Exercise and Multiple Sclerosis

22

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Abstract

Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system (CNS) with an estimated prevalence approaching 1 million adults in the United States. The disease pathogenesis and resulting damage express as dysfunction (e.g., walking and cognitive impairment) and symptoms (e.g., fatigue and depression) that compromise quality of life (QOL) and full participation. There has been a steadily increasing body of research on the outcomes of exercise among persons with MS, and this has accelerated sharply over the past decade. The current chapter provides a review of exercise and its outcomes, safety, and prescription in MS. This chapter initially reviews the evidence for benefits of exercise based principally on meta-analyses and literature reviews. The chapter then reviews evidence on the safety of exercise in MS and lastly provides guidelines for exercise prescription in MS. Collectively, this chapter serves as an overview and reference for researchers and clinicians interested in the benefits, safety, and prescription of exercise in MS.

Keywords

Neurological disease · Physical activity · Fitness · Exercise · Multiple sclerosis

22.1 Overview of Multiple Sclerosis

Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system (CNS) with secondary neurodegenerative processes in its pathogenesis [1]. This disease has an estimated prevalence approaching 1 million adults in the United States and occurs nearly three times more often among women than men [2]. There is a shifting age demography of MS such that it is most common among adults between the ages of 55 and 64 years in the United States [2]. MS is clinically characterized by relapses, lesions in the CNS, and progression of neurological disability. Those clinical expressions are brought about by periods of inflammatory demyelination and transection of axons as well as neurodegeneration involving loss of trophic support of neurons. The disease pathogenesis and resulting damage express as dysfunction (e.g., walking and cognitive impairment) and symptoms (e.g., fatigue and depression) that compromise quality of life (QOL) and full participation.

MS itself is typically treated through disease-modifying therapies (DMTs) that target immunological signaling proteins (e.g., interferons,

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cytokines) and/or populations of immune cells (e.g., lymphocytes). Such DMTs reduce relapse rates and slow progression of disability by controlling inflammatory activity. The DMTs do not control neurodegenerative processes nor cure the disease and further do not target dysfunction nor the symptoms of MS. Accordingly, persons with MS still experience residual symptoms and dysfunction and worsening of QOL, and this highlights the importance of identifying other approaches that can improve function, manage symptoms, and optimize QOL and participation in activities of daily living.

There has been a steadily increasing body of research on the outcomes of exercise among persons with MS, and this has accelerated sharply in the past decade [3]. The current chapter provides a review of exercise and its outcomes, safety, and prescription in MS. This chapter initially reviews the evidence for benefits of exercise based largely on meta-analyses and literature reviews. Such an approach is necessary, as over 54 clinical trials have been undertaken on exercise in MS over the past decade alone [3] and a selective review of papers would be arbitrary and extend beyond the word limits of this chapter. The chapter further reviews evidence on the safety of exercise in MS and lastly provides guidelines for exercise prescription in MS. Collectively, this chapter serves as an overview and reference for researchers and clinicians interested in the benefits, safety, and prescription of exercise in MS.

22.2 Scope of Exercise Benefits in MS

One recent review provided a general picture regarding the range of exercise benefits for people with MS based on 54 clinical trials performed between 2006 and 2016 [3]. The papers generally reported that exercise was associated with positive effects on walking/mobility, neurological disability, pain, cardiorespiratory fitness, muscular strength and endurance, body weight, balance, mental health (i.e., depression, anxiety, cognitive function, fatigue), and QOL [3]. Other reviews have focused on the benefits of exercise for disease modification in MS [4, 5]. This section of the chapter presents data on the benefits of exercise in MS, and it is organized based on the International Classification of Functioning, Disability and Health (ICF) model. Such an organization scheme is consistent with a previous review paper [6] and includes sections on MS pathogenesis, body functions, activities, and participation outcomes. The application of the ICF model essentially facilitates the classification of existing evidence on benefits of exercise into focal categories along the MS-disease process.

22.2.1 Effect of Exercise on MS Pathogenesis

Researchers have recently developed arguments that exercise may represent a disease-modifying behavior by impacting the latent MS pathogenesis [4, 5]. One group of researchers provided a literature review on the topic of exercise as a DMT [5] by first identifying metrics for evaluating disease modification and progression in MS (i.e., relapse rate, neurological disability and its progression, brain lesion volume, and neuro-performance outcomes of walking and cognition) and then reviewing evidence for exercise as a DMT. The evidence indicated that exercise was associated with reduced relapse rate, neurological disability and progression, and lesion volume and further yielded improved neuro-performance, particularly walking outcomes. Of note, one review of 26 randomized controlled trials (RCTs) that included 1295 participants with MS reported relapse rates of 4.6% and 6.3% for exercise and control conditions, respectively; those rates yielded a relative risk of relapse for exercise training of 0.73 compared with control conditions (i.e., 27% reduction in relapse rate for exercise training) [7].

