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Resistance training improves strength and functional capacity in persons with multiple sclerosis

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The purpose of this study was to evaluate the effect of an eight-week progressive resistance training programme on lower extremity strength, ambulatory function, fatigue and self-reported disability in multiple sclerosis (MS) patients (mean disability score 3.7 ± 0.8). Eight MS subjects volunteered for twice weekly training sessions. During the first two weeks, subjects completed one set of 8–10 reps at 50% of maximal voluntary contraction (MVC) of knee flexion, knee extension and plantarflexion exercises. In subsequent sessions, the subjects completed one set of 10–15 repetitions at 70% of MVC. The resistance was increased by 2–5% when subjects completed 15 repetitions in consecutive sessions. Isometric strength of the quadriceps, hamstring, plantarflexor and dorsiflexor muscle groups was assessed before and after the training programme using an isokinetic dynamometer. Magnetic resonance images of the thigh were acquired before and after the exercise programme as were walking speed (25-ft), number of steps in 3 min, and self-reported fatigue and disability. Knee extension (7.4%), plantarflexion (52%) and stepping performance (8.7%) increased significantly ($P < 0.05$). Self-reported fatigue decreased ($P < 0.05$) and disability tended to decrease ($P = 0.07$) following the training programme. MS patients are capable of making positive adaptations to resistance training that are associated with improved ambulation and decreased fatigue.
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Introduction

Multiple sclerosis (MS) is a degenerative inflammatory disease of the central nervous system, which may involve the brain, optic nerve and spinal cord,[1] and is the most common disabling neurologic disease of young adults in the USA.[2] MS is thought to be an autoimmune disorder that leads to the destruction of myelin, oligodendrocytes and axons.[3] Functional impairments in MS such as abnormal walking mechanics, poor balance, muscle weakness and fatigue typically result from axonal degeneration and conduction block. These and other symptoms reduce individuals' ability to perform activities of daily living. Therapeutic strategies to promote improvements in muscle strength and endurance are desirable in individuals with MS.[4] Exercise-training programmes designed to enhance fitness would be beneficial in improving the functional capacity of individuals with MS and offset the deleterious effects of their disease.

Aerobic exercise training studies have shown that regular activity improves cardiovascular fitness[5–7] and strength,[6,8] reduces depression[6] and fatigue,[6–8] and contributes to improved ambulatory function, thus enhancing quality of life. However, the impact of resistance training on functional capacity in MS subjects remains relatively unexplored. Thus, the primary purpose of this study was to evaluate the effectiveness of resistance training on muscle strength, ambulation, fatigue and perceived disability in individuals with MS. We hypothesized that lower body progressive resistance training in subjects with MS would result in increased leg strength and improved functional measures.

Methods

Eight individuals with MS (one male and seven females) (25–55 years) volunteered to participate and had physician clearance prior to study enrolment. Subject inclusion criteria consisted of physician-diagnosed MS with a self-assessed Kurtzke Expanded Disability Status Scale (EDSS) score between 1 and 5.[9] All subjects participated in light physical activity for three months prior to the study. Subjects using MS disease-modifying drugs (interferon beta 1α and 1β, glatiramer acetate) were included. Individuals with cardiovascular disease, thyroid disorders, gout

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or orthopaedic limitations were excluded. Individuals using prednisone or antispasmotic drugs were also excluded. All subjects signed an informed consent approved by the University Institutional Review Board. Subject characteristics are presented in Table 1.

Study design

Subjects participated in a 13-week experimental period wherein the first three weeks consisted of participant screening, study orientation and baseline measurements of lower limb muscle strength, muscle activation, quadriceps cross-sectional area (CSA), body composition, walking speed, stepping rate, perceived fatigue and self-reported disability. During the next eight weeks subjects participated in a twice-weekly resistance-training programme with 48-hour rest between exercise sessions. During the final two weeks of the experimental period, all initial measures were re-evaluated.

