Exercise in Multiple Sclerosis

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KEYWORDS

• Multiple • Sclerosis • Exercise • Resistance • Endurance • Training

KEY POINTS

- Exercise is an intervention that may be used in the management of multiple sclerosis (MS).
- Certain exercise physiology characteristics are commonly seen among persons with MS, particularly in the more debilitated.
- Studies have shown numerous beneficial effects of exercise in MS.
- There are general guidelines that may be followed for proper exercise prescription for the MS population.
- There are several recommendations that may help improve the quality of future MS exercise trials.

INTRODUCTION

Views regarding exercise in persons with MS have been evolving over the years. The old paradigm was to discourage persons with MS from exercising to avoid increases in core body temperature that would exacerbate MS-related signs and symptoms.[1–3] It was believed that this strategy would conserve energy and make it available for activities of daily living (ADLs).[3] Furthermore, because fatigue is a common symptom in MS, it was previously thought that fatigue would prevent persons with MS from tolerating much exercise.[1] The more recent paradigm is to encourage an appropriate level of exercise in persons with MS in an effort to reduce MS-related symptoms and to promote general wellness.

The impairments seen in MS may result from either the disease process per se or from deconditioning.[3–8] Impairments from the disease process itself (ie, due to demyelination and axonal degeneration) are probably not reversible with exercise. Impairments from deconditioning (ie, as a consequence of reduced physical activity levels) are probably reversible with exercise.

There are well-known detrimental effects of a general lack of exercise. A sedentary lifestyle is strongly associated with increased morbidity and mortality rates among

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Phys Med Rehabil Clin N Am 24 (2013) 605–618
http://dx.doi.org/10.1016/j.pmr.2013.06.010 pmr.theclinics.com
1047-9651/13/$ – see front matter

non-MS adults.[9–11] These individuals have an increased risk of developing chronic health problems, such as obesity, cardiovascular disease,[1] type 2 diabetes, cancer, osteoporosis, and fatigue.[3,12,13] Physiologically, these individuals have reduced aerobic capacity, decreased muscle strength, and increased muscle atrophy.[3,14,15]

Similar findings are seen among persons with MS, with the more sedentary individuals displaying an increased incidence of cardiovascular disease, osteoporosis, and obesity.[9,16–21] Other preexisting MS-related symptoms, such as depression and fatigue, may worsen.[1,3] Very low activity levels in persons with MS often coincide with a loss in leisure activities, social contacts, or usual ADLs that are important for self-esteem and psychological well-being.[1,5,6]

Conversely, there are well-documented benefits of increased physical activity and exercise. Physical activity is associated with the following benefits: decreased risk of chronic health problems (such as cardiovascular disease, diabetes, osteoporosis, obesity, and depression), decreased incidence of premature mortality, and favorable effects on mental health.[9,22–24]

Given the overwhelming recommendations promoting increased physical activity and exercise in the general population, there has been great interest to determine if similar recommendations may be applied to persons with MS and reap similar benefits.

PHYSIOLOGIC CHARACTERISTICS OF PERSONS WITH MS

Studies have searched for characteristics unique among persons with MS in terms of cardiovascular and muscle physiology that are distinct from those of the general population. It may be difficult to generalize these characteristics among all persons with MS given the wide spectrum of prevalent impairments and disabilities. Specific MS-related physiologic characteristics likely are most evident in the more severely debilitated, whereas those with only mild MS may not be too physiologically different from their healthy, age-matched counterparts.

Generally speaking, and again these may be more evident in more debilitated individuals, the following physiologic characteristics were noted among persons with MS:

1. Decreased aerobic capacity (maximum oxygen consumption [$\dot{V}O_2max$]),[3,25,26] which was approximately 30% lower than in healthy controls[27]; even greater deficits were seen in maximum work rate at aerobic threshold, which suggests a very low training level and marked deconditioning[26,27]
2. Decreased maximal muscle strength, both during isokinetic[3,28–31] and isometric[3,7,8,28,32–38] muscle contractions, with strength impairment more prominent in the lower extremities than in the upper extremities[3,36]
3. Reduced comfortable and maximal gait velocity[3,39,40]
4. Lower health-related quality of life (HRQL)[3,41]

The following physiologic characteristics of persons with MS were inconsistent among various studies and are harder to generalize:

1. Increased resting heart rate[3,25,42–44]
2. Increased diastolic blood pressure[3,42,44]
3. Increased muscle atrophy[3,7,8,31]
4. Decreased rate of force development[3,32–35,38]
5. Decreased muscle mass[3,7,8,31,32,45,46]
6. Decreased fat-free mass at the whole-body level[3,45,46]
7. Shifts in muscle fiber–type composition from type I to type IIa and IIax (as seen in immobilized non-MS individuals)[3,46,47]

