Effects of a 6-month exercise program on patients with multiple sclerosis
A randomized study

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Abstract—Objective: To improve walking and other aspects of physical function with a progressive 6-month exercise program in patients with multiple sclerosis (MS). Methods: MS patients with mild to moderate disability (Expanded Disability Status Scale scores 1.0 to 5.5) were randomly assigned to an exercise or control group. The intervention consisted of strength and aerobic training initiated during 3-week inpatient rehabilitation and continued for 23 weeks at home. The groups were evaluated at baseline and at 6 months. The primary outcome was walking speed, measured by 7.62 m and 500 m walk tests. Secondary outcomes included lower extremity strength, upper extremity endurance and dexterity, peak oxygen uptake, and static balance. An intention-to-treat analysis was used. Results: Ninety-one (96%) of the 95 patients entering the study completed it. Change between groups was significant in the 7.62 m (p = 0.04) and 500 m walk tests (p = 0.01). In the 7.62 m walk test, 22% of the exercising patients showed clinically meaningful improvements. The exercise group also showed increased upper extremity endurance as compared to controls. No other noteworthy exercise-induced changes were observed. Exercise adherence varied considerably among the exercisers. Conclusions: Walking speed improved in this randomized study. The results confirm that exercise is safe for multiple sclerosis patients and should be recommended for those with mild to moderate disability.

NEUROLOGY 2004;63:2034–2038

In a chronic disease, such as multiple sclerosis (MS), the primary goal of exercise is to maintain and improve functional independence.1 The beneficial effect of aerobic exercise on cardiorespiratory fitness, fatigue, and quality of life in patients with MS has been shown in independent studies.2-4 Together with aerobic exercise, a comprehensive training program should also include exercises that increase muscular strength and endurance.5

The benefit of strengthening exercises on functional ability in MS remains to be determined. One earlier study indicated that 4 to 6 weeks of resistance training improved muscular strength and endurance in three and psychological well-being in all of the five subjects with a wide range of disability.6 Lower limb muscle strength is related to walking speed.7,8 It has been proposed that the prevention of walking deficits serves as a rationale for strengthening exercises in MS patients.7 On the other hand, aerobic exercise, such as cycling or aquatics, may increase isometric strength, isokinetic force production, or muscle endurance in MS patients.2,5 Further, aerobic exercise has been used to improve the functional gait of persons with MS.10,11 These studies, with a small number of patients and without any control group, have only shown slight exercise-induced effects on walking velocity and gait measures.10,11

Typically, exercise studies in MS have been conducted in laboratory or otherwise well-controlled conditions.2,4,6 Although these studies provide important knowledge regarding exercise responses in MS, it is essential to examine the effects of an exercise intervention performed under less ideal environments. Home exercise is a practical way of maintaining benefits obtained in formal rehabilitation settings.12 Studies of populations other than MS indicate that home exercise is convenient, cost-effective, and efficient.13-15

The purpose of this study was to evaluate the effects of a progressive 6-month exercise program (3 weeks during inpatient rehabilitation followed by 23 weeks at home) on walking and other aspects of physical function in MS patients with mild to moderate disability.

Methods. Design. Patients were evaluated at baseline and at 6 months in a randomized controlled two-center intervention study. A trained, non-blinded, independent examiner carried out the clin-
ical tests of physical function at the Masku Neurologic Rehabilitation Centre according to recommended guidelines. Other measurements were carried out in the laboratory of the Research Department of the Social Insurance Institution.

The patients in the intervention group completed an exercise program of 26 weeks. At the time of baseline visits, the control patients were advised to avoid any greater changes in their physical activity habits during the next 6 months. These patients were contacted three times by phone before the follow-up visit.

Patients. The patients were screened from a waiting list for inpatient rehabilitation at the Masku Neurologic Rehabilitation Centre, Masku, Finland, between 1999 and 2001. The inclusion criteria were diagnosis of clinically or laboratory supported MS,

arm holding a 7 kg (women) or 10 kg (men) dumbbell in both test. Gross manual dexterity was measured using the Box and block hands. The number of repetitions for both arms was recorded. The test protocol has been described in detail elsewhere.

balance disorders in ambulatory MS patients consisting of eight Sweden) was used for measuring peak oxygen uptake (VO2 peak).

tored cycle ergometer (Rodby Ergometer RE 820, Södertälje, Sweden) was used for measuring VO2 peak. The patients in the intervention group completed an exercise program (weeks 1 to 3) and followed by a progressive home-based exercise program (weeks 4 to 26). Ten supervised strength training and aerobic exercise sessions (five times each) were carried out during inpatient rehabilitation. Trained physiotherapists instructed the patients individually about an exercise program to be followed at home. At weeks 4 to 20, the program included three weekly strength training sessions and one aerobic exercise session. For the final weeks (21 to 26) one strength training session was added. At weeks 5, 8, 14, and 20, the patients were contacted by phone to monitor progress, to provide feedback and encouragement, and to answer questions.

