capacity following the protocol of Heine et al.[45] on a cycle-ergometer (R5x cycle; Matrix fitness, Ascoli Piceno, Italy). The peak of oxygen uptake (VO_{2peak}) was collected using a spirometric system (k5; Cosmed Roma, Italy). The test started with 3 minutes of warm-up at 25W, then the power output being increased by 10W per minute with a cadence of 60-80 rpm until the voluntary exhaustion.

Body Composition: Fat free mass and fat mass were estimate using the body impedance meter test (BIA 101, Akern-RJL, Firenze, Italy) in supine position, according to guidelines of the National Institute of Health Consensus Statement. The parameters of body composition were analysed using BODY-GRAM software (Plus 1.0®).

Fatigue: To evaluate the fatigue we used the Modified Fatigue Impact Scale questionnaire (MFIS-21). MFIS is a short version of the Fatigue Impact Scale and assesses the influence of fatigue on physical, cognitive and psychosocial health through 21 questions[62]. Scores higher than 38 is defined as pathological.

Quality of life: Quality of life of the women was tested using the Multiple Sclerosis Quality of Life questionnaire (MSQOL-54)[63]. MSQOL-54 consists of an interview of 54 questions. The scores result in 12 subscales, 2 summary scores about physical and mental health and a total score of overall quality of life.

Psychological condition: To evaluate the psychological condition we used questionnaires for depression (Beck's Depression Inventory, BDI-2)[64] and psycho-pathological symptoms (Symptom Checklist, SCL-90)[65]. BDI-2 is a 21-item questionnaire and it consists of a series of statements related to symptoms of depression, each item is scored from 0 to 3 in terms of intensity. Values above 30 correspond to a severe depression. SCL-90 is an assessment tool for psychological problems and its scores result in 10 subscales and in a global score index.

Neurological disability: To evaluate the neurological disability we used the Expanded Disability Status Scale (EDSS) of *Kurtzke* and the Multiple Sclerosis Severity Score (MSSS). The EDSS range start from "0" (normal neurological condition) to "10" (death related to the disease), with intermediate levels of disability[58]. L. The MSSS is a tool to quantify the disability caused by the disease, the score is a results of an algorithm that combined together EDSS and years of the disease[66].

Statistical analysis

Sample size was calculated from the mean value of maximal voluntary isometric contraction (MVIC; the primary outcome) observed in person with MS[67]: 174,8 Nm (139 to 210 Nm) and assuming an increase of 15% after the 12-week of training, an alpha error of 0.05 and a 95% of power. From the result of 11 per group we added 2 persons (20%) to consider possible dropouts.

A Friedman test with post hoc tests (pairwise t-test comparisons and pairwise Wilcoxon) with significance correction (Bonferroni correction) was performed to assess the differences of MVIC between groups and time. We used Wilcoxon and t-test for paired data to analyze variables before (T0-COM and T1-WTL) and after the training period (T1-COM and T2-WTL) according to the parametric statistics assumptions. A p-value of less than 0.05 was considered a significant result. All analysis was conducted with R Core Team (2013) software.

Ethical aspects

The study respects the European norms for a good clinical practice, in accordance with the Helsinki declaration. Each subject was informed about the study and signed the consensus to process the personal data in anonymous and cumulative presentation by the decree N°101/18. The protocol was approved by the reference local Ethics Committee.

Results

A total of 26 women with MS were screened for eligibility and 21 met eligibility criteria and were randomized between February and March 2018. 16 out of 21 women completed the whole protocol and were analyzed (chart 1). Anthropometric data and disease characteristics of women are shown in table 2.

