

The Importance of Physical Fitness in Multiple Sclerosis

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Abstract

The present review paper provides an overview on the importance of physical fitness in persons with Multiple Sclerosis (MS). We first present a model describing a cyclical association among physical inactivity, physiological deconditioning, and worsening of MS over time. We then provide a comprehensive review of research indicating extensive physiological deconditioning in cardiorespiratory, muscular, motor, and morphological domains of physical fitness among those with MS compared with controls and as a function of disability status. There further is substantial evidence for associations between physiological deconditioning and a variety of consequences of MS (e.g. outcomes of brain structure and function, ambulation, cognition, and fatigue), emphasizing the importance of counteracting and maintaining all domains of physical fitness. Exercise training may be an effective approach for improving physical fitness and managing secondary consequences among persons with MS. To that end, researchers have recently developed evidence-based physical activity guidelines indicating that adults with MS should participate in 2 weekly sessions of 30 minutes of moderate intensity aerobic activity to improve aerobic capacity and 2 weekly sessions of resistance training to improve muscular fitness. We believe that these guidelines provide an important basis for the prescription of exercise training by clinicians as a therapeutic approach for managing many of the consequences of MS.

Keywords: Multiple sclerosis; Physiological deconditioning; Morphological domains

Multiple Sclerosis (MS) is a common and life-altering neurological disease among adults in the United States and worldwide. This disease has an estimated prevalence of 1 per 1,000 adults in the United States [1] with the majority of cases occurring in women of European descent. The MS pathophysiology initially involves episodic periods of immune-mediated demyelination and transection of axons within the Central Nervous System (CNS). This results in the disruption of saltatory conduction of action potentials along myelinated axonal pathways in the brain, spinal cord, and optic nerves. The MS pathophysiology later transitions into a neurodegenerative disease process, presumably associated with insufficient neurotrophic support, and results in the accumulation of irreversible neurologic disability. The degree and location of axonal and neuronal damage within the CNS result in the heterogeneous expression of symptomatic, functional, and participatory consequences among persons with MS [2]. Such manifestations might be initiated or worsened by physical inactivity and resulting physiological deconditioning.

We have previously described a model of physical inactivity, deconditioning, and worsening MS [3,4], and this was based on a similar framework for persons with chronic disease conditions [5] including MS [6]. The model is displayed in figure 1 and indicates that MS onset results in physical inactivity [7,8] that initiates physiological deconditioning (i.e., compromised or reduced physical fitness). This physiological deconditioning, in turn, results in worsening of MS, as indicated by loss of brain structure and function as well as symptomatic (e.g., fatigue) and functional (e.g., walking impairment) manifestations. The worsening of MS results in further physical inactivity and subsequent physiological deconditioning thereby yields a cycle of associations among physical inactivity, deconditioning, and worsening MS that develops over time. This model is important as it conceptualizes the importance of maintaining and improving physical fitness levels in persons with MS. Physical fitness might provide a form of “physiological reserve” that is protective of disease consequences and worsening of MS and this is consistent with other literatures such as cancer [9].

To that end, this paper provides a comprehensive review of research

on physical fitness in persons with MS. We begin by defining physical fitness and its domains as well as differentiating it from physical activity. We then present research on physiological deconditioning (i.e., detraining that manifests as a reduction in domains of physical work capacity or fitness) in persons with MS as well as evidence on the association between markers of physical fitness and consequences of MS. We lastly review research regarding the effects of exercise training on physical fitness and consequences of MS, and conclude with recently developed exercise recommendations for improving physical fitness. Our goal is the provision of a paper that underscores the (a) importance of physical fitness and (b) role of exercise training for its improvement among persons with MS.

Overview of Physical Fitness and Its Components

Bouchard and Shephard [10] have provided clear definitions of physical fitness and physical activity that can be adopted to avoid confusion regarding these two related, but distinct terms. Physical fitness describes one’s capacity for performing work or, in other words, it represents the characteristics of a person that describe the capacity for engaging in physical activity and exercise behavior. Performance-related fitness involves components necessary for optimal work or sport outcomes; whereas health-related fitness reflects components that are influenced favorably or unfavorably by physical activity levels and reflects one’s health status and risks for morbidity and mortality. The latter is the type of fitness that is relevant within the current paper and its reduction over time is consistent with the idea of physiological deconditioning.