EXERCISE PHYSIOLOGY AND MS

Aerobic Capacity

Maximal aerobic capacity is influenced by the degree of physical impairment in persons with MS. Those with greater impairments can only exercise for a shorter period and can only achieve a lower maximal exercise intensity and lower $\dot{V}O_2$max. Aerobic capacity is limited by respiratory muscle dysfunction and deconditioning.[27,48–50]

Among persons with MS who are paraplegic, the upper limbs impose an upper limit to aerobic performance.[27,51,52] Thus, these individuals with limited lower extremity function due to weakness, spasticity, or cerebellar dysfunction may not be able to increase their metabolic rate enough to improve aerobic fitness. Their residual functional muscle mass may be too small to take up enough oxygen to get a cardiovascular workout.[27,53] Thus, the goal of aerobic exercise for the severely impaired should be more maintenance rather than improvement of cardiovascular fitness.[27]

Cardiovascular Dysautonomia

More debilitated persons with MS may exhibit cardiovascular dysautonomia. This is seen as a blunted heart rate and blood pressure response to exercise.[54,55] Regarding blunted blood pressure response, there may be an attenuated rise in blood pressure during exercise.[44,54,56] This may lead to insufficient perfusion of brain or muscle and premature development of exertional symptoms, such as lightheadedness or muscle fatigue. Thus heart rate, blood pressure, and clinical symptoms should be carefully monitored in MS individuals with known or suspected cardiovascular dysautonomia.

Muscle Strength and Endurance

Persons with MS typically have less muscle strength compared with healthy controls,[28,29,35,54–60] a slower rate of muscle tension, and reduced muscle endurance.[36,54] In mild cases of MS, however, muscle function is close to normal.[27]

Flexibility

Persons with MS often have decreased flexibility, especially in those with spasticity. This has to be properly assessed and taken into consideration when designing the exercise prescription.[54]

Heat Intolerance

A frequent concern with exercise in MS is potentially triggering Uhthoff phenomenon. Uhthoff phenomenon was originally described as a transient amblyopia due to overheating from exercise.[27,61] The term has since been expanded to include other symptoms triggered by overheating.[27,62] The exact mechanism of Uhthoff phenomenon is unclear. It may be due to heat-worsened conduction across partially demyelinated axons, fatigue of damaged neuronal pathways with repetitive nerve transmission,[27,63] or a hormonal factor produced with cooling.[4,64]

Exercise-induced Uhthoff phenomenon should not be regarded as a contraindication to exercise.[27] It is usually reversible and often resolves within an hour or even sooner with rapid cooling.[27] Furthermore, it is still more common for heating to produce just general fatigue than an Uhthoff phenomenon with focal neurologic deficits.[27,49]

How much does the body temperature change with exercise? Studies have shown that routine exercise does not significantly increase core body temperature.

Ponichtera-Mulcare and colleagues[55] noted a mean rectal temperature change of 0.1°C during land-based exercise and −0.1°C during water-based exercise.[27] Alternatively, normal thermoregulatory reflexes (eg, sweating and vasodilatation) that maintain a steady core temperature during routine exercise may be impaired in persons with MS. In such cases, a rise in core temperature of even less than 1°C may be enough to trigger heat-related symptoms.[27,65]

The use of cooling devices and strategies seems to provide some modest benefits for persons with MS. One such device, used by Capello and colleagues[66] and Kraft and Alquist,[67] was a head-vest liquid cooling garment. The former found a slight improvement in pyramidal and cerebellar function[27] whereas the latter demonstrated a treatment effect for strength, dynamic coordination, and endurance capacity, with greater heat loss associated with greater motor function gain.[27,67] Syndulko and colleagues[68] saw reduced fatigue and improved ambulation for up to 3 hours postcooling with the use of either the liquid cooling system or an icepack suit.[27]

When engaging in pool-based exercises, the ideal pool temperature for heat-sensitive MS individuals seems between 27°C and 29°C (80°F–84°F).[27,54,69] Temperatures below 27°C can paradoxically increase spasticity.[27,70]

BENEFITS OF EXERCISE IN MS

The general consensus from research to date is that there are many benefits associated with regular physical activity and/or exercise training in persons with MS.[1,9,57,71,72] These benefits are comparable to those seen in healthy, non-MS individuals.