Training protocol

Subjects completed supervised resistance training (twice-weekly) exercises for eight consecutive weeks. Results from the baseline strength testing were used to estimate the resistance load used to prescribe exercise during training. All subjects performed a warm-up set at the beginning of each training session (5 reps at 40% maximal voluntary contraction (MVC) on each machine). During the first week of training, subjects performed one set of 6–10 reps at 50% of MVC. During the second week, subjects performed one set of 10–15 repetitions at 60% MVC. In subsequent sessions, subjects completed one set of 10–15 repetitions at 70% of maximal predicted force for all lower body exercises consisting of knee flexion/extension, plantarflexion and spinal flexion/extension using conventional weight machines. No conventional weight machine was available for training the dorsiflexors. Training duration did not exceed 30 min/session. When subjects were able to complete 15 repetitions in consecutive sessions, the resistance was increased by 2–5%.[10] This protocol was adopted from ACSM resistance training guidelines for apparently healthy (low risk) adults and healthy individuals.[11] Strength measures were reassessed following 8 weeks of resistance training.

Muscle strength testing

Lower limb muscle strength was evaluated using an isokinetic dynamometer (Chattanooga, TN) with subjects positioned specifically for each exercise (knee and ankle flexion and extension) with joints stabilized. Maximal voluntary isometric (MVIC) strength for knee strength was tested with the ankle at 0° plantar flexion and 90° knee flexion, and for plantar/dorsiflexion at 0° plantar flexion. Subjects completed a standardized warm-up prior to strength testing. Maximal isometric strength was defined as the highest torque observed over three contractions (3 seconds each with five minute rest intervals).

Table 1 Characteristics of subjects

Variable	*Mean ± SD*
Age (years)	46 ± 12
Height (cm)	166 ± 8
Mass (kg)	74 ± 17
% Body fat	34 ± 9
BMI (kg/m^2)	27 ± 6
Self reported EDSS	3.7 ± 1

Muscle activation testing

Measures of quadriceps strength were accompanied by an assessment of voluntary muscle activation. Quadriceps activation was determined by superimposing a supramaximal intensity electrical stimulus on a maximal voluntary isometric quadriceps muscle contraction (burst-superimposition technique).[12] Briefly, subjects were seated and stabilized on the electromechanical dynamometer with their hips flexed to 85° and their knees flexed to 90°. The axis of the dynamometer was aligned with the axis of the knee joint and the bottom of the force transducer pad was positioned against the anterior aspect of the leg, proximal to the lateral malleolus. Two 7.6 × 12 cm self adhesive electrodes were placed over the motor points of the proximal rectus femoris and the distal vastus medialis. A Grass S48 stimulator (Quincy, MA) with a Grass Model SIU8T stimulus isolation unit (Grass Instruments, West Warwick, RI) was used to deliver monophasic, rectangular pulses with a 600-μs pulse duration. The stimulator was manually triggered during the testing and data was acquired on a personal computer using Peak Performance software (Peak Performance Technologies Inc., Motus, Englewood, CO). Data were acquired at 15 000 Hz during all testing sessions.

Prior to testing, subjects were allowed two warm-up attempts to familiarize them with the testing procedures. During all testing, subjects were given verbal encouragement and visual feedback from the dynamometer's real-time force display. The intensity of the supramaximal electrical stimulus was determined for each patient by delivering 13 pulse, 100 pps trains to the quadriceps at rest and increasing the intensity of the stimulus until the electrically elicited force production plateaued.

The central activation ratio (CAR) was calculated by dividing the subject's maximum voluntary force produced prior to delivery of the stimulation train by the maximum force produced during the superimposed train.[13] The CAR was used to quantify the degree of volitional activation of the quadriceps during MVIC.

Quantification of the muscle contractile area

Subjects were placed in a supine position aligned with the bore of a 3-Tesla whole body magnet (General Electric) following 30 min of rest in a supine position to minimize fluid accumulation in the legs. Three-dimensional data were collected from the upper thigh to the knee, using a fast gradient-echo sequence, with TR = 100 ms, TE = 10 ms and flip angle of 30°. The images were acquired with an encoding matrix of 256 × 256 × 28, a field of view of 16 × 16 × 19.6 cm and a 7 mm slice thickness. Chemically selective fat suppression optimization was employed to enhance the definition between muscles.[14]

Muscle CSA and volume were determined using the acquired 3D-MR images and an interactive computer segmentation procedure[15] linked to an IDL software programme (Boulder, CO). Nonmuscular regions i.e., subcutaneous fat, bone, nerves and blood vessels were excluded from the muscle area and volume measurements. The CSA of the thigh was recorded and independent analysis of the quadriceps and hamstrings was also performed. Muscle volume was quantified using five consecutive slices above and below the landmark. The landmark was placed one third the distance from the superior margin of the patella and superior margin of the iliac crest as previously reported by White *et al*.[16] Calculation of the fat-free muscle CSA of the posterior and anterior compartment of the thigh was enhanced using a custom-designed interactive computer programme that allows for correction of partial volume filling effects.[14] Subjects were asked to consume the same diet prior to each magnetic resonance scanning session to control for the effects of glycogen storage on CSA measurements.[17] A single investigator, blinded to the study procedures, analysed each data set.