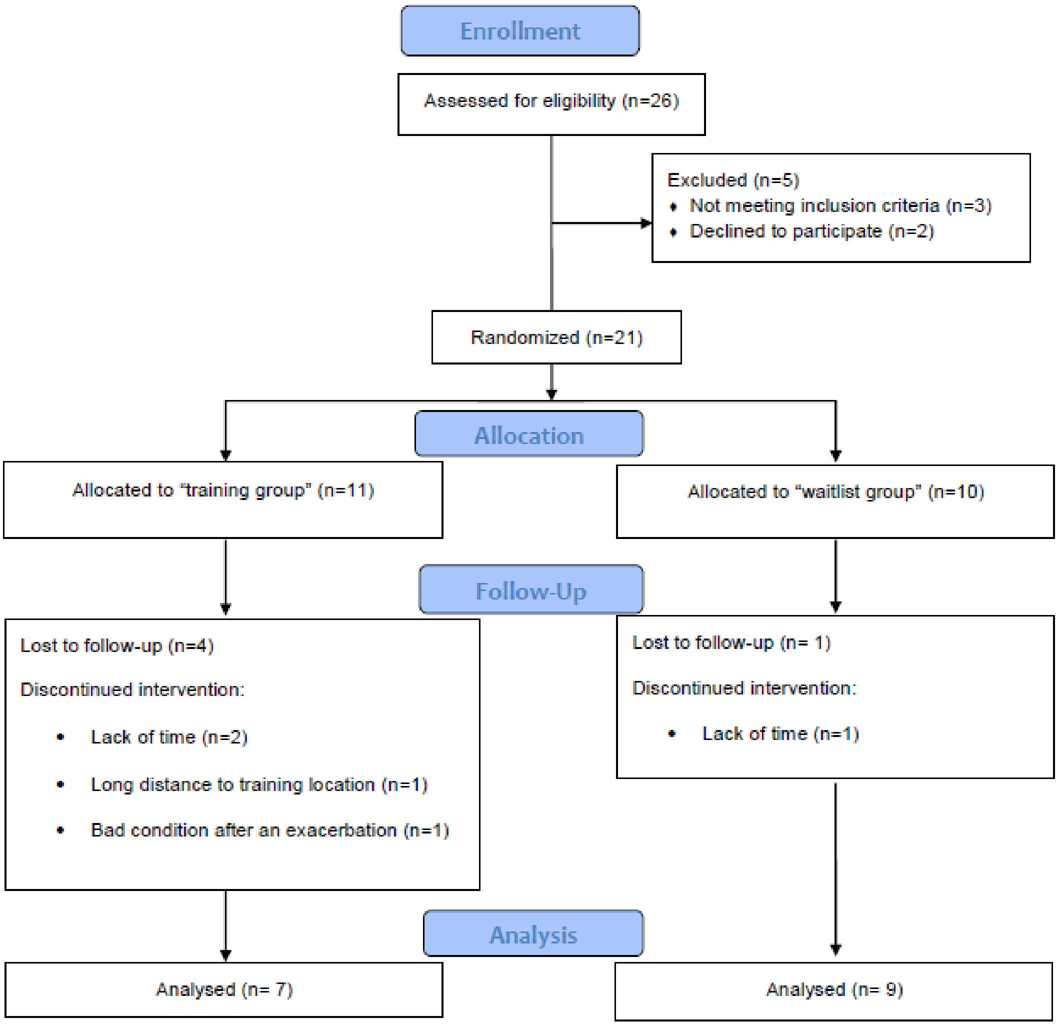


Chart 1 Enrollment flowchart and data lost at the end of the study.

Table 2 Anthropometric data and selected disease characteristics.

	Age (years)	Height (cm)	Weight (kg)	EDSS	Pyramidal FS	Sensitive FS	MSSS
COM (N=7)	43.14 ±8	1.61 ±0.08	51.93 ±8.13	2.5 ±1	1.71 ±0.95	1.57 ±0.98	3158.25 ±2063.50
WTL (N=9)	48.33 ±6	1.61 ±0.07	61.12 ±13.8	2 ±0.68	1.11 ±0.33	1.55 ±1.01	1860.57 ±1135.58
Total	46 ±7.25	1.61 ±0.07	57.1 ±11.88	2.25 ±0.83	1.3 ±0.71	1.5 ±0.96	2332.45 ±1574.60

Values are Mean±SD. No significant differences were found between groups for all variables (p>0.05).