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Physical activity, by comparison, is a behavior described by the movement of one's body through the contraction of skeletal muscles that yields a substantial increase in energy expenditure over resting values. Physical activity can broadly involve active physical leisure-time pursuits, occupational work and household chores, transportation, sport, and exercise. Exercise is a subset of leisure-time physical activity that involves planned, structured, and repetitive bouts of physical activity over an extended period of time with the objective goal of improving aspects of health-related fitness.

Health-related fitness is a broad term and it has several components, much like physical activity. The important components of health-related fitness include cardiorespiratory, muscular, motor, and morphological components. The cardiorespiratory component reflects one's capacity for performing aerobic or endurance forms of physical activity (e.g., walking, bicycling, and jogging) and is often reflected by peak aerobic capacity (VO_{2peak}). VO_{2peak} is measured by analysis of expired respiratory gases during a symptom limited exercise test performed until exertional fatigue (i.e., maximal voluntary exertion). Based on the Fick equation, VO_{2peak} can be described based on the highest rates of delivery (i.e., cardiac output) and extraction (i.e., difference in arterial-venous oxygen content) of oxygenated blood during exercise and reflects one's capacity for engaging in endurance or aerobic physical activity. This domain of fitness has been identified as the most important from the perspective of preventing morbidity and premature mortality as well as maintaining health in the general population [11,12].

The muscular component of fitness reflects one's capacity for work that requires muscle strength and endurance. Muscle strength reflects the ability of a specific muscle or muscle group to exert or generate an external force, whereas muscle endurance reflects the ability of muscle to generate submaximal force across successive repetitions. Muscle strength is most often measured and is based on either maximal force using an isokinetic dynamometer (i.e., maximum voluntary contraction) or the greatest resistance that can be moved through the full range of motion (i.e., 1-repetition maximum). The motor component, particularly upright balance, reflects one's capacity for maintaining a standing posture and is often measured by posturography (i.e., whole body sway based on excursion of the center of pressure). The morphology component reflects fat, lean, and bone components of one's body based on a three-compartment model. This is typically measured with Dual-Energy X-Ray Absorptiometry (DXA), although fat mass can further be reflected by Body Mass Index (BMI) or percentage of one's body that is fat based on skin folds, bioelectrical impedance, or densitometry from hydrodensitometry (underwater) weighting or air displacement plethysmography. These domains of health-related fitness have further been identified as important from the perspective of preventing morbidity and premature mortality.

Evidence for Physiological Deconditioning in MS

One premise of this paper, and the model in figure 1, is that persons with MS experience physiological deconditioning compared with controls, and this worsens over time, for example, as disability progresses (e.g., mild vs. moderate and/or severe MS). To that end, researchers have sought to quantify differences in components of fitness, particularly aerobic capacity, muscular strength, balance, and body composition, between persons with MS and the general population and, in some cases, among persons with MS as a function of disability levels. The body of evidence generally indicates that significant physiological deconditioning occurs in persons with MS, particular as a function of disability progression.

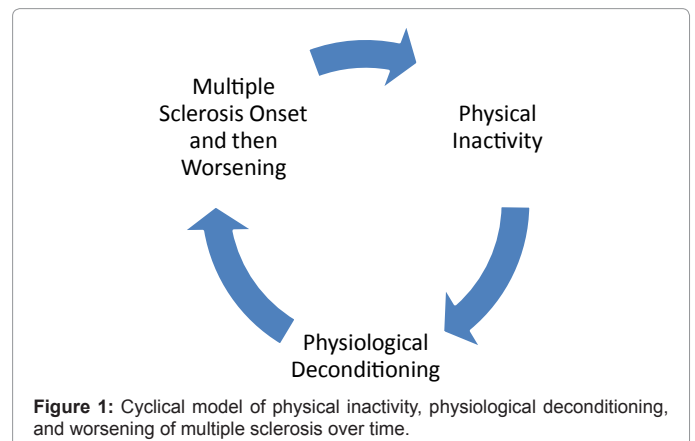


Figure 1: Cyclical model of physical inactivity, physiological deconditioning, and worsening of multiple sclerosis over time.