A Cochrane review evaluated the evidence for exercise therapy for MS.[1] Of all published studies on the topic at the time, the review found only 9 high-quality randomized controlled trials. Analysis of these 9 randomized controlled trials yielded the following conclusions:

1. There was strong evidence for a beneficial effect of exercise on muscle power functions (isometric strength), exercise tolerance functions (physical fitness), and mobility-related activities.
2. There was moderate evidence for a beneficial effect of exercise on upper extremity function and mood.
3. There was no evidence for a beneficial effect of exercise on the Expanded Disability Status Scale (EDSS), fatigue, cognitive impairment, ADLs/instrumental ADLs, HRQL, blood lipids, and body composition.

This Cochrane review also determined that no 1 MS exercise program was any more successful than other (control) exercises,[1] regarding the outcome measures of physical fitness, mobility, fatigue, and HRQL. There was little evidence to support any particular exercise program as superior for persons with MS.[9]

These study findings, however, may not be readily generalizable to more severely disabled MS individuals. The majority of exercise trials only recruited MS subjects with low to moderate disabilities (EDSS<7).[9,27] More disabled MS individuals may not benefit as much from exercise because (1) they may not be able to activate enough muscle mass to generate a training effect, (2) the exercise programs may not be properly designed for them, and (3) their adherence may be poor.[27] For these individuals, a better strategy may be a multidisciplinary outpatient program rather than exercise alone.[27] Such a strategy should be focused more on function maintenance rather than improvement.

EXERCISE TRAINING: RESISTANCE, ENDURANCE, AND COMBINED TRAINING

There are 2 major types of exercises studied in MS exercise trials. These are resistance and endurance exercises. There are also a few studies that investigated the effects of a combination of both resistance and endurance exercises.

Resistance Exercises

Resistance exercises use few muscle contractions against a heavy load with the goal of increasing muscle strength.[3] There are several studies on the effects of resistance training on muscle strength and function in MS.[54] There are, however, fewer studies on resistance training compared with endurance training in the MS population.[3] The few resistance exercise studies in MS are often of low methodological quality, used only moderate training intensities with mild progression, and only included subjects with mild to moderate MS (EDSS<6.5). Although these studies were of heterogeneous designs, the general conclusion is that resistance training of moderate intensity produced improvements in muscle strength and some functional measures among moderately impaired persons with MS.[3,73–80] Resistance exercises were generally safe and well tolerated.[3]

Endurance Exercises

Endurance exercises use multiple muscle contractions against a low load with the goal of increasing aerobic capacity.[3] Endurance training is more extensively studied in the MS population than resistance training.[3] The training regimens used in these studies were often insufficiently described, the training intensities used were poorly controlled (but usually described as low to moderate), and the subjects only had mild to moderate MS (EDSS<7).[3] The training modalities used were heterogeneous, including bicycle ergometry, arm ergometry, arm-leg ergometry, aquatic exercise, and treadmill walking. In general, endurance training of low to moderate intensity produced improvements in aerobic capacity and in measures of HRQL, mood, and depression in persons with mild to moderate MS (EDSS<7).[3] Endurance training was generally safe and well tolerated.[3]

Endurance training produces significant adaptations of the cardiorespiratory and neuromuscular systems that enhance the delivery of oxygen from the atmosphere to the mitochondria and enable a tighter regulation of muscle metabolism.[3,81] Individuals with MS have been shown to make favorable gains in cardiorespiratory fitness within a short span of 4 weeks.[26,54]

Combined Resistance and Endurance Exercises

There are few studies investigating the effects of combined resistance and endurance training in the MS population. Dalgas and colleagues[3] found in their review only 2 qualified randomized controlled trials. Combined training produced small improvements in muscle strength and functional capacity (gait velocity). No changes were seen, however, in aerobic capacity, depression, fatigue, and HRQL.[82–85] Combined training was generally safe and well tolerated.[3]

EXERCISE PRESCRIPTION GUIDELINES

Several published articles offer general guidelines on exercise prescription for the MS population. These guidelines are summarized as follows.

Exercise Staircase Model

Brown and Kraft proposed an exercise staircase model for exercise prescription and progression for a broad spectrum of MS individuals.[27]

At the bottom of the staircase is passive range-of-motion exercises. This serves as the foundation and is appropriate for the most physically and cognitively disabled. These exercises should be performed at least once a day.

The next step up the staircase is active range-of-motion exercises. These are appropriate for less disabled MS individuals and may be performed with or without gravity eliminated as strength allows. Even when weakness is diffuse, resistance exercises of carefully selected muscles, probably not more than 2 per limb, may still allow effective strengthening. In motivated individuals with mild MS, focused muscle strengthening with progressive resistive exercises may be effective.