Body composition

Percent body fat was estimated before and after the strength training programme using a three-site skinfold measurement of subcutaneous fat.[18] The sum of skinfolds was used to calculate body density. Body density was used to estimate body composition according to Brozek *et al*.[19]

Ambulatory function

Two measures of ambulatory function were assessed before and after the eight-week resistance-training programme. The first measure consisted of a 25-ft walking test; the second measure was a three minutes step test. Subjects performed the walk test twice with five minutes of recovery between trials. The average speed was used as the criterion measure for walking the maximal number of steps completed in three minutes was the criterion measure for stepping.

Self-reported fatigue and disability

The modified fatigue impact scale (MFIS)[20] and self-assessed EDSS[2] were completed by each subject upon study enrolment and following the eight-week training period. Subjects were given standard instructions to complete each questionnaire.[2,20]

Nutritional analysis

Subjects recorded a three-day food intake every two weeks for six weeks. Food records were analysed by Nutritionist Pro software (v. 2.0, 2003, First Data Bank, San Bruno, CA, USA). The average nutrient was calculated from the intake from the 3×3-day averages and used to determine total energy and macronutrients intake for each subject. Nutrient intake was compared to Recommended Dietary Allowances (RDA).

Statistical analysis

Comparisons between pre- and post-training measures of strength, muscle CSA and volume, body composition, ambulatory function, and nutrition were analysed using a paired t-test with a Bonferroni correction for multiple t-tests. The CAR, self-reported EDSS and MFIS were analysed with the Wilcoxon signed ranks test. A one-way ANOVA was performed on training data to evaluate changes in training volume during the exercise intervention. Data are presented as mean ± standard deviation (SD). Significance was established when $P < 0.05$.

Results

All subjects completed the resistance-training programme (16 sessions) with 100% adherence. However, some subjects skipped several days between workouts for personal reasons. No MS exacerbations were reported during the eight-week training programme. During the first two weeks of the training period, one subject reported low back muscle soreness and three subjects reported mild leg muscle soreness. Patient reported symptoms diminished after 72 hours.

Strength

Strength measures are reported as strength/weight ratio, and therefore, data are presented as Newton/weight (N/kg) as shown in Figure 1. Significant increases were observed for knee extension (7.4%, $P = 0.03$) and plantar flexion (52%, $P = 0.04$). However, despite the average increase in knee flexion (43%) and dorsiflexion (9%) strength (dorsiflexors remained untrained), these changes were not significant ($P = 0.1$ and $P = 0.3$, respectively). The average absolute strength values for knee extension were 249 ± 69 Newtons (N) (range 150–380 N); knee flexion strength was 131 ± 37 N (range 73–157 N); plantar flexion strength was 463 ± 156 N (range 218–700 N); dorsiflexion strength was

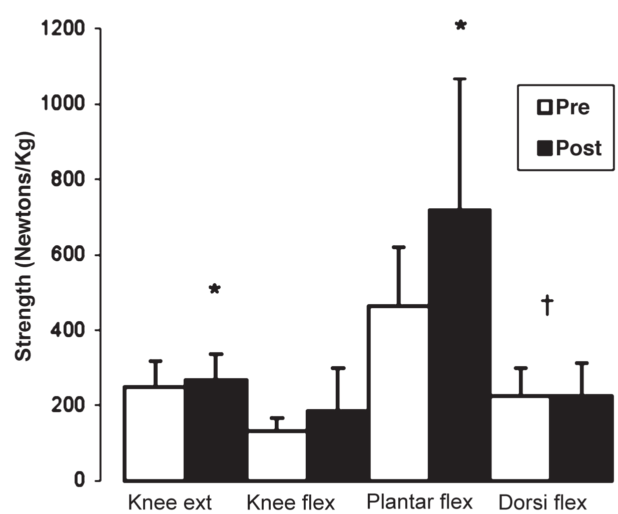

Figure 1 *Muscle strength before and after the eight-week resistance training programme. *Denotes* P *< 0.05; †Denotes muscle not trained.*

224 ± 76 N (range 118–345 N). The hamstring to quadriceps ratio was 0.53 ± 0.13 at baseline and 0.67 ± 0.21 after training ($P = 0.1$).