There is a noteworthy limitation of the existing body of research that must be considered when making the case for exercise as a potential DMT. This limitation involves the quality and quantity of evidence regarding exercise effects on immunological and neurotrophic factors that underpin the pathophysiology of MS based on

clinical and basic science [8]. That research indicates the lack of a clear picture regarding exercise effects on the basic pathophysiology of MS [9]. Collectively, the existing evidence provides a positive, yet preliminary, picture for exercise as a DMT in MS, but requires additional research regarding exercise effects on cellular biomarkers of MS pathogenesis [10].

22.2.2 Effect of Exercise on Mental Body Functions

Fatigue Fatigue represents one of the most common, debilitating, and poorly managed symptoms of MS. An estimated 80% of persons with MS report severe or debilitating symptomatic fatigue [11], and research has demonstrated no significant or systematic benefit of pharmacological management for fatigue in MS [12]. This supports consideration of other approaches for managing fatigue in MS, and exercise training has emerged as a leading strategy that might yield clinically meaningful improvements in fatigue.

One meta-analysis undertook a quantitative synthesis of RCTs examining exercise training effects on symptomatic fatigue in persons with MS [13]. The meta-analysis included 17 RCTs involving 568 persons with MS and reported an overall, weighted mean effect size (ES) of 0.45. The weighted mean ES was slightly heterogeneous, but no moderators were identified for explaining variance in the mean ES. Importantly, the mean ES of 0.45 approached the widely accepted value of 0.5 that has been deemed clinically meaningful in QOL research [14]. Overall, the meta-analysis indicated that exercise training was seemingly efficacious for reducing fatigue in persons with MS and further highlighted two noteworthy limitations regarding the lack of (a) comparative effectiveness research and (b) samples with severe or debilitating fatigue.

Another recent meta-analysis summarized the available research comparing three different approaches, namely, exercise, education, and medication, for reducing fatigue in MS [12]. The meta-analysis included 18 rehabilitation and 7 pharmacological trials targeting fatigue in MS. The average ESs for exercise and education were 0.57 and 0.54, respectively, whereas the ES for medication was 0.07—exercise was as efficacious as education programs for reducing fatigue, and both approaches were seemingly better than common medication approaches for managing fatigue in MS. The authors did highlight the continuing limitation of severe or debilitating fatigue not being an inclusion criterion in RCTs of exercise. This important limitation precludes the classification of exercise as a "treatment" for MS-related fatigue, and the available evidence suggests that exercise can help manage this symptom in MS.

Depression Depression represents another hallmark symptom of MS. An estimated 50% of persons with MS will present with major depressive disorder over the lifetime of this disease [15]. Persons with MS have further reported depressive symptom scores that were nearly 1 SD higher than those of the general population [16]. The existing research does not support conventional pharmacological management of depression in MS and suggests that cognitive behavior therapy is possibly efficacious and may be considered in the treatment of depressive symptoms [17]. There is emerging evidence that exercise might be an additional approach for managing depressive symptoms in MS.

One meta-analysis has examined the overall effects of exercise training on depressive symptoms in RCTs of MS [18]. Exercise demonstrated a small, but statistically significant, overall ES of 0.36, and this indicated an improvement in depressive symptoms compared with control conditions. The overall effect was not heterogeneous and did not support a search for moderator variables. One limitation of the meta-analysis included a lack of focal examination of the effects of specific exercise modalities on depressive symptoms—this hampers recommendations for clinical practice on the efficacy of a specific exercise program. As with meta-analyses regarding exercise effects on fatigue [12, 13], another primary limitation of exercise studies on depressive

symptoms involved the lack of persons with MS who had major depressive disorder or elevated depressive symptomology.