The third and highest step in the staircase is integrated exercises. Integrated exercises use a combination of strength, endurance, balance, coordination, and flexibility exercises. The exact combination of exercises is tailored to individual needs and capabilities. Aquatic exercise is a good example of an integrated exercise.

Pre-exercise Screening

A thorough pre-exercise evaluation should be performed before designing an individualized exercise program. Ideally this is done by an expert in the field who has experience working with MS individuals. This may be a physical therapist, exercise physiologist,[3,9,27,54] or physical medicine and rehabilitation physician. Attention should be given to an individual's chief complaint and reason for exercise referral, which may be fatigue, weakness, imbalance, incoordination, and so forth.[9] The evaluation should include a thorough physical examination and history, including MS, functional, and exercise histories.

A cardiopulmonary function review should also be done.[1,62] Some investigators have recommended getting a baseline EKG or submaximal stress test.[86] There are others who do not find getting such tests always necessary unless indicated by individual cardiovascular risk factors and cardiac history.[27] The individual's other existing medical comorbidities should also be taken into consideration, such as cardiovascular disease, musculoskeletal or mental disorders, obesity, and the exercise program modified accordingly.[9,20,21,87,88]

Petajan and White further classify MS individuals into the following functional categories: (1) normal (no fatigue or heat sensitivity), (2) normal with fatigue, (3) mild to moderate motor disability, and (4) severe motor disability.[9,62] Such classification may further help tailor the exercise prescription.

Exercise Prescription

The individualized exercise prescription is designed to address a patient's chief complaint or goal—to improve strength, endurance, balance, coordination, fatigue, and so forth. It should take into account a patient's baseline impairments and capabilities.[9,54] The prescription should include all the necessary components, such as frequency, duration, intensity, modalities to be used, and precautions to be observed.[9] Examples of common precautions in MS include fall risk, motor fatigue necessitating rest breaks, heat sensitivity, and cognitive changes that may limit learning or safety awareness. Because MS-related symptoms and impairments may fluctuate or worsen over time, the MS individual has to be periodically reassessed and the exercise program modified accordingly.

Pre-exercise Cool Down

Particularly for individuals with heat sensitivity, several investigators have recommended pre-exercise cooling strategies, such as the use of cooling devices,[2,9,62,89] cold water lower body immersion,[2,54] or taking a tepid bath 20 to 30 minutes before (and after) exercise.[27] Individuals should wear light exercise clothing or may even try exercising with a cooling vest. The exercise area temperature should be kept cool through the use of fans or air conditioning.[27]

Flexibility and Stretching

Individuals with MS often have decreased joint range of motion due to spasticity and prolonged immobility. The goals of flexibility exercises are to increase muscle length, increase joint mobility, counteract the effects of spasticity, and improve posture and balance.[54] Flexibility exercises should be performed at least daily for 10 to 15 minutes.[54,90] Stretching should be done before and after workout sessions and should include the upper and lower body muscle groups used in the workout. Spastic muscles should be particularly targeted.

Stretches should be slow, gentle, and prolonged. There should be no bouncing with the stretch. The stretch should be up to the end of the comfort range and held there for 20 to 60 seconds. Stretching should not be painful. Individuals who need help with stretching may use a towel, rope, or partner. For immobilized individuals with spasticity, passive stretching may be done by a therapist or trained caregiver. For higher-functioning MS individuals, stretching exercises may be done through a supervised yoga class.[54,91,92]

Exercise Intensity

Brown and Kraft[27] recommended exercising below maximal workload as a reasonable safeguard to avoid undue cardiac stress, fatigue, and Uhthoff phenomenon. To achieve an exercise intensity of approximately 55% to 60% $\dot{V}O_2max$, the target heart rate for most MS individuals may be computed as $(220 - \text{age}) \times (0.7)$. For MS individuals with marked deconditioning or heat sensitivity, the target heart rate may be computed as $(220 - \text{age}) \times (0.65)$.

These formulae may not be applicable to the more severely disabled MS individuals with cardiovascular dysautonomia and blunted heart rate responses. For these individuals, the target exercise intensity may be better estimated by aiming for a Borg Rating of Perceived Exertion level of 11 to 14, or moderate intensity.[9,54] Morrison and colleagues[93] found that the (modified) Borg Rating of Perceived Exertion scale and other physiologic responses to submaximal and maximal exercise were similar between MS participants and healthy controls.[9] This is despite MS participants reporting higher levels of fatigue than controls.

Resistance Training

It is recommended that resistance training be performed under the supervision of experienced personnel for safety until the MS individual is comfortable with the training program.[3] Additionally, it has been shown that supervised is superior to nonsupervised resistance training.[3,94]

In terms of resistance training modalities, it is recommended that an individual start off using training machines (ie, closed kinetic chains) instead of free weights (ie, open kinetic chains) for safety.[3] If training machines are unavailable, alternatives include the use of elastic bands and body weight as load.