Training volume

Training volume was calculated as the sum of the maximal training weight for 10 repetitions (leg extension and leg curl) completed during each week for all subjects (Figure 2). During the first three weeks of the experimental period, there were no significant changes in weekly training volume compared to week 1 ($P > 0.05$). During weeks 4–8, training volume was significantly higher than baseline (weeks 1–3) values ($P < 0.01$). Week-by-week training volume was not significantly increased during weeks 5–7 ($P > 0.05$) and remained unchanged until week 8 where training volume significantly increased over values recorded during week 4 ($P < 0.05$).

Muscle cross-sectional area (CSA) and muscle volume

Following the training programme, quadriceps and hamstring muscle CSA and muscle volume remained unchanged from pretraining values ($P > 0.05$). Before training, average quadriceps CSA over seven slices was 43.1 ± 3.9 cm^2, while after training was 43.4 ± 4.7 cm^2, representing a 0.7% increase in quadriceps cross-sectional area ($P > 0.05$). Average hamstring CSA over seven slices was 28.6 ± 7.7 cm^2, and after training were 31.3 ± 6.6 cm^2, representing a 9.5% increase in hamstring cross-sectional area ($P > 0.05$). Muscle volume (cm^3) was calculated by multiplying the muscle CSA by slice thickness (7 mm) and then summing the analysed seven slices. Muscle volume in the quadriceps was 211.1 ± 19 cm^3 before training and 213 ± 23 cm^3 after training, representing a 1% increase in muscle volume ($P > 0.05$). Hamstring muscle volume was 140 ± 37.5 cm^3 before training and 153 ± 32.3 cm^3 after training, representing a 9.2% increase in muscle volume ($P > 0.05$). Within samples, the coefficient of variation for

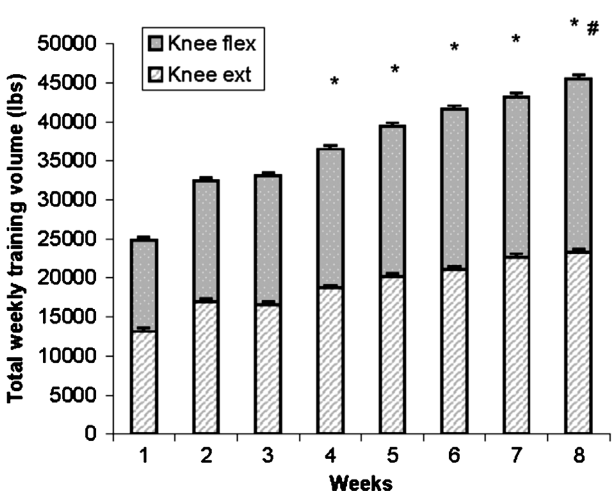

Figure 2 Total weekly training volume (load × repetitions) of the quadriceps and hamstring muscle groups in MS subjects completed during eight weeks of progressive resistance training. Data is expressed as sum ± SD. *P < 0.05 *compared to baseline;* #P < 0.05 *compared to week 4.*

muscle area and muscle volume quantification by the same investigator on different days was 1.38 and 0.8%, respectively. This is consistent with previous reports where the methodological error in assessing muscle volume analysed by the same investigator on different days using a similar procedure is < 2%.[21]

Central activation ratio (CAR)

The derived CAR[13] was 0.95 ± 0.05 at baseline and remained unchanged following eight weeks of resistance training 0.97 ± 0.05 ($P = 0.367$). The values for the CAR ranged from 0.86 to 1.0 at both baseline and following the training programme (Table 2).

Functional measures

There was no significant change in 25-ft walking speed following the eight-week resistance-training programme. The average walking time to complete 25-ft at baseline (6.1 ± 2.1 s) did not change following training (6.2 ± 2.5 s, $P = 0.4$). However, steps completed in three minutes increased significantly ($P = 0.03$) and represented an 8.7% improvement (Table 2).

