United Journal of Physical Medicine & Rehabilitation

Research Article

Circuit Training Can Have Positive Impact on Muscle Strength, Balance, Depression and Fatigue in Multiple Sclerosis Patients: A Randomized Controlled Study

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5Endowment fund Impuls, Prague, Czech Republic

Volume 1 Issue 1 - 2019

Received Date: 13 Mar 2019

Accepted Date: 28 Mar 2019

Published Date: 02 Apr 2019

Keywords

Multiple sclerosis; Exercise; Aerobic training; Resistance training; Circuit training

Abstract

Background: Positive effect of aerobic or resistance training has been described in patients with multiple sclerosis (MS); however, only a few studies were dedicated to the use of combined circuit training in patients with MS.

The aim of this study was to evaluate the impact of regular exercise in the form of circuit training (aerobic-resistance circuit training or resistance circuit training) in people with MS.

Design

The study was randomized controlled trial.

Setting

Outpatient exercise training in University Hospital

Population

Adults people with multiple sclerosis

Methods

For 12 weeks participants attended supervised circuit training sessions. The following assessments were completed at baseline, month 3 (at the end of the training program) and month 6 (follow-up): muscle strength in the knee flexors and extensors using a dynamometer and balance assessment with a Balance Master and walking tests. In addition, the following patient-reported outcomes were captured: the Modified Fatigue Impact Scale, Beck Depression Inventory and SF-36.

Results

Fifty patients with MS were included in this study [median age 43 years (range 23–68), median EDSS 3.5 (range 1.5–6), median disease duration 13.5 years (range 1–38 years)]. Following completion of3 months of circuit training, significant improvements in knee flexor strength ($p = 0.01$), knee extensor strength ($p = 0.01$) and balance ($p = 10-7$), as well as decreased fatigue ($p = 0.05$) and depression ($p = 0.01$) were observed. These changes were seen again 3 months after completion of circuit training, at month 6 of the study.

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Citation: Novotna K, Sucha L, Kalincik T, Reznicek P, Sobisek L, Hoskovcova M, Kubala Havrdova E. Circuit Training Can Have Positive Impact on Muscle Strength, Balance, Depression and Fatigue in Multiple Sclerosis Patients: A Randomized Controlled Study. United Journal of Physical Medicine & Rehabilitation. 2019; 1(1): 1-8.

Conclusion: Circuit training was well tolerated by people with mild-to-severe MS and had a positive effect on physical performance as well as on subjective measures of fatigue and depression. Improvements in muscle strength, postural balance and mood, and decreased fatigue outlasted the training by at least 3 months.

Both types of used circuit training (aerobic-resistance circuit training and resistance circuit training) are suitable therapeutic intervention for people with mild-to-moderate MS.

1. Background

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating disease of the central nervous system, predominantly affecting young adults in productive age. Because of the disseminated pattern of lesions, the clinical features of MS differ widely among individual patients. The most prevalent disease symptoms include motor weakness, sensory changes, impaired motor function, gait and balance disorders, fatigue, bladder and bowel difficulties etc [1]. These symptoms result in decreased quality of life [2]. There is strong evidence that people with MS are less active than their healthy peers [3].

In the past, exercise was discouraged for MS patients, because of the belief that it may exacerbate fatigue and other MS symptoms. In contrast, a number of studies showed that exercise therapy is both safe and beneficial for people with MS [4, 5]. Most of these studies examined the effect of regular endurance (aerobic) or resistance training.

Aerobic exercise (endurance training) is beneficial to people with MS, leading to improvements in fitness [6], functional mobility [7] and mood [8], reduction of fatigue [8, 9] and improved quality of life [6, 8, 10]. A study by Wens et al. [11] showed that even high-intensity aerobic training is safe and beneficial for MS patients [11]. Intervention studies reported the association of resistance training with increased muscle strength [12, 13], muscle fibre volume [14], mobility [12, 13], mood [15] and quality of life [13, 15], and decreased fatigue.

The benefits of combined aerobic and resistance training for people with MS have remained largely unstudied. Only a few studies reported improved muscle strength [16], endurance [11] and functional mobility [16-19] in patients who followed an aerobic-resistance training regimen.