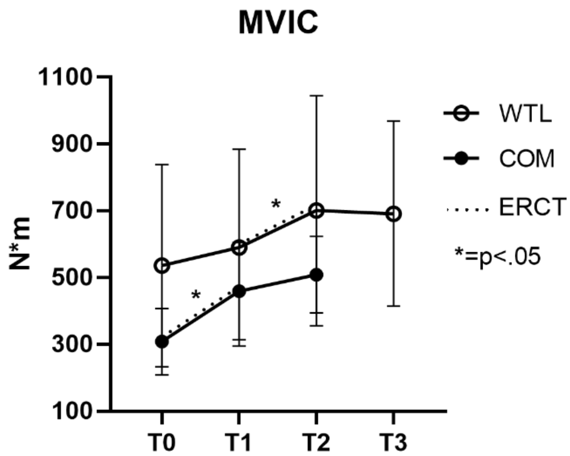


Figure 3 Maximal Voluntary Isometric Contraction (MVIC)

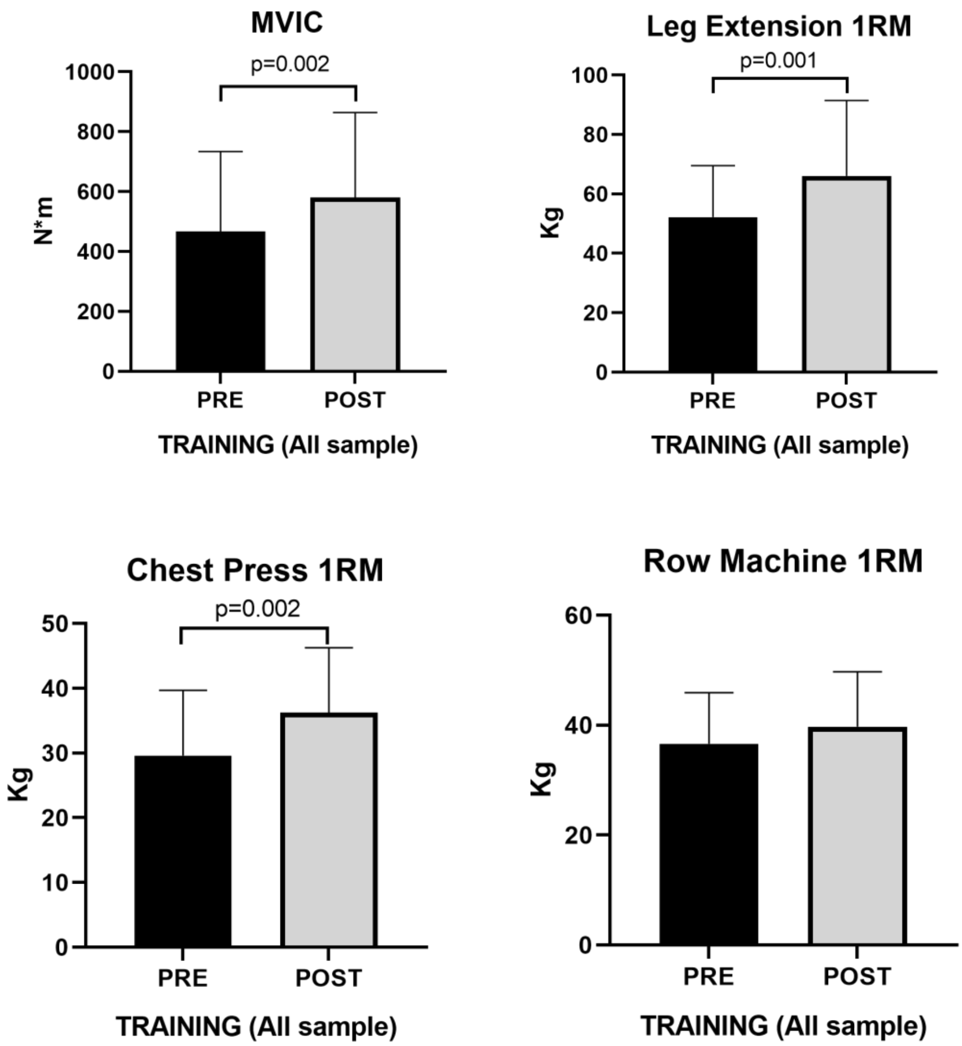
At first, we observed the primary outcome (MVIC) trend during the timeline of the study for both groups (fig. 3). In COM group the MVIC of the Quadriceps muscles started at 308.69±99.54 and after the 12 weeks of ERCT, the values increased at 459.70±145.51 N*m (p=0.015). Similarly, in WTL group, during the training values of MVIC increased from 590.27±294.58 to 701.38±344.59 N*m (p=0.038). These enhancements are statistically significant and show the efficacy of the training to improve isometric strength. Three months after the end of ERCT, the MVIC kept higher than the baseline in both groups.