Self-reported fatigue (MFIS) and disability (EDSS)

The MFIS was used to assess fatigue before and after the eight-week strength training intervention.[20,22] The average fatigue score at baseline was 32 and decreased to 26 following the eight-week training period ($P = 0.04$) (Figure 3). Self-reported EDSS tended to decrease from 3.7 to 3.2 after eight weeks of strength training ($P = 0.072$) (Table 2).

Nutrient intake

The average nutrient intake of our subjects was based on RDA for activity, age and sex. Subjects consumed an average of 1489 ± 424 kcal (range 1014–2111), representing 71% of the daily recommendations. Carbohydrate intake was an average of 191 g (range 105–303 g) (73% of daily recommendations) or 50% of total caloric intake. Protein intake averaged 65 ± 14 g (range 54–110 g) (60% of daily recommendations) or 17.5% of total caloric intake. The average fat intake of our subjects was 56 ± 23 g (range 33–101 g) (80% of daily recommendations) or 32.8% of total caloric intake.

Body composition

Body weight remained unchanged following the exercise programme ($P = 0.88$). The estimated percent body fat of

Table 2 Functional measures and CAR before and after the resistance training intervention in MS participants

	Pre	*Post*	*% Diff*	*N*	P*-value*
CAR	0.95 ± 0.05	0.97 ± 0.05	+4	7	0.367
Walk time (s)	6.1 ± 2	6.2 ± 2.5	+2	7	0.373
Step test (steps)	64.5 ± 13	70.1 ± 19	+8.7	8	0.027*
MFIS	32 ± 18	25.8 ± 17	−24	5	0.040*
Self-reported EDSS	3.7 ± 0.8	3.2 ± 1.4	−15.6	8	0.072

*Denotes significant difference from pretraining values $P < 0.05$.

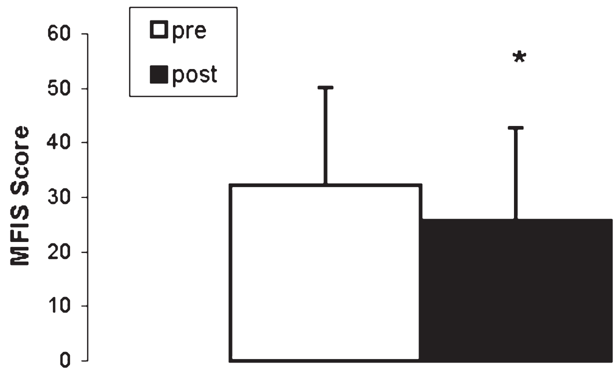

Figure 3 *Self-reported fatigue score before and after resistance training (P < 0.05).*

our subjects was 34 ± 9% and remained unchanged following the exercise programme ($P = 0.46$). Body mass index was 27 ± 6 and also remained unchanged following the training programme ($P = 0.27$) (Table 1).

Discussion

Muscle weakness is a hallmark symptom of MS and is associated with fatigue, reduced functional capacity and increased disability. In this study, we hypothesized that individuals with MS would increase muscle strength in response to a conventional eight-week strength-training programme targeted at the lower limbs. Furthermore, we speculated that increases in strength would be associated with improved ambulatory function and a reduction in fatigue in MS subjects.

Following the eight-week strength-training programme, our subjects showed significant improvements in strength during knee extension (7.4%) and plantarflexion (52%) exercises. Knee flexion strength increased after training (43%), but was not significantly different from baseline ($P = 0.1$). Our results corroborate previously published reports regarding the effect of strength training in patients with neuromuscular disorders such as spinal muscular atrophy or facioscapulohumeral muscular dystrophy. In their study, McCartney *et al*. found improvements in arm (19–34%) and leg (11–50%) strength after a nine-week strength-training programme.[23] In addition, Spector *et al.* found large increases in muscle strength in post polio patients.[24] For example, increases in knee extension (41–61%) and elbow extensor (54–71%) strength were observed following 10 weeks of strength training.[24] Our results suggest that patients with MS can make improvements in skeletal muscle strength after eight weeks of progressive resistance training.

