Multiple Sclerosis and Exercise

A Review of the Evidence

Herbert I. Karpatkin PT, NCS

Compared with other neurologic disorders, relatively little literature exists to define or support the role of exercise in MS. This review describes issues relating to exercise in patients with MS, discusses relevant literature, offers exercise guidelines for persons with MS, and suggests topics for future research. Unique aspects of MS that affect physical therapy are addressed, including disease progression, fatigue, and thermosensitivity. Review of the literature includes discussion of strength training, aerobic exercise, and respiratory training. While physical activity was once contraindicated in persons with MS, current literature supports its therapeutic benefits in these patients. More research could be focused on the specific types of exercise appropriate for this patient population. **Int J MS Care. 2005;7:36-41.**

Multiple sclerosis (MS) is a neurologic disease that can affect any myelinated structure in the central nervous system. It can lead to progressive deterioration of myelinated CNS structures that mediate motor control and lead to long term impairment of movement and function. Although exercise is often employed as a means of managing some of the weakness that occurs in persons with MS, there is a relatively small body of literature to support or describe its use. This is in contrast to other neurologic disorders such as cerebrovascular accident (CVA), traumatic brain injury (TBI), and spinal cord injury (SCI), in which exercise is considered an essential aspect of disease management, and several texts and journal articles are available to guide the clinician.[1-4]

The relative paucity of information on the use of exercise in MS may thwart clinicians in their attempts to provide specific interventions for these patients. Due to the unique nature of the disease, the role and impact of exercise is different in MS in comparison with other diseases. A clear understanding of the role of exercise in MS is essential for therapists who work with this population. The purposes of this review are to 1) describe some of the issues in the use of exercise in persons with MS, 2) provide a review of the relevant literature on MS and exercise, 3) recommend exercise guidelines for persons with MS based on the literature, and 4) suggest topics for further research.

Exercise is differentiated from physical therapy (PT) for the purposes of this report. Although a small amount of literature has examined the effects of PT interventions on persons with MS, this update is limited to assessing the effects of exercise alone. Studies that examined the effects of strengthening or aerobic conditioning protocols were included, while studies that looked at the overall effects of a rehabilitation program were excluded. Studies that looked at the effects of specific PT regimens (such as neurodevelopmental treatment, proprioceptive neuromuscular facilitation, motor learning) were also excluded.

Exercise and MS: Disease-specific Issues

Some of the reasons for difficulties with exercise among persons with MS may be due to the specific nature of the disease. MS differs from other neurologic conditions for which exercise is commonly prescribed. These differences should be taken into account by the clinician administering or prescribing an exercise program to the MS patient. These differences will be discussed in the following sections.

Progression

Unlike other neurologic conditions commonly treated by physical therapists—such as stroke, spinal cord injury, or traumatic brain injury—MS is a variable and usually progressive condition. The disease is capable of exacerbating at any time, resulting in an extension of neurologic disability. Gains in fitness that are made as a result of exercise may be lost at any time, requiring the formulation and implementation of a new exercise protocol. In addition to the frustration that this may cause for the patient and the therapist, treatment planning must take into account the unpredictable nature of this phenomenon. Unlike non-progressive conditions such as those listed above, in which a static lesion does not change appreciably over time, the clinician working with an MS patient must formulate a treatment plan with the knowledge that sudden and unpredictable worsening is a possibility, and disease progression is probable over time.

Heterogeneity

The lesions of MS can occur in any myelinated structure in the CNS, with a predilection for white matter tracts. The literature has documented involvement of the motor tracts,[5] cerebellar tracts,[6] sensory tracts,[7] vestibular apparatus,[8] cognitive structures,[9] and visual tracts.[10] Deficits in any of these areas can result in sensory and motor impairments; in MS there is the possibility that deficits can occur in all of these areas in a single patient with varying intensity. This heterogeneity presents challenges to the clinician who must be adept at evaluating and treating a diverse collection of dysfunctions which may vary from patient to patient. This heterogeneity may also be a limiting factor in performing credible research on exercise and MS, as assembling homogenous subjects in sufficient number may be difficult.