Table 3 Physical performance before and after training protocol.

All sample (N=16)	Before Training	After Training	p-value
MVIC Leg Extension (N*m)	467.1±266.57 403 (262.6 - 540.5)	580.54±283.38 455.5 (379.4 -665.5)	0.002§
1RM Leg extension (Kg)	52.18±17.39 48 (44.5 - 57)	66±25.49 58.5 (51 - 73.25)	0.001†
1RM Chest Press (Kg)	29.62±10 29 (20 - 37.5)	36.21±10 37 (30.25 - 43.75)	0.002†
1RM Rowing Machine (Kg)	36.32±9.30 36 (32 - 40)	39.71±10 43 (37 - 44)	0.083§
Handgrip (Kg)	22.75±5.63 23 (18.25 - 28)	24.92±6.37 26 (17.75 - 29.75)	0.015†
VO2peak (ml/kg/min)	17.5±4.67 17 (14.9 - 18.6)	22±5.93 22 (18.2 - 24.4)	0.02§
Sit and Reach (cm)	4.93±13.2 3.5 (-6.5 - 16.25)	5.42±13.71 3.5 (-4.75 - 15)	0.796†

Values are mean±SD; median (25r-75r). §Wilcoxon test; †T-test.

Figure 4 Strength tests before and after exercise protocol.



Before and after the exercise protocol, we observed significant enhancements in almost all physical parameters except for 1RM in Rowing Machine and Sit and Reach (tab. 3). There was also a significant improvement in 1RM test in Leg Extension confirming that the strength increased also during isotonic contraction (fig. 4). The values of Leg Extension test before and after the 12-week training increased by +26.5% (p=0.001). In the same way, we observed an increased by +22.2% of

1RM in Chest Press test from 29.62±10 to 36.21±10 Kg (p=0.002). VO_{2peak} too increased significantly by 25.7% (p=0.02).

Table 4 Body composition.

COM	T0	T1	T2
Phase Angle°	5.99±0.99	5.87±1.07	6.68±1.22
Body cell mass index	8.30±1.12	8.19±0.78	9.03±0.90
Body cell mass	21.60±3.64	21.30±2.93	23.67±4.33
Fat free mass (Kg)	40.40±4.24	40.54±4.27	41.60±5.05
Fat mass (Kg)	11.53±4.59	10.33±5.46	10.47±5.39
Total body water	28.44±3.51	28.91±3.82	29.10±3.89
Extracellular water	13.10±1.83	13.59±2.74	12.55±2.03

WTL	T0	T1	T2	T3
Phase Angle°	5.52±0.69	5.50±0.99	5.27±0.41	5.51±0.43
Body cell mass index	8.18±0.97	8.38±1.29	8.27±0.83	8.38±0.87
Body cell mass	21.36±3.11	21.90±3.69	21.84±3.46	22.15±1.43
Fat free mass (Kg)	41.86±4.67	43.12±5.22	43.72±6.05	43.25±5.98
Fat mass (Kg)	19.25±9.56	18.53±9.08	20.54±8.78	20.04±8.82
Total body water	30.34±3.89	31.20±4.31	32.04±4.56	31.61±4.49
Extracellular water	14.65±1.99	15.14±2.56	15.77±2.11	15.20±2.14

Table 5 Psychological outcomes before and after training protocol.