Resistance training resulted in increased strength that could not be accounted for from our data based on either muscle contractile volume or muscle activation. It is possible however, that a shift in fibre type or improved contractile efficiency occurred in our subjects. Studies using a larger sample size or longer duration may improve our understanding of muscle-specific adaptations to resistance training in ambulatory MS patients. Our results are consistent with Hakkinen *et al.*,[25] who found no increases in muscle CSA after six months of strength training despite increases in leg strength. The thigh CSA of our MS subjects are similar to those reported for healthy individuals of similar characteristics (43 cm^2 in MS versus 40 cm^2 reported in healthy females).[25] Beelen *et al*. found that quadriceps CSA was lower in polio subjects compared to healthy matched controls.[26] Furthermore, polio subjects had a significantly smaller CSA of the affected leg compared to the nonaffected leg (28.6 versus 64.3 cm^2 respectively).[26] However, we cannot rule out the possibility that the modest training intensity and duration was an insufficient stimulus for hypertrophic adaptations. In addition, the reported nutrient intake of our subjects revealed inadequate caloric and protein intake further compromising possible anabolic adaptations in skeletal muscle of our subjects.

Self-reported fatigue, assessed through the MFIS, decreased significantly (24%) following the training programme, supporting our hypothesis and indicating that a short-term exercise regimen reduced self-perceived fatigue. Approximately 65% of individuals with MS report fatigue limitations, and 14–28% report that it is the most disabling symptom.[27,28] Fatigue can significantly interfere with functional ability at home or work, and may be the most prominent symptom in a patient who otherwise has minimal activity limitations. Although the mechanism of MS-related fatigue remains controversial, our results suggest that fatigue may be reduced with regular strength training. Improving strength in individuals with MS can enhance functional reserve, thus making daily activities less fatiguing.

Our subjects had a baseline BMI of 27, which falls into the overweight category.[10] Excess body weight may contribute to increased fatigue.[29] Thus, in individuals with high fatigueability, a reduction in body fat may be advantageous. There was no change in BMI or body composition following the experimental period.

Our subjects improved their stepping rate by 8.7% following the eight-week strength training programme, which supports our hypothesis that muscle strength gains would be associated with improved stepping. Our results show that strength training in MS is associated with improved stepping. In contrast, 25-ft walking speed and walk time remained unchanged following the training programme, which is consistent with a previous investigation.[30] Our subjects had a mean walk time of 6.2 seconds, which is reflective of moderately disability levels in individuals with MS.[31] Given the short test distance, we may have not been able to detect subtle changes in walking ability. It has been suggested that large increases (20%) in 25-ft walk time may reflect detrimental changes in gait.[31] A longer walking test may be more sensitive to changes in walking speed associated with exercise interventions in individuals with MS.

The hamstring to quadriceps ratio (H/Q ratio) in our subjects was 0.53 at baseline and 0.67 following training. According Kannus *et al*.,[32] healthy individuals have a hamstring to quadriceps ratio of 0.50–0.60 and therefore our subjects were within the normal range. Assessment and tracking of the H:Q may be valuable in the clinical setting because a coupling of weak hamstring muscles with strong quadriceps may interrupt the optimal derotation of the pelvis and may contribute to low back pain and injuries.[33] The deficits in the H:Q ratio at a level of ≤ 0.45 are implicated in the severity of low back injury in active individuals.[33] The occurrence of these muscle imbalances may be caused by the presence of hypertonic or weak muscles.[33] In the clinical rehabilitation setting, the assessment of muscle balance (e.g., agonist/antagonist and bilateral) strength evaluation is recommended for prescribing training programmes to optimize function in the MS population.

Self-reported disability tended to decrease in all subjects following the exercise programme suggesting an improvement in their disability after two months of strength training (from EDSS 3.7 to 3.2, $P = 0.07$). This finding in combination with the improved muscle strength, stepping performance and reduced fatigue suggests those patients with MS can offset the decline in strength and disability through a programme of strength training. Our findings show similar outcomes to those reported for aerobic exercise training programmes.[5,6]