Fatigue

Fatigue is the most common symptom experienced by persons with MS. Paty and Ebers[11] separated fatigue seen in MS into fatigability and lassitude. Fatigability has been described as a single muscle or group of muscles which becomes weaker after repetitive use and recovers after rest. Lassitude refers to a persistent sense of tiredness. Lassitude and fatigability can occur separately or simultaneously. The fact that persons with MS present with a pathologic fatigue may influence their ability to exercise, and may therefore limit their ability to benefit from exercise programs, particularly if those programs require vigorous exercise. Fatigue may also be secondary in MS, occurring as a result of inactivity or disuse and can be considered separate from central causes.[12] Fatigue that is due to inactivity may be improved by an exercise program, while lassitude and fatigability—due to central nervous system involvement—may not be. Although some authors have been able to differentiate these two types of fatigue in a laboratory setting, no way currently exists to differentiate between the two in the clinic. The clinician cannot be sure whether fatigue that the patient is experiencing as a result of exercise is due to central causes resulting from the disease, or due to inactivity and loss of fitness.

Thermosensitivity

Thermosensitivity, or heat sensitivity, is common in MS; over 80% of MS patients have been noted to develop increased neurological signs as a result of a raise in core temperature.[13] This can limit the ability of a person with MS to exercise, as the increase in core temperature normally associated with exercise may lead to an increase in neurologic symptoms. Earlier writings on MS and exercise implied that exercise was harmful for persons with MS because it was thought to trigger an exacerbation.[14] This transient increase in symptoms following a raise in core temperature has been more accurately termed a pseudoexacerbation, and occurs due to transient increased blockade of nerve conduction in demyelinated fibers.[15] This has led to the use of cooling as a therapeutic modality for persons with MS. If cooling in fact offers persons with MS an improved ability to exercise and a chance to achieve greater exercise gains, then it could become an essential tool for the clinician constructing exercise protocols for persons with MS.

Inactivity/Disuse Atrophy/Sedentary Lifestyle

Weakness in MS can be due to two primary reasons. Weakness due to involvement of the motor tracts represents the primary impact of the disease.[1] It is unlikely that exercise can have a meaningful impact on this. However, weakness in MS may also occur from disuse atrophy, brought on by inactivity resulting from the disease.[12] The person with MS may become less active due to the primary weakness itself, disease-related fatigue, depression, or a belief that exercise may cause either a worsening of the disease or a wish to avoid the transient increase in symptoms that exercise may cause. For any of these reasons, a person with MS may choose to not exercise which may result to secondary weakness. This weakness may therefore be at least partially prevented or reduced by exercise. None of the research noted in this review examining the effects of exercise on MS noted a change in disease activity as a result of the exercise, while improvements in exercise parameters such as aerobic capacity, $VO_{2\ max}$, and measures of strength were noted. These improvements probably represented remediation of the effects of the inactivity.

Early vs. Advanced Disease

MS can result in mild to severe disability; an MS patient may experience both over the course of a lifetime. An MS exercise protocol that is appropriate for a person with mild disease may not be appropriate for someone with advanced disease. The majority of exercise protocols examined were for persons with relatively mild to moderate involvement due to MS.

Exercise in a person with more advanced disease is problematic for many reasons. With greater involvement, ability to exercise may become progressively lessened. The ability to engage in aerobic training via a treadmill or ergometer may not be feasible due to the impact of such symptoms as spasticity, ataxia, weakness, or fatigue. Conventional resistance training may similarly be infeasible for these patients. Cognitive impairment may prevent compliance with exercise protocols. However none of these factors are truly contraindications to exercise—they may represent reasons why exercise may be difficult, but not reasons that exercise should be avoided. Persons with advanced disease may derive benefit from exercise, but they require a program suited to their current capabilities.