There is evidence that persons with MS have diminished VO_{2peak} compared to the general population [6,13]. For example, one study compared the VO_{2peak} recorded during a maximal, incremental exercise test on a cycle ergometer among 32 women with relapsing-remitting MS who had minimal disability with 16 sex, age, height, and weight-matched controls [14]. The researchers reported that the persons with MS demonstrated significantly and moderately reduced absolute ($d=0.56$) and relative ($d=0.53$) VO_{2peak} compared with the matched controls. There is further evidence that VO_{2peak} differs between persons with MS who have mild and moderate-to-severe disability [15, 16]. For example, one study compared VO_{2peak} recorded during a maximal, incremental exercise test performed in a semi-recumbent position on a cycle ergometer between 11 persons with mild disability and 8 persons with moderate-to-severe disability [15]. The researchers reported that persons with MS who had moderate-to-severe disability demonstrated significantly and moderately (27%) reduced absolute VO_{2peak} compared with those who had minimal disability.

There is additional evidence that persons with MS have worse musculoskeletal fitness (i.e., characteristics of muscular strength/fatigue) than the general population [6,13]. One study examined lower limb strength asymmetries (i.e., relative differences in the strength of a particular muscle group between strong and weak limbs) and muscle fatigue (i.e., endurance) in 52 persons with Clinically Isolated Syndrome (CIS) (i.e., the precursory diagnosis of MS) compared with 28 age and sex matched healthy controls [17]. Those with CIS demonstrated greater strength asymmetries in the ankle muscles as well as muscle fatigue compared with the controls, and this indicates that muscle weakness manifests even in the earliest stages of MS. Another study of 9 persons with MS and 11 healthy controls reported that persons with MS had a substantially smaller maximal voluntary contraction of ankle dorsiflexors, measured using a force transducer, compared with controls [18]. This difference in maximal voluntary contraction might be explained by persons with MS requiring greater central motor drive to achieve the same relative force during a maximal muscle contraction as healthy controls [19]. The weakness of lower extremity muscles seems to differ as a function of disability in those with MS. For example, one study compared the peak isometric and isokinetic torque in the knee extensors and flexors between 31 persons with MS who had mild disability and 21 persons with moderate disability [20]. The researchers reported that all muscle strength variables were significantly worse in the subgroup with moderate disability compared with those who had mild disability.

Persons with MS have worse balance, indexed by posturography,

than the general population. For example, one study of 12 women with MS and 12 age-matched controls examined differences in postural stability using a force plate (i.e., static posturography). Participants stood quietly on the force plate for 20 seconds with eyes open and directed forward gaze. Overall, the women with MS had greater Center-of-Pressure (COP) sway in the antero-posterior direction (mean=7.52 mm) than the age-matched controls (mean=4.33 mm) [21]. Another study of 16 persons with MS and 16 sex-matched controls used a similar static posturography protocol (i.e., participants stood quietly on a force plate with eyes open and directed forward for 30 seconds) [22]. This study reported that persons with MS had significantly greater COP sway area, sway velocity, and medio-lateral sway compared with controls [22]; those balance metrics were worse in participants with greater spasticity compared with persons with MS who had lesser spasticity and controls [22]. An additional study of 19 persons with mild MS disability (EDSS range=2.0-3.5) and 26 persons with moderate MS disability (EDSS range=4.0-6.5) examined the possibility that COP sway differed as a function of disability in persons with MS [23]. All participants stood quietly on a force plate for 30 seconds for measurement of COP sway. Persons with moderate disability had greater COP sway than the mildly disabled persons with MS, and, in the overall sample, COP sway was associated with disability ($r=0.36$), further suggesting that persons with worse MS disability had greater COP sway [23].

There is some emerging evidence that persons with MS have poor body composition based on BMI, body fat percentage, and waist circumference. Indeed, persons with MS have similar rates of overweight and obesity as the general population [24,25], and this is problematic given the rates in the general population of adults [26]. For example, one study reported an average BMI of 27.0 kg/m² in a large sample of persons with MS (n=8983); this average BMI value is comparable with the general population, but suggests that many persons with MS are overweight [25]. Another study of 123 women with MS reported that participants had higher BMI, waist circumference, and total body fat percentage than recommended by the World Health Organization [26]. As persons with MS have similar body composition characteristics as the general population [27], body composition metrics do not seem to vary as a function of

disability in persons with MS. For example, studies of small (n=17) [28] and large (n=68) [29] samples of persons with MS have reported no associations of body composition measures (e.g., fat percentage, lean mass percentage, and bone mineral density assessed by DXA) and EDSS score [28,29].