Circuit training was developed by Morgan and Anderson in 1953 at the University of Leeds. A 'circuit' consists of 9–12 exercises (resistance, aerobic or both), performed at a moderate intensity. Each exercise session consists of several circuits with short breaks between circuits. The exercise protocol alternates between different types of exercise, so as to allow the exercised muscle groups to recover. Circuit training enables one to perform more exercise in the same period of time, mainly because of better fatigue management. The benefits of this type of training have been described in healthy volunteers and in populations with different conditions. Only a small number of studies conducted on MS patients have been published, and these used only task-oriented circuit training [20-22].

The aim of this randomized controlled trial was to describe the feasibility and immediate and delayed effects of aerobic-resistance circuit training in patients with MS. We chose a design with an active comparator (resistance circuit training), as the positive effect of exercise on MS outcomes is well known [23].

2. Methods

2.1 Subjects

The inclusion criteria consisted of a definite diagnosis of MS (according to the McDonald criteria 2010), clinically stable disease and the ability to ambulate independently (EDSS range 1–6) and to attend exercise lessons twice a week. Subjects were excluded if they (i) experienced a relapse within the 30 days preceding screening, (ii) had been diagnosed with other medical conditions or cognitive impairment that would interfere with their ability to exercise or (iii) were pregnant.

Participants were randomly allocated to either combined aerobic-resistance circuit training or resistance circuit training only. Randomization used the a priori defined variables age, sex, EDSS and group size in a block-matched design. Patients were blinded to group allocation. The sample size was based on previous consultation with statistician.

This study was approved by the Ethical Committee of First Faculty of Medicine and General University Hospital in Prague, Czech Republic. Written consent was obtained from each patient prior to their enrolment.

2.2 Interventions

The present study is a two-arm, single-blinded, randomized control trial including a post study follow-up period of 12 weeks. MS patients were randomized either to repeated aerobic-resistance circuit training or resistance circuit training, lasting 3 months, with assessments at months 0, 3 and 6.Interventions were administered twice a week over 12 weeks (3 months) and consisted of a

5-minute warm-up,50 minutes of exercise and a 5-minute cool-down.

The intervention was administered in groups of five subjects to enable individual adjustment of the quantity and quality of exercise. While the 'resistance' group received resistance training only, the 'aerobic-resistance' group received both types of training during each cycle, alternating between aerobic and resistance stations.

Aerobic training included cycling, rowing, walking on treadmill and elliptical training. Training intensity was tailored to individual needs according to general recommendations. Individual training intensity was assessed through heart rate [recorded by a sport tester or estimated by using the subjective Borg scale (RPE)]. Participants were encouraged to maintain their RPE levels between 11 and 13, which correspond to„ fairly light" and „somewhat hard" exercise intensities. An exercise session at each aerobic station last for 3 minutes of active exercise.

Resistance training included leg press, strengthening of the hip extensor and hip abductor muscles, training of the back and abdominal muscles with body weight and stepping up and down. The level of resistance was adjusted to individual needs using a combination of Swiss balls, exercise bands, friction training boards (Flowin®) and balance boards. Each station was designed to address muscle strength in the lower limbs and balance. Each resistance station included 40 seconds of active exercise.

The exercise lessons were held in the physiotherapy gym of the Department of Neurology, First Faculty of Medicine and General University Hospital in Prague and were supervised by a physiotherapist.

2.3 Assessment

To describe the complex impact of circuit training on participants, many different outcome measures (subjective and objective) were chosen. Muscle strength, gait performance, balance, fatigue, depression and quality of life were assessed at baseline, after 12 weeks to determine the immediate effect of intervention and after a further 12 weeks (week 24) to determine if any benefits of the program had been sustained. The assessment tools are described below.

2.3.1. Patient-reported outcomes

Quality of life

Quality of life (QoL) was measured using the short SF-36 questionnaire. This assessment tool is a 36-item scale divided into eight dimensions covering physical, mental and social aspects of health. For each dimension, a score from 0 to 100 was calculated according to standard procedures. These scores were subsequently transformed into physical or mental component scales, higher scores indicating better QoL [24, 25].

Fatigue

The Modified Fatigue Impact Scale (MFIS) was used to quantify fatigue. The scale includes 21 items (10 items related to mental fatigue and 11 items to physical and social fatigue). A higher score indicates a greater impact of fatigue on activities of daily living. A value of 38 has been published as a threshold for clinically significant fatigue [26, 27].

Depression

The level of depression was measured by using the Beck Depression Inventory-II (BDI-II).This scale consists of 21 items, with possible total scores ranging from 0 to 63 [28].