Literature Review

Studies on exercise in MS have examined particular types of exercise (aerobic, resistive, respiratory) or the environment in which the exercise occurs (aquatic therapy, precooling).

Types of Exercise

Aerobic

The use of aerobic training in persons with MS has been examined by many researchers. As lack of aerobic fitness is considered to contribute to fatigue, use of aerobic training as an intervention appears warranted. Additionally, the effects of a sedentary lifestyle adopted many persons with MS may be mitigated by an aerobic training program.

Petajan et al[16] examined the effects of a 15-week aerobic training program on 21 persons with relatively mild MS as defined by a mean Expanded Disability Status Score (EDSS) of 3.8, and 25 matched MS controls. Subjects participated three times a week in 30-minute sessions of combined arm and leg ergometry at 60% $VO_{2\ max}$ for 15 weeks. $VO_{2\ max}$, isometric strength, body composition, and blood lipid profiles were all measured, as were the effects of the aerobic training on fatigue and various aspects of quality of life (QOL). Disability status, as measured by the EDSS, was determined before and after the 15-week intervention. The exercise group demonstrated significant gains in $VO_{2\ max}$, upper and lower extremity strength, significant decreases in skinfolds, triglycerides, and very low density lipoprotein. Depression, anger, and fatigue were reduced in the exercise group. No changes were seen in the non-exercising controls. There was no change in disease activity, as measured by the EDSS. The changes in fitness seen in the MS patients were similar to the changes seen in non-disabled persons who undertake an exercise program, suggesting that persons with MS respond similarly to exercise as persons who are disease free. The number of exacerbations was equal in the exercising and non-exercising groups, suggesting that the exercise did not result in an increased frequency of exacerbation.

Mostert et al[17] conducted a similar study with somewhat more advanced MS patients (mean EDSS 4.6), over a shorter period of time (four weeks). Like the Petajan study, an improvement was seen in anaerobic threshold and in QOL measures. Unlike Petajan, no improvements were seen in $VO_{2\ max.}$ There were no reports of disease exacerbations, and symptom exacerbation was seen in only 6% of all of the training sessions. The authors suggested that the relatively higher level of disability and the shorter duration of training may have accounted for the differences seen between the two studies.

Rodgers et al[18] examined the effects of a six-month aerobic training program on kinematic and kinetic parameters of gait. Eighteen patients with relatively mild MS (EDSS 3.6) received three 30-minute training sessions per week on a cycle ergometer. No control group was used. Similarly to Petajan, improvements were seen in $VO_{2\ max,}$ supporting the possibility that longer training periods are needed to improve this parameter. Favorable improvements were seen in hip adduction/abduction and internal/external rotation. Declines were seen in velocity, cadence, and maximal dorsiflexion angle. Six of the patients demonstrated neurologic decline during the training period, which may have been due to the relatively long period of intervention. The lack of improvement in gait parameters was probably due to the non-specific nature of the intervention, and the specific nature of the outcome measures.

Strength Training

Persons with MS are reported to have reduced strength compared to non-MS controls.[19,20] Lack of strength may have significant functional repercussions for mobility in this population, and exercise protocols that emphasize strengthening may help to offset this. However, the variability of MS may make the designing of strength-related treatment protocols difficult. Only a small number of studies have examined the effects of resistance training on persons with MS.

Svennson et al[21] reported five case studies involving persons with MS with EDSS scores ranging between 2 and 7. Subjects received four to six weeks of training (2 to 3 times/week) with the aim of increasing the peak torque of knee flexors throughout a series of repeated maximum knee flexions. Subjects performed 3 x 10 repetitions. As an outcome measure, each subject performed 50 repeated maximum knee flexions of the most symptomatic limb using an isokinetic dynamometer. Three of five patients achieved higher peak torque levels throughout the endurance tests after training. One subject showed no change following the endurance training, and one showed a decrease in peak torque in the post-test. The subjects had no change in mean power frequencies as a result of the training while experiencing subjective increases in fatigue, indicating that fatigue experienced in these patients was of central rather than peripheral origin. Three of the five subjects increased in strength and endurance. All of the subjects reported improvements in perception of fatigue, and four of the five subjects reported improvements in functional activities. The neurologic status of the subjects remained stable over the training period, suggesting that the weakness seen in the subjects pretest was due to inactivity.