All sample (N=16)	Before Training	After Training	p-value
Beck depression inventory (BDI-2) total	15.68±9.68	10.30±7.79	<0.001†
	16 (7 - 22.7)	9 (5 - 16)	
Symptom checklist (SCL-90)			
Somatization	1.24±0.70	0.76±0.51	0.002§
	1.2 (0.7 - 1.6)	0.7 (0.4 - 0.9)	
Obsession-compulsion	1.28±0.80	1.06±0.70	0.059†
	1.3 (0.6 – 2)	1.1 (0.4 - 1.3)	
Interpersonal sensibility	0.89±0.63	0.58±0.38	0.009§
	0.7 (0.4 - 1)	0.6 (0.3 - 0.7)	
Depression	1.09±0.79	0.87±0.56	0.221§
	0.8 (0.4 - 2)	0.7 (0.3 - 1.3)	
Anxiety	0.96±0.61	0.61±0.32	0.010†
	0.9 (0.4 - 1.5)	0.6 (0.4 - 0.7)	
Hostility	0.78±0.46	0.52±0.35	0.031†
	0.6 (0.5 - 1.1)	0.4 (0.3 - 0.6)	
Phobic anxiety	0.47±0.39	0.27±0.26	0.009§
	0.4 (0.1 - 0.7)	0.2 (0 - 0.5)	
Paranoid ideation	0.81±0.66	0.50±0.39	0.010§
	0.5 (0.4 - 1.5)	0.3 (0.1 - 0.8)	
Psychoticism	0.55±0.41	0.42±0.33	0.064§
	0.5 (0.2 - 0.8)	0.3 (0.2 - 0.6)	
Sleep disorder	1.56±1.10	1.26±0.81	0.120†
	1.3 (0.8 - 2.5)	1.1 (0.6 - 1.5)	
Global score index	0.95±0.52	0.68±0.32	0.006†
	0.8 (0.5 - 1.4)	0.7 (0.3 - 0.8)	

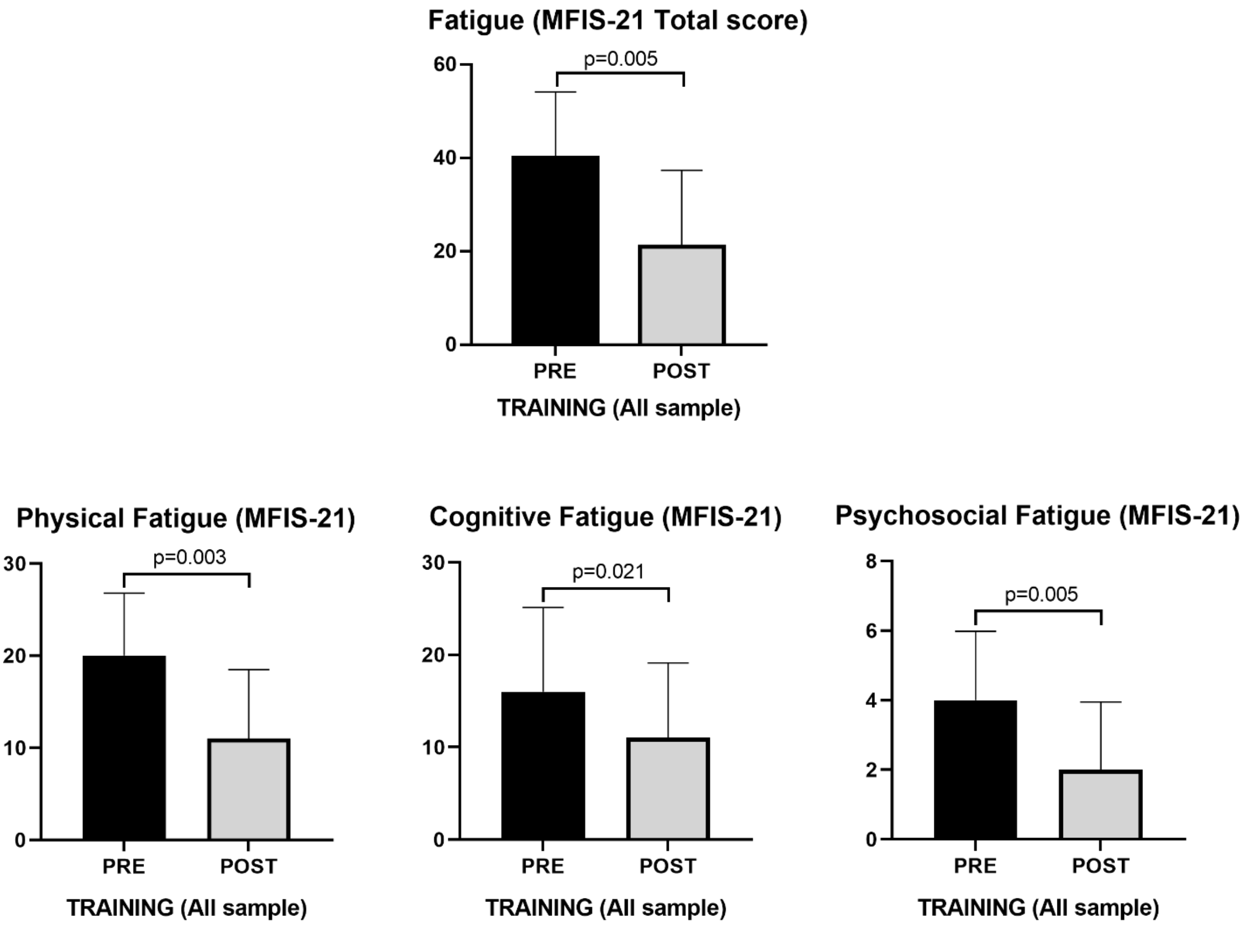
All sample (N=16)	Before Training	After Training	p-value
Modified Fatigue Impact Scale (MFIS-21)			
Cognitive	16±9.2	11±8.1	0.021†
	18 (10.7 - 23.2)	12.5 (3.2 - 16.7)	
Physical	20±6.7	11±7.4	0.003†
	19.5 (17 - 24)	10 (5.2 - 16.7)	
Psychosocial	4±1.98	2±1.95	0.005§
	4 (3 - 5)	2 (0 - 2)	
Total	40±14.19	21±16.37	0.0005†
	40.5 (34 - 49.7)	18 (9 - 33)	
Multiple Sclerosis Quality of Life (MSQOL-54)			
Physical limitation	62.18±37.98	69.23±37.01	
	75 (25 - 100)	75 (25 - 100)	
Emotional limitation	50±38.49	71±32.91	0.190§
	50 (24.9 - 75)	100 (33.3 - 100)	
Pain	67.25±35.20	74.86±27.67	0.563§
	84 (36.6 - 100)	85 (60 - 93.3)	
Emotional well-being	54.5±20.01	65.84±18.73	0.137†
	54 (39 - 70)	68 (52 - 76)	
Energy	44.25±19.94	53.53±22.71	0.254†
	42 (34 - 54)	40 (40 - 72)	
Health perception	49.68±22.61	53.84±21.99	0.795†
	45 (33.7 - 72.5)	50 (40 - 70)	
Social function	69.27±26.99	74.99±18.93	0.115†
	70.8 (64.6 - 91.6)	75 (58.3 - 83.3)	
Cognitive function	61.56±25.21	73.07±17.74	0.014†
	60 (50 - 80)	70 (55 - 85)	
Health distress	64.06±26.59	75.76±16.56	0.091†
	67.5 (52.5 - 81.2)	80 (65 - 85)	