One limitation of previous research on deconditioning in persons with MS is that the studies measured single domains of physical fitness. One recent study examined differences in *multiple* domains of fitness between persons with MS and matched controls [30]. This study measured VO_{2peak}, muscle strength asymmetry of knee extensors and flexors, and upright balance based on posturography in 31 ambulatory persons with MS and 31 healthy controls matched by age, sex, height, and weight [30]. Persons with MS had substantially worse VO_{2peak} ($d=-0.72$) and balance ($d=0.91$) compared with healthy controls, and the differences between groups were moderate in magnitude for lower limb strength asymmetries of the knee extensors and flexors (d 's~0.50). This study provides evidence for comprehensive deconditioning in persons with MS, although it did not assess metrics of body composition.

Collectively, the published evidence generally supports the hypothesis that persons with MS exhibit physiological deconditioning (i.e., worse physical fitness) compared with the general population, particularly in aerobic, strength, and balance domains. There are not differences in body composition, although a large number of those with MS are overweight and obese. There is additional evidence that physiological deconditioning differs among persons with MS as a function of disability, such that persons with worse MS disability exhibit greater reductions in the physical fitness domains of aerobic capacity, muscle strength, and balance. The aforementioned evidence is consistent with our proposed model of physiological deconditioning developing in MS and progressing over time based on a comparison across disability levels [3,4].

Consequences of Physiological Deconditioning in MS

Another premise of this paper is that physiological deconditioning is associated with many of the consequences of MS. To that end, this section of this paper will describe evidence of associations among

Consequence/Outcome	n	Participant characteristics	Domain of deconditioning	Results
Brain Structure and Function				
Axonal and neuronal loss [34]	21	Age: 44.2 years (1.9 years) EDSS: 2.2 (range 0-6) Course: RRMS Duration: 7.3 years (0.1 years)	CRF	Worse CRF associated with reduced WM integrity, reduced GM volume, and higher lesion load
Mobility				
Walking and gait outcomes [41]	31	Age: 43.4 years (7.7 years) EDSS: not reported (PDDS: 2 (range 0-5)) Course: RRMS Duration: 8.6 years (6.3 years)	CRF Muscular Strength Balance	Worse CRF and worse lower limb strength asymmetries associated with slower T25FW performance, shorter 6MW distance, slower gait velocity, shorter step length, more time in double support
Cognition				
Cognitive processing speed [30]	31	Age: 43.4 years (7.7 years) EDSS: not reported (PDDS: 2 (range 0-5)) Course: RRMS Duration: 8.6 years (6.3 years)	CRF Muscular Strength Balance	Worse CRF, worse balance, and worse muscular strength asymmetries associated with slower CPS (PASAT, SDMT)
Fatigue				
Self-report fatigue [42]	25	Age: 36.9 years (9.5 years) EDSS: 4.4 (2.6) Course: Not reported Duration: 6.0 years (4.5 years)	CRF	Worse CRF associated with greater fatigue (Fatigue Severity Scale)

*Note: EDSS=Expanded Disability Status Scale; RRMS=Relapsing-remitting multiple sclerosis; CRF=Cardiorespiratory fitness; WM=white matter; GM=gray matter; PDDS=Patient-Determined Disease Steps; T25FW=Timed 25-Foot Walk; 6MW=Six-Minute Walk; CPS=Cognitive Processing Speed; PASAT=Paced Auditory Serial Addition Test; SDMT=Symbol Digit Modalities Test

Table 1: Summary of exemplar studies for consequences of physiological deconditioning in persons with multiple sclerosis.

aerobic capacity, muscle strength, balance, and body composition/morphology with brain structure/function, walking, cognitive, and fatigue outcomes in persons with MS. We selected these outcomes as there is existing research and because each represents a major and life-altering feature of MS. We have provided examples of exemplar studies on consequences of deconditioning in table 1.