Harvey et al[22] compared a lower extremity weight training exercise protocol to a general mobility and balance program and a control group in 17 ambulatory subjects with MS. EDSS scores were not reported. The length of the training intervention was eight weeks, with frequency of the intervention not noted. Post intervention measures included a 50-meter timed walk, HR during timed walk, EMG after maximal voluntary contraction (MVC) of the quadriceps, and time to transfer from one chair to another 100cm apart. No significant differences were seen between groups for EMG and MVC, and walking time. Chair transfers were faster at follow-up for the exercise group suggesting a functional improvement due to the exercise. No change in neurologic status was reported during the intervention for any of the subjects. The lack of improvement noted in EMG and MVC may have been due to the small number of subjects in each group.

Kraft et al[23] examined the effects of a three-month progressive resistive exercise (PRE) program on four MS patients with mild (EDSS 3.0) disability and four with more advanced disease (EDSS 6.0). Both groups of patients had improvements in functional tasks (ambulation and stair climbing) as well as quantitative improvements in muscle strength of the exercised limbs. No adverse effects on clinical status were noted. All of the subjects encountered fatigue which lessened within 24 to

48 hours of training, and no incidence of exacerbation was noted.

Respiratory Training

Although MS is rarely considered to be a fatal disease, morbidity and mortality have been found to occur as a result of secondary complications such as respiratory dysfunction.[24] For this reason, exercises which address respiratory function are often included in exercise programs for MS, especially for patients with more advanced disease. A small number of studies appear to support the use of respiratory muscle training. Smeltzer et al[25] studied a three-month expiratory muscle strengthening program for MS patients with moderate to severe disability (EDSS 6.5 to 9.5) and found improvements in expiratory pressure when compared to a sham strengthening group. The effect of the strengthening on clinical outcomes was not discussed. Foglio et al[26] assessed the relationship between respiratory muscle weakness in MS and exercise function via arm ergometry in 24 patients with MS (mean EDSS 5.3). Arterial blood gas and lung function tests were normal, but both maximal inspiratory pressure and maximal expiratory pressure were reduced, indicating decreased respiratory muscle function. The authors concluded that reduced exercise tolerance in MS may be due in part to respiratory muscle dysfunction. Although the authors offered no clinical suggestions, the article suggests that respiratory muscle training may improve exercise tolerance in persons with MS.

Environmental Issues for Exercising

Precooling

Thermosensitivity is a well-established symptom of MS.[13] The rise in core temperature that accompanies exercise has led to examination of the use of interventions that limit temperature rise by lowering the individual's core temperature, either concurrently with exercise or prior to exercise (precooling). Methods for cooling for use by the MS patient include immersion in cold water, cold showers, ice packs, iced drinks, and the use of an artificial cooling system such as a liquid cooling garment. [27-29] If thermosensitive persons with MS could exercise without a notable increase in core temperature, they might be able to exercise for longer periods of time, and therefore achieve greater exercise gains.