2.3.2 Outcome measures

Spiroergometry

To measure safe exercise intensity each participant´s fitness level was assessed using a graded exercise test on a cycle ergo meter with pulmonary gas analysis. The cardiovascular response to exercise was measured using heart rate (HR) and Borg´s Rating of Perceived Exertion (RPE) scale [29]. Every 2minutes, the load was increased by one level. The test was stopped when the participant was unable to continue or when the end point on the ergometer was reached. Oxygen uptake (VO2), expiratory volume and heart rate using a 12-lead ECG device were monitored during the test.

Balance assessment

The Balance Master (NeuroCom International, Inc, Clackamas, OR) is the standard clinical tool for balance evaluation. The clinical test for sensory integration (SOT) was chosen to evaluate standing stability. The SOT test is a six-condition assessment that identifies abnormalities in the patient's use of the three systems that contribute to postural control: somatosensory, visual and vestibular [30, 31].

Muscle strength

The maximal power of a voluntary isometric muscle contraction of the knee flexors and extensors (900 knee angle) wasmeasured with a dynamometer. Participants were assessed in a seated position with the trunk stabilised with bands. Three trials of maximal isometric knee extension (duration 4seconds) and flexion (4seconds), followed by a 30-second rest interval were performed. The greatest isometric flexion and extension peak torque (N) were recorded.

Functional gait assessment

Gait performance was measured using the timed 25-foot walk (T25FW), the 4-minute walk test and the Timed Up and Go test

(TUG). The timed 25-foot walk measures the time an individual requires to walk adistance of 25 feet (7.62 m). This test is widely used in clinical practice and trials as part of the Multiple Sclerosis Functional Composite [32]. The 4-minute walk test was chosen as avariation of the 2- and 6-minute walk tests. This test measures how many meters the subject is able to walk in 4 minutes [33]. The Timed Up and Go test is a test of postural and ambulatory balance. The test measures the time required by a subject to stand up from a chair, walk 3 m, including a 180-degree turn, and then return to aseated position [34].

Tolerability of training

The feasibility of training was measured as the percentage of subjects who completed the trial of 3 months of training. Attendance at ≥75% of all exercise sessions was required. Adverse events that occurred during the exercise period were recorded.

2.4. Statistical analysis

Statistical analysis was completed with R. Linear mixed-effect models were used to compare outcome measures between matched patients, with the patient pair as the grouping variable and the time point (month 0, 3 or 6) as the indicator of time. The effect of time on the difference between matched treatment groups was studied by includingthe time point as a fixed effect. No difference between the two exercise regimens was found;therefore we combined the two groups to evaluate the change in outcome measures at months 3 and 6 relative to baseline, and at month 6 relative to month 3. Similarly, linear mixed-effect models were employed, with the patient as the grouping variable and the time point as the fixed effect of interest. These models were also adjusted for age, gender, BMI, EDSS, disease duration and training regimen. The observed associations were considered statistically significant when α≤0.05, after applying the Benjamini-Hochberg correction to control the false discovery rate.

3. Results

Fifty people with MS (including 44 females) were included in this study. The patients ‘baseline demographic characteristics are displayed in **Table I**. The two randomised groups were largely comparable, with the exceptions of marginally older age and longer disease duration in the aerobic-resistance group.

In both groups, some of the objective parameters as patient outcome measures were improved after training. All results of assessed parameters are presented in **Tables II** and **III**. There were no changes in the participants ‘EDSS levels.

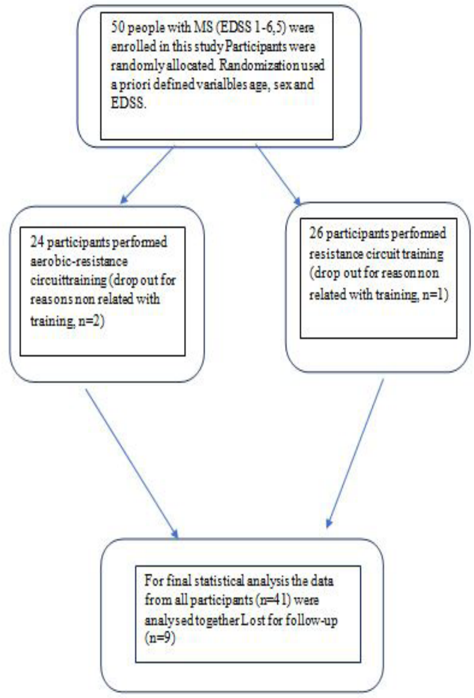

Figure 1: Flow chart of participants through the study.