Findings from aerobic exercise training studies indicate that MS patients can gain a wide variety of benefits from individualized aerobic exercise programmes. Importantly, prescribed exercise does not appear to increase the rate of MS exacerbations[6] as was the case in our study. The benefits of regular aerobic exercise in MS include enhanced fitness, reduced fatigue, improved mood and the ability to perform tasks of daily living with increased energy. For example, Petajan *et al*. found that regular aerobic exercise enhanced strength, improved bladder and bowel function, reduced fatigue and depression, improved positive attitude, and increased participation in social activities.[6] Regular exercise may help prevent comorbidities such as obesity, heart disease, diabetes and osteoporosis. In another autoimmune disease, rheumatoid arthritis (RA), exercise is used as a therapeutic technique. According to Hakkinen *et al*.,[34] twice weekly progressive resistance training exercise using single sets at a 50–70% of 1 RM enhance muscle strength, reduce clinical disease activity and promote walking speed in RA patients.[25,34] Hakkinen and colleagues also suggested that individuals with autoimmune disease such as RA may need continuous physical activity to prevent losses in muscular strength and functional capacity.[25]

In spite of the precautionary stance regarding exercise in MS, regular activity has been repeatedly shown to have important health benefits in patients with MS.[35,36] Under appropriate supervision, resistance training appears to be a well tolerated intervention for improving strength and ambulatory function while also reducing fatigue in MS patients. Continued research to further understand the role of exercise in maintaining muscle mass, functional status as well as the potential impact on disease progression is warranted.

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References

1 Wolinsky JS. The diagnosis of primary progressive multiple sclerosis. *J Neurol Sci* 2003; **206**: 145–52.
2 Frohman EM. Multiple sclerosis. *Med Clin North Am* 2003; **87**: 867–97, viii–ix.
3 Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. *N Engl J Med* 2000; **343**: 938–52.
4 Armstrong LE, Winant DM, Swasey PR, Seidle ME, Carter AL, Gehlsen G. Using isokinetic dynamometry to test ambulatory patients with multiple sclerosis. *Phys Ther* 1983; **63**: 1274–79.
5 Ponichtera-Mulcare JA, Matthews T, Barret PJ, Glaser RM. Change in aerobic fitness of patients with multiple sclerosis during a 6-month training program. *Sports Med Train Rehabil* 1997; **7**: 265–72.
6 Petajan JH, Gappmaier E, White AT, Spencer MK, Mino L, Hicks RW. Impact of aerobic training on fitness and quality of life in multiple sclerosis. *Ann Neurol* 1996; **39**: 432–41.
7 Mostert S, Kesselring J. Effects of a short-term exercise training program on aerobic fitness, fatigue, health perception and activity level of subjects with multiple sclerosis. *Mult Scler* 2002; **8**: 161–68.
8 Gehlsen GM, Grigsby SA, Winant DM. Effects of an aquatic fitness program on the muscular strength and endurance of patients with multiple sclerosis. *Phys Ther* 1984; **64**: 653–57.
9 Scheinberg LC, Feldman FM, Ratzker EA. Self-assessment of neurological impairment in multiple sclerosis. *Neurology* 1986; **36**: 284.
10 ACSM. ACSM's guidelines for exercise testing and prescription, sixth edition. Philadelphia, PA: Lippincott Williams & Wilkins, 2000.
11 Phillips WT, Ziuraitis JR. Energy cost of the ACSM single-set resistance training protocol. *J Strength Cond Res* 2003; **17**: 350–55.
12 Stackhouse SK, Stevens JE, Lee SC, Pearce KM, Snyder-Mackler L, Binder-Macleod SA. Maximum voluntary activation in nonfatigued and fatigued muscle of young and elderly individuals. *Phys Ther* 2001; **81**: 1102–109.
13 Kent-Braun JA, Le Blanc R. Quantitation of central activation failure during maximal voluntary contractions in humans. *Muscle Nerve* 1996; **19**: 861–69.
14 Elliott MA, Walter GA, Gulish H, Sadi AS, Lawson DD, Jaffe W, *et al.* Volumetric measurement of human calf muscle from magnetic resonance imaging. *Magma* 1997; **5**: 93–98.
15 Clarke LP, Velthuizen RP, Camacho MA, Heine JJ, Vaidyanathan M, Hall LO *et al*. MRI segmentation: methods and applications. *Magn Reson Imaging* 1995; **13**: 343–68.
16 White LJ, Robergs RA, Sibbitt WL Jr, Ferguson MA, McCoy S, Brooks WM. Effects of intermittent cycle exercise on intramyocellular lipid use and recovery. *Lipids* 2003; **38**: 9–13.