White et al[30] compared exercise performance for six neurologically stable persons with mild MS (mean EDSS 2.0 to 4.5) for precooled and non-precooled conditions. Precooling was accomplished via cold water immersion for 30 minutes prior to exercise. The precooled condition resulted in lowered exercise heart rate, decreased 25-foot walk time, and decreased step frequency immediately after exercise. Subjects reported less fatigue during and after the precooled exercise. The improvements did not persist 30 minutes after cooling. A later study also by White et al[31] extended these findings to more advanced patients (EDSS 4.0 to 6.5). The NASA/MS Cooling Study Group[32] examined 84 patients with mild to moderate MS (EDSS < 6.00) and found significant improvements in timed 25-foot walk test following one hour of cooling using a liquid cooling garment. Ku et al[33] examined physical capabilities of MS patients after wearing various types of cooling suits, and found that the effects of cooling lasted up to 1.5 hours after removal of a cooling suit in 26 patients with moderate disability (EDSS 5.0 to 7.5). Although studies such as these suggest that cooling appears to be beneficial to physical performance in MS, no studies to date have compared the effectiveness of an exercise training program in MS patients who were precooled to those who were not.

Aquatic Exercise

The use of aquatic therapy (or exercising in water) has been examined as a possible intervention for MS. The buoyancy of the water decreases the amount of work the patient has to perform thus hypothetically limiting cumulative fatigue, while the coolness of the water limits thermosensitivity. The water may also provide a resistive element for ataxia and dysmetria.[34] Although widely used and advocated in MS, few studies have examined the efficacy of aquatic exercise.

Gehlsen et al[35] examined 11 persons with MS (EDSS 4.0) to determine the effects of aquatic therapy on gait parameters. All subjects participated in a 10-week aquatic exercise program consisting of freestyle swimming and shallow water calisthenics. Three 60-minute exercise sessions were held with the training intensity 60% to 75% of the subjects' estimated maximal heart rate. Exercise progression was based on the subjects' feelings of fatigue, physicians' recommendations, and resting, recovery, and maximal heart rate responses. Although no changes in gait parameters were seen, the subjects reported feeling less fatigue and being able to work harder as a result of the intervention. In an earlier work, Gehlsen[36] also examined the effects of a 10-week aquatic fitness program on 10 persons with MS and found improvements in muscular strength and endurance. A case report by Petersen[37] described a patient with MS during an exacerbation who underwent a six-week training period in a heated pool. Despite the seeming contraindication of a heated pool for a person with MS, the patient tolerated the procedure without any adverse change in neurologic status. Paradoxically, some persons with MS have been found to actually be aided by heat, while hindered by cold.[38] These findings suggest that clinicians ought to evaluate their MS clients' exercise needs on an individual basis, rather than assume stereotypical presentations.

Precautions About Exercise in MS

The literature reports one area where exercise could be harmful in persons with MS. An autonomic dysfunction in response to exercise, sometimes referred to as the pressor response, has been observed to occur in persons with MS.[39] This is suspected to be due to lesions in the cardiovascular autonomic nuclei in the paraventricular regions of the brain, as well as in areas of the spinal cord containing B fibers of sympathetic nerves. Pepin et al[40] found 54 of 104 persons with MS to have blunted cardiovascular responses to isometric handgrip exercises. This suggests that some persons with MS may not be able to maintain adequate perfusion to muscles during exercise, potentially resulting in inability to maintain exercise, as well as the risk of exercise induced syncope. An alternative hypothesis was offered by Ng,[41] suggesting that the pressor response was due to blunted muscle metabolic response and differences in contracting muscle mass, rather than generalized dysautonomia.

Exercise Recommendations for MS patients

Based on the literature presented, persons with MS clearly appear to benefit from exercise. Persons with MS respond to exercise the same way as those without MS: they become more fit. Benefits appear to be specific to the type of training employed: persons who engaged in aerobic training improved in aerobic fitness, while persons who engaged in resistive training improved in strength and persons who engaged in respiratory training improved in measures of respiratory fitness. None of the studies indicated that exercise was related to an increase in disease activity, and when exacerbations did occur, it appeared to be due to natural expression of the disease, not the exercise. Clinicians should therefore be confident in prescribing exercise for patients with MS.

Precooling clearly seems to be of some benefit to persons with MS, as it appears to allow for improvements in physical performance and lessening of transient neurologic deficits by limiting core temperature rise. Although there has been no study on the long-term effectiveness of precooling in MS, no adverse effects have been reported following its use. There is no evidence supporting the use of one cooling modality over another.