Table 1: Demographic characteristic of participants.

Parameter	All participants Circuit training N=50 Mean (SD)	Aerobic-resistance Circuit training N=24 Mean (SD)	Resistance circuit training N=26 Mean (SD)
Age (years)	42.3 (10.8)	45.3 (10.6)	39.6 (10.5)
Gender	6 males	3 males	3 males
Height (cm)	169.8 (6.6)	170.7 (6.3)	169.1 (6.8)
Weight (kg)	72.7 (15.5)	73.6 (13.6)	72.1 (17.1)
BMI	25.4 (5.0)	25.6 (4.7)	25.2 (5.3)
HF rest (beats/minute) -Heart frequency	72.6 (10.4)	71.8 (9.9)	73.2 (11.1)
EDSS	3.4 (1.2)	3.65 (1.5)	3.3 (1.0)
EDSS median (range)	3.5 (1-6)	4 (1-6)	3 (1.5-6)
Disease duration (years)	12.8 (9.1)	14.8 (10.3)	11.1 (7.7)

Out of the 50 included patients, only 3patients (6%) chose to withdraw from the study (**Figure 1**). The reasons for drop out included lack of time, health problems (not related to MS) and unplanned departure. No adverse events were reported. Overall, more than 80% of the training sessions were completed. On average, the subjects completed 20 out of 24 exercise sessions.

Comparison of the two forms of circuit training

There were no discernible differences in study outcomes and patient-reported outcomes between the two randomised groups at baseline, month 3 and month 6 **(Table II**).We therefore combined the observations made in the two groups to further evaluate the effect of exercise on the study and patient-reported outcomes at the end of the intervention (month 3) and 3 months later (month 6).

Effect of 12 weeks (3 months) of circuit training

The SOT test showed a 3.5-point improvement after 3 months of

Table 2: Comparison of results of aerobic-resistance and resistance circuit training.

	Aerobic-resistance circuit training			Resistance circuit training			
Parameter	Base-line Mean (SD)	Assess-ment after 3 months Mean (SD)	Follow-up After 3 months Mean (SD)	Baseline Mean (SD)	Assess-ment after 3 months Mean (SD)	Follow-up After 3 months Mean (SD)	p-value
Strength knee flex-ors (N)	90.3 (40.9)	102 (44.15)	101.2 (48.4)	85.5 (33.65)	111.5 (36.1)	107.6 (54.9)	0,35
Strength knee extensors (N)	198 (73.8)	216.5 (84.15)	237.3 (107.1)	179.2 (76.3)	225.4 (77.9)	158.4 (84.3)	0,39
The 4 min-ute walk test (m)	302.9 (83.6)	304.6 (84.4)	315.7 (78.8)	332.3 (68.6)	351.8 (59.4)	324.8 (68.6)	0.40
The 25 foot walk test (sec)	4.85 (1.4)	4.94 (1.3)	4.89 (1.2)	4.55 (0.8)	4.52 (0.8)	4.52 (0.8)	0.70
Timed Up and Go test (sec)	6.70 (1.7)	6.71 (1.4)	6.58 (1.7)	6.59 (1.5)	6.27 (1.2)	6.4 (1.3)	0.73
SOT-Sensory orientation test	71.0 (15.2)	72.6 (14.2)	76.0 (13.5)	79.7 (9.2)	79.7 (9.2)	81.5 (8.5)	0.16
MFIS	31.4 (17.9)	28.9 (16.5)	28.1 (17.3)	35.6 (17.2)	28.8 (15.5)	30.1 (14.7)	0.39
SF-36 phys	50.2 (5.8)	50.3 (5.4)	50.3 (5.4)	51.6 (4)	50.8 (4.3)	51.6 (3.4)	0.81
SF-36 mental	47.2 (5.3)	47.7 (3.2)	46.1 (5.5)	48.4 (5.3)	48.3 (4.1)	47.7 (3.9)	0.92
BDI	11.09 (7.9)	9.1 (7.0)	8.1 (6.5)	9.0 (7.4)	7.2 (5.9)	7 (6.25)	0.72