17 Nygren AT, Karlsson M, Norman B, Kaijser L. Effect of glycogen loading on skeletal muscle cross-sectional area and T2 relaxation time. *Acta Physiol Scand* 2001; **173**: 385–90.
18 Jackson AS, Pollock ML. Generalized equations for predicting body density of men. *Br J Nutr* 1978; **40**: 497–504.
19 Brozek J, Grande F, Anderson JT, Keys A. Densitometric analysis of body composition: revision of some quantitative assumptions. *Ann N Y Acad Sci* 1963; **110**: 113–40.
20 Flachenecker P, Kumpfel T, Kallmann B, Gottschalk M, Grauer O, Rieckmann P, *et al*. Fatigue in multiple sclerosis: a comparison of different rating scales and correlation to clinical parameters. *Mult Scler* 2002; **8**: 523–26.
21 Trappe TA, Lindquist DM, Carrithers JA. Muscle-specific atrophy of the quadriceps femoris with aging. *J Appl Physiol* 2001; **90**: 2070–74.
22 Gillson G, Wright JV, DeLack E, Ballasiotes G. Transdermal histamine in multiple sclerosis, part two: a proposed theoretical basis for its use. *Altern Med Rev* 2000; **5**: 224–48.
23 McCartney N, Moroz D, Garner SH, McComas AJ. The effects of strength training in patients with selected neuromuscular disorders. *Med Sci Sports Exerc* 1988; **20**: 362–68.
24 Spector SA, Gordon PL, Feuerstein IM, Sivakumar K, Hurley BF, Dalakas MC. Strength gains without muscle injury after strength training in patients with postpolio muscular atrophy. *Muscle Nerve* 1996; **19**: 1282–90.
25 Hakkinen A, Sokka T, Kotaniemi A, Hannonen P. A randomized two-year study of the effects of dynamic strength training on muscle strength, disease activity, functional capacity, and bone mineral density in early rheumatoid arthritis. *Arthritis Rheum* 2001; **44**: 515–22.
26 Beelen A, Nollet F, de Visser M, de Jong BA, Lankhorst GJ, Sargeant AJ. Quadriceps muscle strength and voluntary activation after polio. *Muscle Nerve* 2003; **28**: 218–26.
27 Fisk JD, Pontefract A, Ritvo PG, Archibald CJ, Murray TJ. The impact of fatigue on patients with multiple sclerosis. *Can J Neurol Sci* 1994; **21**: 9–14.
28 Bergamaschi R, Romani A, Versino M, Poli R, Cosi V. Clinical aspects of fatigue in multiple sclerosis. *Funct Neurol* 1997; **12**: 247–51.
29 Sartorio A, Fontana P, Trecate L, Lafortuna CL. Short-term changes of fatigability and muscle performance in severe obese patients after an integrated body mass reduction program. *Diabetes Nutr Metab* 2003; **16**: 88–93.
30 Yates HA, Vardy TC, Kuchera ML, Ripley BD, Johnson JC. Effects of osteopathic manipulative treatment and concentric and eccentric maximal-effort exercise on women with multiple sclerosis: a pilot study. *J Am Osteopath Assoc* 2002; **102**: 267–75.
31 Kaufman M, Moyer D, Norton J. The significant change for the timed 25-foot walk in the multiple sclerosis functional composite. *Mult Scler* 2000; **6**: 286–90.
32 Kannus P, Jarvinen M. Long-term prognosis of conservatively treated acute knee ligament injuries in competitive and spare time sportsmen. *Int J Sports Med* 1987; **8**: 348–51.
33 Koutedakis Y, Frischknecht R, Murthy M. Knee flexion to extension peak torque ratios and low-back injuries in highly active individuals. *Int J Sports Med* 1997; **18**: 290–95.
34 Hakkinen A, Sokka T, Kotaniemi A, Kautiainen H, Jappinen I, Laitinen L, *et al*. Dynamic strength training in patients with early rheumatoid arthritis increases muscle strength but not bone mineral density. *J Rheumatol* 1999; **26**: 1257–63.
35 Poser S, Kurtzke JF. Epidemiology of MS. *Neurology* 1991; **41**: 157–58.
36 Sutherland G, Andersen MB. Exercise and multiple sclerosis: physiological, psychological, and quality of life issues. *J Sports Med Phys Fitness* 2001; **41**: 421–32.