Brian Structure and Function and Fitness Outcomes

Researchers have examined physical fitness variables and the association with brain structure and function based on Magnetic Resonance Imaging (MRI) in persons with MS, and this line of research was largely undertaken based on examinations of physical fitness and brain structure/function in the gerontology literature [31-33]. One study examined the associations between aerobic fitness levels (VO_{2peak}) and brain gray matter volume, white matter integrity, and lesion load in 21 persons with relapsing-remitting MS and minimal disability. The researchers reported that low aerobic fitness was associated with reduced structural integrity of white matter tracts in the left posterior thalamic radiation ($pr=0.40$) and the right anterior corona radiata ($pr=0.44$); reduced grey matter volume in the right post-central gyrus ($pr=0.45$) and midline cortical structures ($pr=0.45$); and higher lesion load volume ($pr=-0.44$) [34]. There is additional evidence that lower aerobic fitness levels (VO_{2peak}) were associated with less activation in the right inferior and middle frontal gyri ($pr=0.46$) and increased activation in the anterior cingulate cortex ($pr=-.44$) during performance of the Paced Visual Serial Addition Task (PVSAT) in 24 persons with relapsing-remitting MS who had minimal disability [35]. Other researchers have reported that muscle strength of the ankle dorsiflexors and hip flexors, assessed using a hand-held dynamometer, has been associated with brain imaging abnormalities along the intracranial corticospinal tract in 47 persons with moderate MS-related disability [36]. One study reported that larger postural sway amplitude (i.e., worse balance) was associated with reduced structural spinal cord integrity (i.e., cerebrospinal-fluid-normalized magnetization-transfer imaging) in 42 persons with MS who had moderate disability (mean EDSS=3.7) [37]. To date, there are no published studies examining the relationship between outcomes of morphological fitness and brain structure or function in persons with MS. Collectively, the existing research suggests that lower levels of aerobic fitness, muscle strength, and balance are associated with changes in brain structure and/or function in persons with MS.

Walking outcomes

Researchers have examined multiple domains of physical fitness as correlates of walking outcomes in persons with MS. For example, one study of 24 persons with mild MS examined the association between O_2 cost of walking (i.e., a physiological marker that reflects submaximal aerobic efficiency) and self-reported walking impairment based on Multiple Sclerosis Walking Scale-12 (MSWS-12) scores [38]. O_2 cost of walking under comfortable, fast, and slow walking speeds demonstrated moderate-to-large correlations with MSWS-12 scores (r^2 's=0.62-0.64) such that greater O_2 cost of walking was associated with worse perceived walking performance and quality [38]. Another study reported that persons with mild MS-related disability who had a higher O_2 cost of walking took slower ($r=-0.25$) and shorter ($r=-0.32$) steps, while spending a greater percentage of time in double support ($r=0.27$), based on measurements from a GaitRite electronic walkway during comfortable walking pace [39]. Other studies have reported that lesser peak isometric torque and greater torque asymmetries were associated with worse timed 25-foot walking (T25FW) performance in MS [20,21]. One study examined the association of peak torque in

knee flexors and extensors with 2-minute walk test (2MWT) distance in 52 persons with mild and moderate MS disability. Peak torque was measured with a Biodex isokinetic dynamometer, and peak torque of both knee extensors and flexors was moderately associated with 2MWT distance in the mild disability group (r^2 's=0.43-0.50), whereas only peak torque of knee flexors was associated with 2MWT distance in the moderate disability group (r^2 's=0.59-0.70). There is some evidence that balance, measured by static posturography, is associated with walking performance in persons with MS, as one study of 12 women with MS reported that greater antero-posterior COP sway (i.e., worse static balance) was moderately associated with slower walking speed (r^2 's=0.47-0.55) [21]. There is evidence that body composition is associated with walking performance in MS. One study classified 168 ambulatory persons with MS as normal, overweight, or obese, based on BMI, and compared the groups on multiple walking outcomes. Obese persons with MS had slower T25FW performance, shorter six-minute walk (6MW) distance, and took fewer steps per day under free-living conditions with these effects being small in magnitude (d 's=0.27-0.29) [40].

One recent study involved a comprehensive examination of the associations among aerobic capacity, balance, and lower limb strength asymmetries with walking performance (i.e., T25FW performance and 6MW distance) and spatiotemporal parameters of gait (i.e., velocity, cadence, step length, base of support, and time spent in double support) in 31 persons with MS and 31 controls matched by age, sex, height, and weight [41]. Regression analyses indicated that worse aerobic capacity and greater lower limb strength asymmetries independently explained variance in worse T25FW performance ($R^2=0.44$), shorter 6MW distance ($R^2=0.58$), slower gait velocity ($R^2=0.32$), shorter step length ($R^2=0.41$), and more time spent in double support ($R^2=0.32$) in persons with MS [41]. Interestingly, balance did not explain significant variance in any mobility outcome, however, in this study, worse balance was correlated with slower T25FW performance ($r=0.35$) and shorter 6MW distance ($r=0.32$), though these correlation coefficients were small in magnitude. Collectively, such evidence suggests that reduced aerobic fitness, muscular strength, worse balance, and poor body composition are associated with worse walking performance, across a variety of outcomes.