Strength training. At weeks 1 to 3, an adaptation of circuit resistance training method was used. The patients did 10 exercises with 10 to 15 repetitions in two sets. The total circuit included four exercises for both lower and upper extremities, and two exercises for the trunk. At weeks 4 to 26, the strengthening exercise was mainly represented by resistance band exercises. Two exercises were done in a standing position for imitation of walking patterns. The patients were given two elastic bands (Theraband), one for the lower and the other for the upper extremities. At weeks 4 to 8, the program included two sets of 10 to 12 repetitions of each exercise. At week 9, the amount of repetitions was increased to 12 to 15. At week 15, new, stiffer elastic bands were delivered. Now, the repetitions were decreased to 10 to 12 for the rest of the exercise period.

Aerobic exercise. For weeks 1 to 3, aquatic training was chosen as a mode of aerobic exercise. For weeks 4 to 26, the patients were encouraged to continue with aquatic training, or with their earlier preferred mode of other aerobic exercise.

Exercise adherence. The patients kept a diary for each day of exercise. Adherence was determined for all exercise and for strength training and aerobic exercise separately using the number of exercise sessions reported as a percentage of exercise sessions prescribed for the home exercise period.

Sample size. Sample size was based on calculation for the 7.62 MWT. We defined a change of 20% to indicate a clinically meaningful improvement. To detect a difference of this magnitude between the groups, a minimum of 62 patients was needed to provide 90% power at two-sided α = 0.05. In sample size estimation we used as a reference a study in which the EDSS ranged from 1.0 to 3.5. Because we also considered patients with higher EDSS scores, and to allow for a reasonable dropout rate, we aimed to recruit a total of 100 patients.

Statistical analysis. The baseline characteristics between groups were compared using the t-test, Wilcoxon’s test, Mantel-Haenszel-test, or the χ2 test. Primary and most secondary outcomes were analyzed using a general linear model with repeated measures. Group and sex were included in the model as a between subject factor and time as a within subject factor. Covariate adjustment was applied if any imbalance was detected between groups, or if the covariate correlated with the outcome. As potential covariates, we chose EDSS and established biologic determinants of physical function. The Tukey-Cramer method was used to adjust for individual α level when multiple tests were done. In the Equiscale, differences between the groups were compared using the signed rank test. All group comparisons were based on an intention-to-treat analysis. The effect size statistic was calculated for the measures of the primary outcome. To interpret effect sizes, we used Cohen’s classification, where a value of 0.2 is small, 0.5 medium, and 0.8 or higher is large. All statistical analyses were done using the SAS for Windows package (SAS Institute, Cary, NC).

Results. Patients. Over an 8-month period in 2001, 276 patients were screened, and of these 114 were randomized to either the E or the C group. Data from 95 patients were included in the analyses (figure). Baseline subject characteristics were similar in both groups in most of the variables (table 1). There were no differences between the groups at baseline in either pyramidal functions (p = 0.11) or cerebellar functions (p = 0.46) of Kurtzke’s Functional Systems Scales.

Disease progression. No change (p = 0.93) over time was seen in neurologic status as measured by EDSS. The
Disability Status Scale; MS

The results of this randomized study show that long-term exercise led to significant and clinically meaningful changes in the walking speed of patients with mild to moderate MS. This was accompanied by significant improvements in upper extremity endurance. The intervention showed no effect between the groups on lower extremity endurance.
strength, VO2 peak, static balance, or manual dexterity. The clinical relapses of MS were evenly distributed between the two groups, showing that exercise has no detrimental effect on MS activity.