Table 3: Results of all parameters

Parameter	Baseline, month 0 Mean (SD)	Assess-ment after 3 months Mean (SD)	Follow-up After 3 Mean (SD)	p-value (months 0, 3 and 6)	p-value (months 3 and 6)
Strength knee flexors (N)	173.63 (67.68)	212.8 (69.43)	208.84(106.82)	**0.013**	1.00
Strength knee extensors (N)	368.07 (149.41)	426.91 (140.28)	415.89 (160.68)	**0.014**	0.98
The 4 minute walk test (m)	318.9 (76.4)	330.2 (75)	320.6 (72.8)	0.88	0.96
The 25 foot walk test (sec)	4.69 (1.1)	4.71 (1.0)	4.69 (1.04)	0.95	0.96
Timed Up and Go test (sec)	6.64 (1.6)	6.46 (1.3)	6.48 (1.0)	1.00	1.00
SOT-Sensory orientation test	71.56 (13.63)	76.51 (11.84)	78.62 (11.22)	**10^{-6}**	0.75
Squat 0L (%)	49.3 (4.9)	48.3 (6.6)	49.7 (5.4)	0.95	1.00
Squat 0 R (%)	50.6 (4.9)	51.6 (6.6)	50.2 (5.4)	0,95	1.00
Squat 30L (%)	48.4 (5.3)	49.2 (4.6)	48.2 (4.9)	0.61	0.87
Squat 30 R (%)	51.5 (5.3)	50.7 (4.6)	51.7 (4.9)	0.61	0.87
Squat 60 L(%)	49.2 (6.8)	47.6 (7.0)	48.2 (5.2)	1.00	0.66
Squat 60 R (%)	50.7 (6.8)	52.3 (7.0)	51.7 (5.2)	1.00	0.66
Squat 90 L (%)	50.1 (6.6)	48 (5.6)	47.4 (5.6)	0.86	0.96
Squat 90 R (%)	49.8 (6.6)	52 (5.6)	52.5 (5.6)	0.86	0.96
MFIS	33.7 (17.4)	28.8 (15.8)	29.2 (15.8)	**0.05**	1.00
SF-36 phys	50.9 (4.9)	50.6 (4.8)	51.0 (4.5)	0.93	0.87
SF-36 mental	47.8 (5.3)	48 (3.7)	47 (4.7)	0.27	0.53
BDI	10 (7.5)	8.1 (6.4)	7.5 (6.3)	**0.01**	0.98

Legend: the p-value for months 0-3-6 studied mainly the change relative to baseline, and the p-value for months 3-6 evaluated the difference between the two follow-up time points

training (p = 10-6). Knee flexor strength improved immediately by 19.5 N (p = 0.013) and knee extens or strength, by 33.5 N (p = 0.014; Table III).We did not find any evidence of statistically significant improvement in functional walking tests: the 4-minute walk test, T25FT or TUG test (p>0.80).

Twenty-three patients reached an MFIS score of 38 or higher at baseline, which is indicative of clinically significant fatigue. At 3 months, immediately after completing the exercise program, only 15 patients reached an MFIS score of 38 or higher. The mean decrease in MFIS was 4.9 points (p = 0.05).On average, the patients did not report an increase in self-reported quality of life (SF-36). On the other hand, the self-reported level of depressive symptoms measured by BDI-II was lower in the included patients after they completed 3 months of exercise (10.0 vs. 8.1, p = 0.01).

Sustained effects at 6 months (3-month follow-up)

Improvements in balance in the standing position (SOT test), muscle strength, fatigue and depressive symptoms persisted for 3 months after the conclusion of training, at month 6. All other parameters remained without significant improvement.

4. Discussion

In this study, we have demonstrated that regular exercise in form of combined aerobic-resistance circuit training or resistance circuit training is tolerable and effective in improving muscle strength in the lower limbs, sensory integration and mood, and decreasing fatigue in people with mild to moderate severe MS. The effects of the exercise program outlasted its duration by at least 3 months. Most patients expressed a wish to continue regular exercise training after completing this exercise program.