Aquatic exercise in MS, although intuitively rational, does not appear to have sufficient research to state that it offers any unique benefit for persons with MS. No study has compared aquatic therapy to non-aquatic therapy protocols. It is therefore not known whether the studies finding improvements in persons with MS following aquatic therapy protocols have done so due to the influence of the water, or simply the exercise itself. However, no adverse outcomes have been reported from aquatic therapy, and it may therefore be considered a reasonable option for persons with MS.

Future Research

Several authors have suggested that much of the weakness and lack of cardiorespiratory fitness noted in MS is caused by inactivity and disuse, rather than from primary effects of the disease.[42,43] This may be one of the reasons that the exercise programs for persons with MS are successful, as they relieve secondary effects of the disease, rather than primary effects. However, it can be difficult for a clinician to know when fatigue and disuse are primary or secondary. Whereas exercise should probably be encouraged in secondary fatigue, it should be avoided in primary fatigue. Future research might examine the differences between primary and secondary fatigue, and how they can be clinically differentiated. Although multiple authors have contended that much of the fatigue that occurs in MS during exercise is due to inactivity and disuse, there remains no way of determining this in a clinical setting. Future studies could examine ways of clinically differentiating between types of fatigue.

The question of exercise dosage remains unanswered. All of the aerobic exercise studies used a relatively similar protocol of submaximal exercise three times a week. However, it is not known whether greater fitness gains could be achieved with more vigorous exercise. Although it appears counterintuitive, the fact that submaximal exercise resulted in no adverse effects, coupled with the finding that persons with MS show fitness gains similar to non-MS exercisers, suggests that vigorous exercise may be similarly well tolerated. A similar question must be asked in the case of the patient whose status is worsening. Do the exercise needs of an MS patient change with worsening neurologic status? Should a patient try to maintain their exercise regimen following an exacerbation? Is complete rest necessary, and if so, for how long? As MS is a disease which may worsen over time, these are research questions which need to be answered for the clinician working with these patients.

The question of exercising for MS patients with more advanced disease has not been addressed by the literature. Few studies have examined the effects of exercise on patients with advanced disease. MS can result in severe disability, but the majority of the research on the effects of exercise have looked at persons with relatively mild MS. Smeltzer included patients with an EDSS of 6.5 to 9.5, but only respiratory exercise was included. Although improvements were found in the exercising group, there was no breakdown as to how the subjects with more advanced disease fared compared to those with less disease. Gappmaier et al[44] found greater cardiorespiratory response using arm/leg ergometry compared to treadmill walking in persons with neurogenic lower extremity weakness due to MS, suggesting that nonambulatory persons with MS would benefit from this type of exercise. However, the maximal EDSS score was 6.0, making application of this to persons with more advanced disease difficult. Many persons with MS seek physical therapy at times when their disease is more severe, and it is not clear from the literature whether patients with advanced disease would benefit from exercise. Future studies could address the impact of exercise on patients with advanced MS.

The heterogeneity of MS makes research on the effects of exercise difficult. Exercise that may be appropriate for a person with ataxia may not be appropriate for patients whose primary symptom is weakness or sensory loss. Much research conducted on exercise in MS has grouped subjects by EDSS score. However, the EDSS groups patients by disability rather than clinical presentation. Future research can address this issue by examining the effects of exercise in MS based on primary symptomatology. For example the effects of exercise in populations whose primary symptom is fatigue, spasticity, sensory loss, or weakness can be examined.

Conclusion

With improvements in medical management of MS over the last decade, the need for physical therapy interventions for these patients has increased. Exercise, previously thought to be contraindicated for persons with MS, is now supported by a number of studies. Exercise enhances the fitness of persons with MS without affecting the disease itself, suggesting that the changes occur peripherally rather than centrally. Due to the unique nature of MS, many questions remain regarding particular aspects on the use of exercise. **MS**

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