Another recent meta-analysis examined the effects of exercise on depressive symptoms in adults with neurological disorders (including MS) and highlighted the possible importance of meeting public health guidelines for physical activity within the context of a given exercise intervention [19]. That meta-analysis included 26 RCTs of exercise involving 1324 participants with 7 different neurological disorders, including Alzheimer's disease (n = 4 trials), migraine (n = 1), MS (n = 13), Parkinson's disease (n = 2), spinal cord injury (n = 1), stroke (n = 2), and traumatic brain injury (n = 3). The meta-analysis yielded an overall ES of 0.28; this favored a reduction in depressive symptom outcomes after exercise compared with a control condition. Of note, exercise programs that met physical activity guidelines yielded an overall ES of 0.38 compared with an ES of 0.19 for studies of exercise that did not meet physical activity guidelines. This meta-analysis provides initial evidence that exercise, particularly when meeting physical activity guidelines, can improve depressive symptoms in adults with neurological disorders.

One recent meta-analysis examined moderators of exercise training effects on depressive symptoms among people with MS [20]. The meta-analysis included 24 ESs derived from 14 RCTs that included a total of 624 people with MS. Overall, exercise training significantly reduced depressive symptoms by a heterogeneous mean ES of 0.55, and the overall ES exceeded the 0.5 guideline for clinical meaningfulness [14]. Interestingly, improvement in fatigue moderated the overall effect of exercise on depressive symptoms such that there were significantly larger antidepressant effects in trials where exercise significantly improved fatigue (ES = 1.04) compared with trials where there was no significant improvement in fatigue (ES = 0.41). These data suggest that exercise-induced improvements in fatigue significantly moderated exercise training effects on depressive symptoms in MS. Nevertheless, one continuing limitation of the research is the lack of persons with MS who have major depressive disorder or elevated depressive symptomology. This limits our understanding of exercise as a "treatment" of depression in MS.

Cognition Cognitive dysfunction is another common and burdensome consequence of MS. An estimated 65% of persons with MS demonstrate impaired cognitive performance based on objective neuropsychological testing, and cognitive dysfunction is a primary determinant of employment status, instrumental activities of daily living, and QOL [21]. Of note, pharmacological approaches have been ineffective for managing cognitive problems in MS, and the efficacy of cognitive rehabilitation has only recently been established in clinical trials [22], but this approach alone is not completely beneficial for restoring cognitive function [23]. There is an abundance of evidence from the general population indicating that exercise training may improve cognitive function across the lifespan [24]. This has prompted considerable interest in the possibility that exercise might yield similar effects in MS [25].

Researchers recently conducted a systematic review of exercise training as well as physical activity and physical fitness effects on cognition in MS [26]. The review identified 26 usable papers regarding exercise, physical activity, and physical fitness effects on cognition in persons with MS. There were conflicting evidence for the effects of exercise training on cognition in MS and overall positive, but not necessarily definitive, evidence for the effects of physical activity and physical fitness on cognition. The lack of definitive evidence supporting physical activity and physical fitness benefits on cognitive performance was largely based on Class III and Class IV evidence (i.e., cross-sectional, within-subjects designs). Overall, the primary conclusions were that there is insufficient research from well-designed studies to definitively conclude that exercise, physical activity, and/or physical fitness can improve cognition in MS. This was based, in part, on methodological issues of Class I and II (i.e., randomized controlled trials) studies, namely, inclusion of cognition as a secondary

outcome, poorly developed exercise interventions, and paucity of research on cognitively impaired persons with MS. The promising evidence from Class III and Class IV studies may be useful for informing the development of high-quality interventional research for clarifying the possibility that exercise, physical activity, and fitness may be useful for managing and treating cognitive impairment in MS.

22.2.3 Effect of Exercise on Cardiovascular and Neuromuscular Body Functions

There is substantial evidence for physiological deconditioning involving the cardiovascular and neuromuscular systems of persons with MS. Persons with MS demonstrate reduced aerobic capacity and muscle strength compared with healthy adults who do not have MS [27], and these differences are larger as a function of disability status [28]. The declines in cardiovascular and neuromuscular capacity might be associated with reduced walking performance [29] and fatigue [30]. The ideal approach for improving cardiovascular and neuromuscular functioning in persons with MS involves exercise training.

One recent review provided a quantitative synthesis of 20 RCTs that examined the effect of exercise training on muscular and cardiorespiratory fitness in persons with MS [31]. The mean overall ES was 0.27 for muscular fitness outcomes and 0.47 for cardiorespiratory fitness outcomes. The weighted mean ES was not heterogeneous for either muscular or cardiorespiratory fitness outcomes. Such evidence supports that exercise training is associated with small improvements in muscular fitness and moderate improvements in cardiorespiratory fitness outcomes in persons with MS.

