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Multiple sclerosis and brief moderate exercise. A randomised study

OH Bjarnadottir[1], AD Konradsdottir[1], K Reynisdottir[1] and E Olafsson[2,3]

This is a randomised control study, to determine the effect of aerobic and strength exercise on physical fitness and quality of life in patients with mild multiple sclerosis (MS). Sixteen outpatients with definitive MS, aged 18–50, with an Expanded Disability Status Scale (EDSS) <4, completed the study. Every patient was evaluated according to physical fitness with peak oxygen consumption ($V'O_{2peak}$), workload and anaerobic threshold; quality of life (SF-36); and degree of disability (EDSS). The patients were then randomised to an exercise group (EG) ($n = 6$) or a control group (CG) ($n = 10$). The EG exercised three times a week for five weeks, and the CG did not change their habits regarding exercise.
In the EG, the mean change in workload was 0.34 W/kg (95% confidence interval (CI): 0.09–0.58), the mean change in $V'O_{2peak}$ was 4.54 mL/kg per minute (95% CI: 1.65–7.44), and the mean change in anaerobic threshold was 0.32 L/min (95% CI: 0.08–0.57). There was a tendency towards improved quality of life, and no change was detected in the degree of disability. This study confirms that brief, moderate, aerobic exercise improves physical fitness in individuals with mild MS. No evidence was found for worsening of MS symptoms in association with exercises. *Multiple Sclerosis* 2007; **13**: 776–782. http://msj.sagepub.com

Key words: aerobic exercise; multiple sclerosis, physical fitness, randomised study

Introduction

Multiple sclerosis (MS) is a common neurological disease primarily affecting young people, frequently causing impaired physical fitness (PF) and a decrease in quality of life [1,2]. Physical exercise improves the fitness of healthy individuals, decreases mortality and morbidity, and reduces depression [3–6]. Physical exercise for MS patients has been controversial in the past, because of the possible deleterious effects it might have on the disease. Studies of physical exercise among people with MS have shown increased fitness, decreased fatigue, and improved quality of life [7–10]. Today, physical exercise is generally considered safe in MS, but few randomised trials of aerobic exercise in MS patients, using peak oxygen consumption ($V'O_{2peak}$) as endpoint, are available [10–12].

We performed a randomised, controlled, study, to determine the efficacy and safety of aerobic and strength exercise on PF and quality of life in patients with mild MS.

Methods

Participants

The goal was to recruit patients with mild MS from the general MS population. The patients were recruited among members of the MS Society of Iceland, and through practicing neurologists. Individuals with mild MS, who were ambulatory and able to exercise, were potentially eligible for the study. Each individual had to fulfill all four inclusion criteria: (1) definite MS; (2) Expanded Disability Status Scale (EDSS) <4 by neurological examination; (3) age <50 years of age; and (4) the ability to ride a stationary bicycle [13,14]. Individuals were excluded if they met one or

[1] Reykjalundur Rehabilitation Center, 270 Mosfellsbaer, Iceland
[2] Department of Neurology, Landspitali University Hospital, Reykjavik, Iceland
[3] School of Medicine, University of Iceland, Reykjavik, Iceland
Author for correspondence: Olof H Bjarnadottir, MD, Reykjalundur Rehabilitation Center, 270 Mosfellsbaer, Iceland. E-mail: olofb@reykjalundur.is
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more of the six following exclusion criteria: (1) MS relapse during one month immediately prior to study onset (defined as new neurological symptom(s)/sign(s) or increase in EDSS ≥ 1); (2) primary progressive MS; (3) disability due to other diseases (eg, radiculopathy or rheumatism) or impairment that interferes with aerobic exercise (eg, cardiovascular or lung diseases); (4) active engagement in an exercise program during one month prior to the study onset; (5) cognitive impairment that would interfere with participating in the study; (6) ongoing corticosteroid treatment.

A total of 36 MS patients were identified, and all were contacted by telephone by a researcher (OHB). A considerable reluctance to participate in a training study was evident, which was at least partially due to the long held belief that training may be harmful for MS patients. Eleven individuals were excluded based on the inclusion and exclusion criteria, and an additional two individuals chose not to participate. Informed consent was obtained from the remaining 23 individuals, and their records were reviewed to verify diagnosis. The National Bioethics Committee and the Data Protection Authority approved the study.

Instruments of measure

Physical examination

All patients were examined by one researcher (OHB). The results are expressed by EDSS, where '0' is no impairment, '4' is ability to walk some 500 m without aid, and '10' is death due to MS.