Cognitive outcomes

There are a limited number of studies examining associations among domains of physical fitness and cognitive outcomes in MS, with the majority of studies focusing on cardiorespiratory fitness and Cognitive Processing Speed (CPS). For example, one study included 24 persons with relapsing-remitting MS and reported that worse cardiorespiratory fitness was associated with worse performance on the Paced Serial Auditory Addition Test (PASAT) [35]. However, worse cardiorespiratory fitness was not significantly associated with performance on the selective reminding task ($pr=-0.22$) or the spatial reminding task ($pr=-0.12$), measures of verbal and visuospatial learning, respectively [35]. Another study reported that worse cardiorespiratory fitness was associated with worse scores on a composite measure of CPS in persons with MS and healthy controls [34]. One study recently examined the relationships among multiple domains of physical fitness (e.g., cardiorespiratory fitness, muscle strength asymmetry, and balance) and CPS in 31 persons with MS and 31 controls matched by age, sex, height, and weight [30]. In the MS subsample, worse aerobic capacity ($r=0.44$), worse balance ($r=-0.52$), and greater knee extensor asymmetry ($r=-0.39$) were significantly associated with slowed CPS, accounted for differences in CPS between persons with MS and controls, and explained a statistically significant

amount of variance in CPS ($R^2=0.39$) in the MS subsample [30]. We are unaware of research that has directly examined associations among domains of physical deconditioning with other domains of cognition that are impaired in MS (e.g., executive control). We are further not aware of published studies on the associations of measures of body composition and cognitive performance in this population.

Fatigue

There is some evidence to suggest a relationship between physiological deconditioning and symptomatic fatigue in persons with MS; very little is known about fitness levels and other symptoms of MS. In a sample of 25 persons with MS (mean EDSS=4.38), aerobic capacity (VO_{2peak}) determined on an arm-crank ergometer was significantly, strongly, and negatively correlated with fatigue assessed using the Fatigue Severity Scale (FSS; $r=-0.70$) [42]. Submaximal aerobic efficiency, or the O_2 cost of walking, was significantly correlated with scores on the FSS ($r=0.31$) in a sample of 44 persons with MS with minimal disability (median PDDS score=1) [39], suggesting that increased energetic demands of movement are associated with worse symptomatic fatigue. With respect to muscular strength, knee extensor power asymmetry (i.e., the relative difference in strength between muscles on opposite sides of the body) measured on a seated dynamometer has correlated significantly with symptomatic fatigue assessed using the FSS ($r=0.50$) and the Visual Analog Fatigue Scale ($r=0.67$) in 12 women with moderate MS (mean EDSS=4.0) [21]. Balance impairment assessed using dynamic posturography was significantly associated with symptoms of fatigue assessed using the Modified Fatigue Impact Scale ($r=-0.78$) in a sample of 17 ambulatory individuals with MS [43]. Individuals in this study with cerebellar and brainstem involvement, determined by a clinical neurological exam, presented with greater concurrent balance impairment and symptomatic fatigue compared to those who did not present with involvement of these systems. This suggests impaired balance is associated with symptomatic fatigue in MS, and this association may differ depending on neurological system involvement. There is evidence for an association between morphological fitness, assessed as BMI, and symptomatic fatigue in MS. In a sample of 53 participants with moderate MS (mean EDSS=3.4), a higher BMI was associated with higher scores on the Multidimensional Fatigue Symptom Inventory physical fatigue subscale ($r=0.36$) [44]. Collectively, the existing research suggests physiological deconditioning in multiple domains might be related with more frequent and severe symptoms of fatigue in persons with MS.