All sample (N=16)	Before Training	After Training	p-value
Sexual function	71.89±27.70	75.01±23.81	0.547†
	83.3 (56.3 - 91.7)	83.3 (58.3 - 100)	
Change in health	46.87±22.12	61.53±26.25	0.105§
	50 (25 - 50)	50 (50 - 75)	
Sexual satisfaction	56.25±26.61	59.61±24.01	0.532§
	75 (50 - 75)	50 (50 - 75)	
Physical health	57.18±22.21	71.92±22.59	0.005§
	61 (49.5 - 75.3)	67.3 (61.3 - 78.4)	
Mental Health	48.47±18.02	59.77±14.64	0.056§
	45.5 (34.4 - 62.8)	64 (44.8 - 74.3)	
Overall QoL	59.45±20.96	67.68±17.78	0.177†
	60 (49.1 - 63.3)	60 (51.7 - 73.3)	

Values are mean±SD; median (25ʳ-75ʳ). §Wilcoxon test; †T-test.

Compared after training, all subscales of fatigue decreased significantly (tab. 5). Regarding the psychological condition, we measured depression and the main psychological symptoms: we reported a significant improvement in depression after the training. Most of the symptoms measured with the Symptom Checklist-90 changed significantly during the training. In particular, table 5 shows the enhancements in somatization, interpersonal sensibility, anxiety, phobic anxiety and paranoid ideation. Finally, QOL improved significantly in physical and cognitive functions.