Quality of life

Quality of life was assessed using the Short Form-36 Health Survey (SF-36), which measures self-perception of health status and quality of life [15]. The results are reported on a scale of 0–100, where '100' indicates the most favorable health state.

Physical fitness

Physical fitness (PF) was determined by a graded exercise test on a cycle-ergometer. The workload was gradually increased while the patient was encouraged to maintain a constant pedaling speed of 60 rpm. The starting workload was 20 W for males and 15 W for females, and was gradually increased by 20 W/minute for males and 15 W/minute for females, until the $V'O_{2peak}$ was reached. The test was symptom-limited and was stopped if one of the following occurred [5]: (1) patient complained of exhaustion or could not continue cycling; (2) oxygen saturation decreased; (3) electrocardiogram (EKG) changes developed; (4) abnormal decrease or increase in blood pressure was detected. The test was conducted by a physical therapist, who was blinded to the results of randomisation, and applied standardised motivation. The test was supervised by a physician (OHB). Blood pressure was measured every minute and EKG was continuously monitored. The PF was quantified by measuring oxygen consumption ($V'O_2$), which increases with improved PF. The $V'O_2$ is determined by measuring the difference between O_2 content of inhaled and exhaled air [16]. The highest value obtained is defined as the $V'O_{2peak}$. Both $V'O_2$ and carbon dioxide production were measured 'breath-by-breath' (Vmax 29; Sensormedics, Yorba Linda, CA). Gas analysers were calibrated before each test.

The Borg scale

The Borg scale was used to rate the patients perceived exertion (RPE) at $V'O_{2peak}$ and runs from 6 to 20 with verbal descriptions, where 7 is 'extremely light', and 19 is 'extremely hard' [17]. When the Borg reaches 15–17 points, the effort of a 30–50 year old individual is considered maximal [17].

Anaerobic threshold

Anaerobic threshold is another measure of PF and increases with improved PF. Anaerobic threshold is defined as the point where a marked increase in CO_2 is seen in exhaled air, heralding the onset of lactic acidosis. Anaerobic threshold was determined by the 'computerised V-slope method' [18].

Efficacy

Efficacy was defined as the ability of physical training to produce improved PF among patients with mild MS.

Safety

Safety was defined as the absence of MS relapse and the absence of treatment complications during training. The patient was monitored for transient increase in MS symptoms. Additionally, the Borg scale and HR was used to prevent overexertion during training.

Intervention

Examination and measurement took place at baseline and after five weeks of exercise. A total of 23 individuals were enrolled in the study and randomised (Figure 1) to either exercise group (EG) or control group (CG), and the results were placed in a sealed envelope and only revealed to the investigators and the patients after the baseline information had been obtained. Six of the 11 patients who were assigned to the EG, and 10 of the 12 patients assigned to the CG completed the intervention phase.

Exercise group

The exercise took place in the afternoon and was carried out on an outpatient basis. The exercise part of the study was conducted in a rehabilitation center by two researchers (ADK, KR), who are experienced physical therapists. The EG trained for 60 minutes, three times a week for five weeks, or a total of 15 hours. The exercise period was divided into three parts as follows: (i) aerobic exercise was performed on a Monark cycle-ergometer. Warming up and cooling down was carried out over 3 minutes at 33% of $V'O_{2peak}$. The cycling continued for 15–20 minutes at the subject's anaerobic threshold, which was about 55% of the subject's $V'O_{2peak}$. During the last 5 minutes, the trainers recorded the heart rate (HR) and RPE. The goal was to increase the workload by at least 15% during the exercise phase. The HR, RPE and patient's motivation were used as guidelines for increasing the workload during the exercise. (ii) Resistance exercise included 13 exercises involving the major muscle groups (upper and lower extremities, back, abdomen and chest). During the first two weeks, each exercise period was repeated at least 15 times. An attempt was made to increase the number of repetitions to 20, and increase the weight if motivation and RPE (Borg scale <13) allowed. (iii) Stretching and relaxation was carried out under supervision during the last 5 minutes. General information about the importance of activity was incorporated in the program and discussion and supervision about training symptoms.

Control group

The CG recorded in a diary all physical activity exceeding 20 minutes and occurring more than twice a week.

After the five weeks exercise program, the same information was collected, as in the beginning.