This study adds to the growing body of evidence that exercise helps preserve functional capacity in people with MS and subjectively improves some aspects of patients' wellbeing, for example, it is associated with a decrease in self-reported fatigue and low mood. Similar positive associations were reported for decreased depression and fatigue after 10 or 12 weeks of aerobic training in a group of people with moderately advanced MS [9, 35]. Two other studies showed that muscle strength, fatigue and quality of life improved after 12 weeks of aerobic or combined aerobic-resistance training [19][36]. Moreover, 12 weeks of progressive resistance circuit training were associated with improvement in fatigue, depression and quality of life scales [15] and in muscle strength and functional mobility [12]. This result mirrors the findings of Garett et al. [37], who found a positive effect of 10 weeks of exercise intervention on symptoms of MS [37]. The positive effect on mood in people with MS could have been due to the format of small group-based training (five participants in each exercise group), which made exercising a more social activity. Results from a study by Voss et al. suggest that participating in enjoyable recreational activity (such as exercise) may contribute to positive affect in people with MS [38].

Fatigue in one of the most frequent symptoms in people with MS that, in combination with a low level of physical activity, leads to impairment of activities of daily living [39]. Our data confirm the results of previous randomized controlled studies [13, 15, 37] that regular exercise (aerobic, resistance or yoga) can reduce fatigue. Therefore, it can be used as a treatment option for a debilitating symptom.

Surprisingly, in our study, circuit training was not associated with an improvement in functional mobility tests, despite the fact that muscle strength in our participants increased. Some previous studies described improvement in functional mobility after aerobic [7, 18, 40] or resistance training [12, 41]. On the other hand, a study by Dodd et al. found similar results to ours, that increased muscle strength did not lead to functional improvement after 10 weeks of training [13]. The reasons for this disparity in findings are unclear. However, it is possible that previous studies with positive findings used randomized controlled trials with higher training frequencies and intensities. A detailed comparison of different studies remains difficult for several reasons: studies used different exercise frequencies (1–3 times a week or unsupervised home exercise), different exercise intensities (based on RPE, VO2max, maximal heart rate) and different exercise durations (20–60 min). To induceneuroplastic changes and functional mobility improvement, hundreds of repetitions for hand and arm functions and thousands of repetitions for leg functions are needed. For functional improvement of gait performance, task-specific training is a more suitable therapeutic approach than aerobic, resistance or holistic physiotherapy exercise only [42]. Another possible explanation for the lack of functional mobility improvement could be the fact that in the current study only 38% of participants (19/50) had limitations in functional mobility.

Both types of circuit training (aerobic-resistance and resistance circuit training) were associated with improvement in balance in a standing position, as measured by the Sensory Orientation Test. Balance problems and falls are very common symptoms in MS [43], so this finding is useful for planning therapeutic interventions. These results show improved ability to maintain postural stability under combinations of different conditions (eyes open, eyes closed, firm surface, foam surface).Importantly, positive changes in the sensory integration test were sustained over at least 3 months after patients completed the supervised training program, in keeping with previously published research [44].

Aerobic-resistance circuit training combines the benefits of both types of training, aerobic and resistance: positive effects on muscle strength, balance and fatigue levels due to improved cardio respiratory fitness. Our findings are therefore both clinically meaningful and statistically significant. The findings of the present study suggest that this type of interval training intervention in the form of circuit training is, in people with MS, better tolerated than continuous exercise [45]. With the supervision of a physiotherapist, this type of exercise training can be conducted either in the hospital gym or in a community setting (such as the local gymnasium or fitness centre). There were no adverse events during circuit training, indicating that it is a relatively safe form of exercise regimen for people with MS. There was no increase in the symptoms of muscle spasm or muscle stiffness. These findings are consistent with the results of a previous study [13]. Supervision by a physiotherapist during exercise is, for most patients with MS, very important and motivating, especially when the patients worry about possible harmful effects of exercise training. We agree with the conclusion of a previous study that close supervision, a gradual increase in exercise effort and continuous encouragement are very important [46].

This study was limited by the restricted study sample. This trial did not use a non-inferiority design. Therefore, our ability to comment on the comparability of the two training regimens may be limited. The outcomes of this study are limited to people with mild to moderate severe MS (EDSS 6 and lower). Studies of similar interventions in more advanced MS are needed.

5. Conclusion

In summary, the results of this active-comparator randomised trial support the use of aerobic-resistance circuit training or resistance circuit training in people with mild to severe MS. Participation in a circuit training program on regular basis for 3 months was well tolerated and had significant effects on physical parameters as well as on subjective perceived fatigue and depression in the studied sample. Circuit training should be considered as option in this patient group.

Acknowledgement

Supported by the Czech Ministry of Education project Progres Q27/LF1 and Endowment fund Impuls.

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