Figure 5 Fatigue before and after exercise protocol.



Discussion

PwMS suffer from strength deficit and muscle mass reduction as consequence of demyelization lesions that are implicated in motor function[5–11].

Previous studies showed a positive effect of exercise to enhance strength and other physical capacities in MS[24,42,54]. However, a tailored combined training and the psychological outcomes were not studied adequately. For example, when pwMS were trained in a group, changing in QoL and in psychological condition could be altered by social or group effect independent of physical exercise.

The aim of this study was to explore the benefits of a supervised ERCT on physical and psychological outcomes.

In the present study, women with mild to moderate disability performed an adapted exercise protocol. In accordance to previous studies, our results show physical and psychological enhancements in people with mild to moderate MS.

In fact, after a 12-week training, similarly to previous studies[40,41], strength increased significantly both in isometric and isotonic contraction (tab. 3). This change is crucial during the MS course because it led to a reduced fatigue in daily activities and depression. Furthermore, high levels of strength could guarantee more physical health and performance during the disease progress.

Similarly, VO_{2peak} increased significantly in pwMS. This improvement could lead to a better endurance and toleration of fatigue during exercise. In adjunction, VO_{2peak} is used to asses physical health. A higher aerobic capacity could prevent comorbidity of MS as cardiovascular and metabolic diseases. Furthermore, as strength, aerobic capacity contributed also to reduce fatigue perception and consequently could enhance physical activity level and walking autonomy.

As it was assumed, fat-free mass and fat mass did not change after the training protocol (tab. 4) because the resistance training of the protocol was not designated to promote a change in body composition and especially because it was not planned a dietary intervention.

To best of our knowledge, we collected data for the first time of body composition in person with MS including nutritional measurement as phase angle[68,69]. Values of Phase Angle were similar to those of other clinical population and lower than values of general healthy adults[69,70].

Our results suggest that a supervised ERCT could be useful to enhance not only functional parameters but also psychological outcomes in women with mild to moderate MS.

In fact, depression decreased significantly ($p<0.001$) and we reported a positive change in *somatization*, *interpersonal sensibility*, *anxiety*, *hostility*, *phobic anxiety*, *paranoid ideation* and in the *global score index* of SCL-90.

Our findings of cognitive, physical and psychosocial outcomes connected to fatigue (fig. 5) are in line with previous studies[21,22,24,54] and confirmed the relevant role of ERCT in ameliorate daily fatigue thanks to an enhancement of functional capacities. Also, QoL could be influenced by these changes. Even if, we reported significant improvements only in physical health and cognitive functions sub-scales of MSQOL-54 questionnaire. It could be possible that, with a longer period, positive effects extend significantly also to other outcomes.

Limits/strength

We are aware that our study has some limitations. Firstly, only women were recruited creating a gender bias. However, this choice was necessary to establish a coherent exercise protocol especially in training loads calculation (to obtain the same loads for men we should have chosen different resistance protocol). In consequence of this, training loads were not established starting from the maximal tests because the training protocol was without isotonic machines. Furthermore, aerobic training was managed with heart rate monitors and intensity was planned on a limited range (50-70%HRR) because, due to fatigue, it was difficult to reach high intensity of heart rate.

Despite these limitations, our study has also some strengths. It was designed to include all subjects to training activities: all subjects got benefits of training. It was a long study, we tested and supported participants for all 12 months. Additionally, every session was supervised by qualified personal trainers in continuous interaction with the neurologists to support properly the subjects during the protocol.

Conclusion

Improvements in training group after the exercise protocol in comparison with the results of the waitlist group during the first 12-week, suggest that a tailored and supervised training should be recommended to people with MS. In fact, when the waitlist group performed the same 12-week training protocol the improvements were similar to the training group.

As we expected, 12 weeks of ERCT increases functional capacities as strength and oxygen consumption in people with MS and the beneficial effect was maintained for at least 12 weeks after the end of intervention.

In conclusion, the training appears to offset the typical difficulties of MS such as fatigue and depression and to enhance quality of life. The promotion of exercise is ripe for becoming a central part of the clinical care and management of MS patients by healthcare providers.

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Flow Chart of Study

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