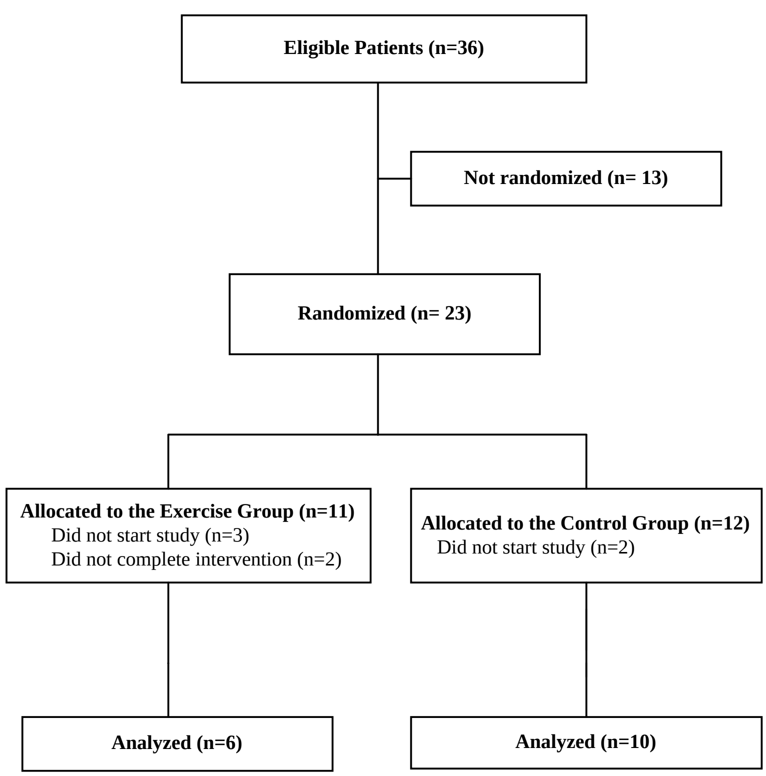

Figure 1 Flow diagram of study.

Statistical analysis

The difference in test results at baseline and the following five weeks of exercise by the EG were determined for all participants. This value is called the 'pre-post difference' (PPD). The mean value of the PPD is calculated for both groups (EG and CG). The EG and CG are then compared by the mean PPD values for each 'instrument of measure'. The difference of those mean values is the estimate of the effect associated with the intervention in the study [19].

The values were first analysed with a non-parametric Mann–Whitney *U*-test, and subsequently with the Student's *t*-test. The level of significance was set at 0.05 and 95% CI was provided for estimates.

Results

Participants

All patients had relapsing remitting MS. Two individuals withdrew from EG subsequent to randomisation (steroid treatment (1); illness in the family (1)), and three withdrew during the intervention (intercurrent illness (1); MS exacerbation (1); lack of motivation (1)). Two withdrew from the CG (intercurrent illness (1); MS exacerbation (1)). Patient characteristics are listed in Table 1. Both groups were comparable with respect to build, activity and physical fitness on baseline testing. Each individual in the EG attended exercise at least 12 times.

Physical fitness

Exhaustion was the limiting factor in the graded exercise test, and all participants stopped cycling because of exhaustion. None experienced any other reason for stopping the graded exercise test. An increase of 14.7% in $V'O_{2peak}$, 18.2% in peak workload, and 27.3% in anaerobic threshold, was observed in the EG following the exercise program. No significant change was observed in the CG (Table 2), and none had changed their habits regarding exercise. The perceived exertion at $V'O_{2peak}$, as measured by Borg scale, was identical for both groups at onset compared with the end of the study. The mean values for the Borg Scale were 17.2 at the onset, and 17.0 at the end of the study in the EG, and 16.6 and 17.2 in the CG.

Table 1 Characteristics of the two groups

	EG ($n=6$)	CG ($n=10$)	*P*-value
Sex (F/M)	3/3	8/2	0.30
Age (years)	38.7	36.1	0.41
EDSS	2.1	1.8	0.16
Duration of MS (years)	8.7	8.3	0.70
Weight (kg)	67.3	74.4	0.23
Height (cm)	172	171	0.91
Body mass index (kg/m^2)	22.9	25.4	0.19
Smoking	1	3	1.00
Employed or in school	4	9	0.52
Beta interferon	3	3	0.61
FVC (L)	4.8	4.2	0.30
FEV1 (L)	3.9	3.5	0.36
$V'O_{2peak}$ (mL/min per kilogram)	27.3	23.4	0.33
$V'O_{2peak}$ (L/min)	1.9	1.7	0.91

Quality of life

Quality of life, as measured by the SF-36, demonstrated a tendency towards improved quality of life in five of eight parameters (Table 3), but only reached a statistical significance for 'vitality'.