Training frequency should be 2 to 3 days per week. Training intensity should be in the range of 8 to 15 repetition maximum (RM), with initial starting intensities approximately 15 RM. This should gradually be increased over several months toward intensities of approximately 8 to 10 RM. Resistance can be safely increased by 2% to 5% when 15 repetitions are correctly performed in consecutive training sessions.[54,75] The rate of progression should allow for full recovery between training sessions to prevent musculoskeletal overuse injuries.[54] The individual should start with 1 to 3 sets, which can be gradually increased over a few months to 3 to 4 sets of each exercise. Allow rest breaks of 2 to 4 minutes between sets and exercises.

In terms of number of exercises, a whole-body program containing 4 to 8 exercises is recommended. In general, exercise large muscle groups before small muscle groups, and perform multiple-joint exercises before single-joint exercises.[3,95] Prioritize lower extremity over upper extremity exercises. It has been shown that in MS individuals the lower extremity strength deficit is greater than that of the upper extremity.[3,36] Make sure to include legs, back, shoulders, chest, and arms, observing any contraindications based on individual impairments.[54]

In terms of precautions, weight lifting should be done in a seated position (as in most weight machines) to minimize the risk of falls with free weights. If an individual has impaired proprioception or coordination, the exercise should be done under supervision.[54]

Endurance Training

Recommended endurance training modalities include bicycle ergometry, arm-leg ergometry, arm ergometry, treadmill walking, and aquatic exercise.[3,54] For higher-functioning MS individuals, additional options include the treadmill, elliptical, running, and rowing.

Training frequency should be 2 to 3 times per week. Training duration should be 10 to 40 minutes, depending on the level of disability. Training intensity should initially begin with approximately 50% to 70% $\dot{V}O_2max$, corresponding to 60% to 80% of maximum heart rate. If an individual has a blunted heart rate response, an alternative measure is to aim for a Borg Rating of Perceived Exertion level of 11 to 14, or moderate intensity.[54]

In terms of training progression, previously sedentary individuals should start aerobic exercises at a comfortable level and then increase the intensity and duration at weekly or monthly intervals.[27,96] For the first 2 to 6 months, the training volume may be increased by either prolonging the training duration or by adding an extra training day. After this period, it should be tested whether the individual can tolerate a higher training intensity. This can be done by replacing 1 training session with interval training using intensities of up to 90% $\dot{V}O_2max$.

Combined Resistance and Endurance Training

Resistance training may need to be done first before endurance training, particularly among MS individuals with significant strength deficits.[3,54] Muscle strength deficits may limit the ability of MS individuals to engage in aerobic exercise of sufficient intensity and duration to enhance cardiorespiratory fitness.[54] Thus, initial resistance training may make subsequent endurance training possible for such individuals.

Training frequency should be 2 days per week of resistance training alternating with 2 days per week of endurance training. These exercise periods should be separated by an interval of 24 to 48 hours to allow for recovery.[5,90]

RECOMMENDATIONS FOR FUTURE RESEARCH

There are several common recommendations for future research proposed by currently available studies. These include the following.

1. Subjects: Stratify subjects on the basis of MS types and degree of disability (EDSS). Studies should recruit subjects with greater disability (EDSS>6.5), including

semiambulatory and nonambulatory individuals, those with longer durations of MS, and more elderly MS individuals.
2. Methodology: Ideally there should be larger sample sizes, proper blinding, randomization, and accounting for all dropouts. Longer exercise training periods (>12 weeks) should be used to adequately detect a training effect.[3,97]
3. Interventions: More studies on resistance training and combined resistance and endurance training programs are needed.[3] More detailed descriptions of the training regimen used should be provided in published articles to allow for better reproducibility and comparison among studies.[3] Different training intensities should be evaluated to see if MS individuals could tolerate and benefit from more intense training.[3]
4. Measures: Reach a consensus on a core set of standardized outcome measures to be used in exercise trials.[1] At present, individual exercise trials use varying outcome measures, making result comparison and generalization difficult. Ideally, outcome measures should routinely include measures of ADLs and HRQL.

SUMMARY

Exercise offers many benefits for persons with MS, just as it does for the general population. Certain exercise physiology characteristics are commonly seen among persons with MS, particularly in the more debilitated. Properly prescribed exercise programs can improve modifiable impairments in MS. Exercise is generally safe and well tolerated. There are general guidelines that may be followed for exercise prescription for the MS population. The quality of MS exercise trials may be improved by applying several recommendations.

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