Our study adds important data on exercise responses in MS. Previously, three other randomized studies have examined the effects of regular exercise in MS patients.2,4,30 Unlike our study, two of them used aerobic training under supervision as an intervention. Their exercise period was also shorter than ours: 4, 8, and 15 weeks.2,4,30

We observed an improvement of 12% (7.62 MWT) and 6% (500 MWT) in walking speed in exercisers compared to 6% and no change in control patients. According to effect size statistics, the exercise group showed moderate or slight improvements in walk tests vs negligible changes in the control group. The fact that 22% of the exercisers exceeded the threshold of 20% improvement on the 7.62 MWT indicates a true change in function.27,31 Walking speed can be considered a key indicator of MS patients’ general mobility already at the early stages of the disease.32,33 Thus, there is a need to maintain and improve walking speed and other components of gait. Two earlier nonrandomized exercise studies in the field have given negative results.10,11

We chose walking speed as the primary outcome for several reasons. Restricted walking affects MS patients’ ability to participate in family, social, vocational, and leisure activities. In addition, walking speed, in the psychometric sense, is a continuous variable with a sensitivity to change over time superior to traditional ordinal scales such as EDSS.20,31 Third, walking deficits are major determinants of overall impairment in ambulatory MS patients.20 This was made concrete by our finding that a 1-point increase on EDSS meant about 47 seconds slower walking on the 500 MWT. We applied two walk tests, because the 7.62 MWT is basically a test of walking speed, whereas the 500 MWT measures ambulatory endurance.20

Although muscle strengthening was emphasized in the home exercise, we were unable to show any significant difference between the groups in knee flexor and extensor strength. A possible explanation is training specificity: the greatest strength gains occur when the same exercise type is used for both training and testing.34 Our measurement method, recording maximal static torque by a dynamometer, differed from exercises consisting of dynamic performance. In contrast to lower extremity strength, exercise resulted in improved upper extremity endurance, as measured by the dynamic weight lifting test. This supports the influence of training specificity, since one of the two home exercises for upper extremities closely resembled the test.

Our earlier cross-sectional study found no relationship between exercise capacity and leisure physical activity.25 The overall results on the VO2 peak are comparable to this. Yet 20 patients in the exercise group increased their VO2 peak by an average of 27%. It is likely that many of the exercisers increased their total volume of exercise, which in turn would have contributed to beneficial effects on the VO2 peak. For some reason as many as 25 patients in the control group also improved their VO2 peak (mean increase 14%). This may be a consequence of the unblinded study design.

To ensure unbiased group comparison provided by randomization, an intention-to-treat analysis was used. The justification for our approach was evidenced by the large variance in exercise adherence

<table>
<thead>
<tr>
<th>Exercise group</th>
<th>Control group</th>
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<tbody>
<tr>
<td>Change mean (95% CI)</td>
<td>Change mean (95% CI)</td>
</tr>
<tr>
<td>7.62 MWT (s)</td>
<td>5.0 (4.8 to 14.8)</td>
</tr>
<tr>
<td>500 MWT</td>
<td>0.1 (7.4 to 7.6)</td>
</tr>
<tr>
<td>Total time (min)</td>
<td>7.0 (1.2 to 12.8)</td>
</tr>
<tr>
<td>Time for 1st 50m (s)</td>
<td>4.4 (1.9 to 10.8)</td>
</tr>
<tr>
<td>Time for final 50m (s)</td>
<td>0.12 (2.12 to 2.36)</td>
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* Of change between groups with group by time interaction.
among the exercisers—intention-to-treat analysis reflects what might occur in actual clinical practice. Overall exercise adherence (93%) was excellent. However, the adherence rate of 59% for strength training fell markedly below the intended amount. In other studies using home-based resistance training, the adherence with the intervention protocol has been higher (78% or 95%). Continuous guidance and support may be crucial in home exercise. In our study, the frequency of the four phone contacts may have been insufficient to motivate the patients to exercise as requested.

Our study has several limitations. The assessment of exercise adherence was based on self-report diaries. Our impression was that some of the exercisers who assessed walking speed was not completely blinded to group allocation. We tried to overcome this weakness by following strictly the practical guidelines set for independent assessment in randomized controlled trials. Finally, we had to complete the random allocation of the patients to groups before fully confirming their eligibility. The explanation is logistic: all study patients were on the waiting list for inpatient adaptation training courses organized nationally in a rehabilitation center. The course date was negotiated individually with each patient, considering working or family life. Because of possible long traveling distances, the patients could not be examined before admission. Thus, randomization had to be done before setting the date of the inpatient course. We believe that the post-randomization exclusions were justified because the patients never received the intervention, and because an independent adjudication committee systematically reviewed all these patients.

Acknowledgment

The authors thank Saija Aalto, Sanna Arola-Talve, Mailis Ayräs, and Sirpa Reiman-Kiikki for help with data collection.

References