Safety of study

One patient in each group developed a MS relapse during the study, and were immediately withdrawn from the study. Transient increase in MS symptoms was not observed during the study. No change in the neurological status (EDSS) of the participants ($n=16$) was detected during the study period (Table 2).

There were no treatment complications.

Discussion

Physical activity is known to decreases morbidity and mortality in healthy people, and it is likely to have the same effect in MS, but studies are lacking [5]. There is a longstanding concern among physicians that physical training may have harmful effect on the symptoms and course of MS. This view was prevalent among Icelandic MS patients, which adversely affected recruitment to this study. In the last decade, many authors have addressed the importance of exercise in MS, and have generally encouraged physical training, but only a few studies have looked at this using rigorous methodology [10,12].

Several authors have found the physical fitness of MS patients to be below average, and some even lower than among sedentary controls [1,10,12]. The current study found the PF to be low for both males and females. We found the mean PF for females to be 21 mL O_2/kg per minute as the 10th percentile (26.5 mL O_2/kg per minute), and 33 mL O_2/kg per minute for males, which is also low, as 32 mL O_2/kg

Table 2 Measurements of physical fitness

Instrument of measure		Exercise group ($n=6$)			Control group ($n=10$)			Comparison of groups	
		At onset	After 5 weeks	Mean PPD[a]	At onset	After 5 weeks	Mean PPD[a]	Difference[b]	95% CI
Peak oxygen consumption ($V'O_{2peak}$)	mL/kg per minute	27.3	31.3	4	23.4	22.9	−0.5	4.54	1.65–7.44
Peak workload	W/kg	2.2	2.6	0.4	1.8	1.9	0.1	0.34	0.09–0.58
Anaerobic threshold	L/min	1.1	1.3	0.3	1	0.9	−0.1	0.32	0.08–0.57
EDSS	NA	2.1	1.9	−0.2	1.8	1.7	−0.1	−0.07	−0.74 to 0.61

[a]Mean PPD (pre-post difference) is the difference between the measured value at onset and following five weeks of intervention.
[b]The difference between the mean PPD values.

per minute represents the 10th percentile for normal males [5].

The only MS study we are aware of that differentiates between males and females, found PF in males to be 27.0 mL/kg per minute and 21.7 mL/kg per minute for females [20]. We believe these numbers to be comparable, even if small numbers in the current study preclude accurate comparison.

Our training program is based on the ACSM recommendations for developing and maintaining PF, suggesting exercise three to five times a week for 20–60 minutes at 40–50% of $V'O_{2max}$ [21]. We increased the intensity weekly after the first two weeks, which we believe was important in producing the desired effect. We selected five weeks as the duration of the exercise period to determine if a brief period of exercise would be beneficial to individuals with mild MS.

Studies have used different exercise intensity variably based on $V'O_{2max}$, HR, Borg scale and duration. Some studies have not demonstrated improvement in PF, which may be due to inclusion of more severely affected individuals, shorter duration of exercise, inadequate intensity or less motivation than in the current study [11,12]. Detailed comparison of different studies is, however, difficult for several reasons. Programs of physical training include many variables, and description of these has not been included in most studies of MS patients. We have included information about the type of MS, frequency, duration and intensity of the training to facilitate comparison with other studies. This information has not been included in most similar studies [22]. There is variable degrees of physical impairment of MS patients, and individuals may respond differently to training depending on their level of disability. Further studies of exercise among MS patients are necessary, including studies of the value of training among severely affected MS patients [7].

Increase in oxygen consumption and elevation of the AT are both important objective indicators of successful physical training. In the current study, the $V'O_{2peak}$ was increased by 14.7% in the EG during the five weeks exercise program (no increase in the CG), and an 18% increase in AT after short training. This is comparable to $V'O_{2peak}$ increase with training among healthy individuals [5]. Few studies have looked at the oxygen consumption during exercise in MS patients and compared it with a control group of individuals with MS who did not train. A study by Petajan *et al*. of MS patients (EDSS ≤ 6), randomised 21 individual to an EG, and 25 individuals to a non-exercise group [10]. An improvement in PF of 9.1% was observed by five weeks, and 18.6% by 10 weeks in the EG compared with the non-exercise group. A study of MS patients (EDSS 1–6.5) by Mostert *et al*. randomised 13