Exercise Training and Its Influence on Physical Fitness in MS

We have documented that persons with MS demonstrate significant deconditioning that worsens with disability accumulation over time, and this deconditioning is associated with a variety of outcomes ranging from brain structure/function through symptomatic expression of fatigue. Such results highlight the consideration of approaches for prevention of deconditioning as a way of forestalling other consequences and breaking the cycle in figure 1. The third premise of this paper, therefore, is that it conceptualizes the importance of maintaining and improving physical fitness levels for persons with MS. To that end, exercise training may be a way of addressing physiological deconditioning in persons with MS, and improvements in physical fitness may, in turn, result in secondary benefits.

There are over 60 studies that have examined the effect of exercise training in persons with MS [45], and there is evidence for

concurrent improvements in physical fitness along with functional and symptomatic outcomes in many of those studies. Aerobic and combined aerobic and resistance training interventions have improved cardiorespiratory fitness along with beneficial changes in walking performance [46,47], spatiotemporal gait parameters [48], and symptomatic fatigue [46,47,49-51] in persons with MS. For example, 8 weeks (3x/week) of moderate intensity leg cycling resulted in a significant increase in VO_{2peak} measured on a leg cycle ergometer, 6MW distance, and self-reported energy levels in 11 persons with MS who had moderate disability (mean EDSS=3.5) [46]. Exercise training interventions that primarily involved resistance training have improved muscular fitness, as well as walking performance [52-56], and symptomatic fatigue [49,51,55,57] in persons with MS. For example, significant improvements in knee flexor peak torque measured on a seated dynamometer, and T25FW and 500 MW performance were observed following 26 weeks of resistance (4x/week) and aerobic training (1x/week) in 91 persons with MS who had a range of disability (EDSS range=1-5.5) [16]. There are some data suggesting that exercise training influences balance and body fatness as indicators of motor and morphological domains of fitness, and such changes have occurred along with improvements in walking and fatigue outcomes [49,58-60]. Collectively, such research is suggestive that exercise training can improve components of physical fitness in MS and that such improvements often correspond with changes in walking and fatigue outcomes.

To date, no studies have directly examined improvements in physical fitness as direct mediators (i.e., variables that complete the causal link between variables) of the effect of exercise training on changes in secondary outcomes. This limits the ability to draw causal conclusions regarding the importance of counteracting physiological deconditioning in persons with MS. We are aware of two studies that reported associations between improvements in physical fitness and secondary outcomes following exercise training. For example, 15 weeks of aerobic exercise training based on arm and leg cycling training (3x/week) resulted in a 21% improvement in VO_{2peak} , and the improvement in cardiorespiratory fitness was significantly correlated with a reduction in symptomatic fatigue ($r=-0.68$) in 46 persons with moderate MS (mean EDSS=3.8) [49]. Another study reported that improvements in maximal voluntary contraction of the knee extensors measured on a seated dynamometer were significantly correlated ($r=0.26-0.43$) with improvements in lower extremity function including 6 MW and 10 MW performance following 12 weeks (2x/week) of progressive lower extremity resistance training in 31 people with MS [52]. Such evidence provides an important first step in establishing the relationship between changes in fitness outcomes with exercise training and the consequences of improving physical fitness in MS. The next step will be to establish a causal role for physical fitness in improving secondary outcomes that are important in persons with MS as is currently underway [61].

Conclusion

We provide a framework for the importance of maintaining and improving physical fitness in persons with MS as well as a comprehensive review of research on physiological deconditioning in cardiorespiratory, muscular, motor, and morphological domains among those with MS. There further is substantial evidence for associations between physiological deconditioning and a variety of consequences of MS, emphasizing the importance of counteracting and maintaining all domains of physical fitness. Exercise training may be an effective approach for improving physical fitness and managing secondary consequences among persons with MS. Importantly, the

evidence we present herein did not follow the guidelines of a systematic literature review, and we might have missed important articles on the topic of deconditioning and its consequences in MS.

Importantly, researchers have recently undertaken a systematic review of the effects of exercise training in MS [62] to develop evidence-based physical activity guidelines [63]. Based on the review, adults with MS should participate in 2 weekly sessions of 30 minutes of aerobic activity and 2 weekly session of strength training to improve aerobic capacity and muscular fitness, respectively. The amount of literature did not make it possible to identify the prescription necessary for improving other physical fitness outcomes, including balance and body composition. We believe that future research should examine the veracity of these prescriptive guidelines for improving physical fitness along with secondary outcomes in those with MS. We further believe that these guidelines provide an important basis for the prescription of exercise training by clinicians as a therapeutic approach for managing many of the consequences of MS.

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