Table 3 Quality of life as measured by the SF-36

	Exercise group ($n=6$)			Control group ($n=10$)			Comparison of groups	
	At onset	After five weeks	Mean PPD[a]	At onset	After five weeks	Mean PPD[a]	Difference[b]	95% CI
Physical function	81.7	80.0	−1.7	72.0	71.5	−0.5	−1.17	−16.13 to 13.80
Role physical	66.7	70.8	4.2	60.0	67.5	7.5	−3.33	−49.51 to 42.84
Bodily pain	66.2	81.7	15.5	65.9	60.8	−5.1	20.60	−8.00 to 49.20
General health	56.8	62.7	5.8	61.9	57.9	−4.0	9.83	−5.74 to 25.41
Vitality	55.0	66.7	11.7	50.0	43.0	−7.0	18.67	0.08−37.25
Social function	50.8	71.2	20.3	71.2	74.0	2.8	17.53	−15.51 to 50.58
Role emotion	55.5	77.8	22.3	76.7	76.6	−0.1	22.43	−34.67 to 79.53
Mental health	68.0	67.3	−0.7	75.6	80.4	4.8	−5.47	−27.69 to 16.76

[a]Mean PPD (pre-post difference) is the difference between the measured value at onset and following five weeks of intervention.
[b]The difference between the mean PPD values.

patients to exercise and 13 to no exercise [12]. The EG demonstrated a 12% increasing in $V'O_2$ after three to four weeks of exercise, compared with a decrease (−4%) in the CG. The results of both theses studies are similar to the current study, even if they both included individuals with more severe symptoms.

A study of MS patients (age 30−55 years; EDSS 1−5.5) was carried out, where the aerobic part of the 26-week training consisted of 28 training sessions [11]. The study did not show any increase in $V'O_2$ compared with CG. Some of their patients were more severely affected and the intensity of the effort is, however, not specified. This may possibly explain the difference from our findings.

The impression during the study was that physical exercise improved the well being of the participants. We believe that the tendency towards an improved quality of life detected by five of eight parameters used by the SF-36 suggests a clinically important finding, even if it only reaches statistical significance for one of the five parameters. There is a considerable lack of agreement as to what scale is best suited for measuring quality of life measurements among MS patients.

Only people <50 years of age were included to ensure a more homogenous group with regards to age and physical performance. The number of available individuals with mild MS was limited, and power calculations were not used when the study was designed. The study was introduced at a meeting of the MS Society of Iceland, and it received enthusiastic support, but in spite of that, recruitment remained problematic and many potential participants were concerned about participating in physical training. The number of MS patients we were able to recruit limited the study size.

The drop out of patients was due to a variety of reasons, and MS relapse was the cause in one individual in each group, occurring prior to the intervention in both. Worsening of MS symptoms caused by exercise has been a concern in the past, but few authors have actually reported increase in MS symptoms during exercise. Mostert *et al*. reported exacerbation of MS symptoms in 10% of MS patients during a graded exercise test. The symptoms included increased spasticity, paresthesias and vertigo [12]. Petajan *et al*. reported an exacerbation in 13% (7/54) of the individuals, occurring with similar frequency in both the exercise and non-exercise groups [10]. In only two of these seven individuals, the exacerbations were severe enough to preclude further participation in the study. We did not see this, and it is possible that worsening of symptoms is more common in MS patients with more severe (EDSS 1−6, 5 and ≤ 6) compared with EDSS 1−3.5 in the current study.

Adequate motivation is very important in this group of patients, especially when the patients worry about possible harmful effects of the training. Individuals in both the EG and CG delivered their maximal effort, during the pre- and post-study evaluation, as measured by the Borg scale. This indicates that the close attention received by the EG during the intervention, did not differentially affect the effort of the two groups. We believe that close supervision and continuous encouragement was very important. Difference in motivation is hard to assess between studies and may explain some of the apparent differences in published studies.

Based on the results of the current study, we consider an exercise program of five weeks duration, gradually increasing the effort, and emphasis on good motivation, to be adequate to demonstrate increased PF among individuals with mild MS.

Conclusion

This study demonstrates that moderate physical exercise for five weeks improves the physical fitness of people with mild MS. The physical exercise was well tolerated, and there were no complications due to the exercise program. The results of the current study are confirmatory, and agree with the results of previously published studies. This study suggests a method for designing an exercise program where gradual increase in effort required by the patient is systematically monitored, and where proper motivation is encouraged throughout the physical training program.

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