22.2.4 Effect of Exercise on Sensory Body Functions

Balance dysfunction is a common sensory abnormality in MS that can influence walking, falls and falls risk, and activities of daily living in MS [32]. One meta-analysis has examined the effects of 11 physiotherapy interventions on balance in people with MS [33]. Overall, the methodological quality of the studies ranged between poor and moderate. The mean ES for resistance and aerobic training on balance was non-significant and small in magnitude with a mean ES of 0.22. There was a small and non-significant effect of resistance and aerobic exercise training on balance outcomes in people with MS who had mild or moderate disability. That meta-analysis further noted substantial limitations associated with the small quantity and poor quality of the available research on the effects of exercise training on balance outcomes.

Another common sensory abnormality of MS is pain, and this symptom of MS has profound effects on QOL and other outcomes (e.g., fatigue), but is poorly managed. One recent meta-analysis has provided evidence supporting the effect of exercise for managing pain in people with MS [34]. The meta-analysis included RCTs that recruited people with MS where exercise was the intervention and pain was an outcome identified through five electronic databases. There were 10 studies that met the inclusion criteria with a total sample size of 389 persons with MS. The exercise interventions were associated with less pain compared with passive control groups with mean ES of 0.46. There was between-study heterogeneity, but there were no moderators that explained variance in the mean ES. Overall, this meta-analysis provided some evidence that exercise alleviates pain in MS, but there were limitations in study quality associated with a high risk of bias across studies.

22.2.5 Effect of Exercise on Activities

The effect of exercise on activities has typically focused on the outcome of walking. This is logical as walking represents a major activity limitation in MS and greatly impacts participation and QOL outcomes [35]. Walking further represents one of the most valued activities by people with MS [36] and is one of the most visible outcomes of the disease. One meta-analysis examined the overall effects of exercise training on walking mobility in MS [37]. The meta-analysis included 22 papers that involved 66 ESs and 600 persons with MS and yielded a weighted mean ES of 0.19. Of note, there were larger effects for supervised exercise training (ES = 0.32), exercise programs that were less than 3 months in duration (ES = 0.28), and mixed samples of relapsing-remitting and progressive MS (ES = 0.52). Such data collectively support that exercise training is associated with a small improvement in walking mobility in MS, and this may be optimized under conditions of supervised exercise training.

One recent and updated meta-analysis has quantified the benefits of exercise on walking ability in MS [38]. That study focused on average improvements in walking ability based on the 10-m walk test (10mWT), timed 25-foot walk test (T25FW), 2-min walk test (2MWT), 6-min walk test (6MWT), and timed up-and-go (TUG) from 13 RCTs. Exercise yielded a significant, clinically meaningful improvement in walking speed, measured by the 10mWT (mean difference [MD] reduction in walking time of −1.8 s), but a non-significant change in the T25FW (MD = −0.6 s). Exercise further yielded significant improvements in walking endurance as measured by the 6MWT and 2MWT, with increased walking distances of 36.5 m and 12.5 m, respectively. The exercise-related improvement on 2MWT performance was clinically meaningful. By comparison, there was minimal exercise-related improvement for the TUG (MD = −1.1 s). This meta-analysis further supports improvement in speed- and endurance-related walking outcomes with exercise training in persons with MS and that improvements on select outcomes can be considered clinically meaningful.

22.2.6 Effect of Exercise on Participation Outcomes

The ICF category of participation includes health-related quality of life (HRQOL) and overall QOL. HRQOL reflects an individual's perception of physical and mental health status, whereas overall QOL reflects a person's judgment of satisfaction with life based on an evaluation of important life domains. Importantly, both HRQOL and overall QOL are compromised in MS when compared with healthy controls and even persons with other chronic diseases and conditions [39].

One systematic review included evidence from 54 studies regarding the effects of exercise training on multiple outcomes including HRQOL in adults with MS [40]. Overall, there was inconsistent evidence regarding the effects of exercise training on HRQOL, although exercise was associated with improvements in other outcomes (e.g., cardiorespiratory and muscular fitness) that were included in the systematic review. Overall, the evidence suggested that exercise may improve HRQOL among those with MS, but required further, focal examination.

An older meta-analysis has examined the effect of exercise training interventions on QOL outcomes among persons with MS [41]. Thirteen studies were included in the meta-analysis that involved a total of 484 MS patients. The weighted mean ES was 0.23 and favored an improvement in QOL with exercise training. There were larger effects associated with MS-specific measures of QOL. The evidence from this meta-analysis supports a small, but statistically significant, improvement in overall QOL with exercise training among persons with MS.

22.2.7 Summary of Exercise Effects in MS

This section of the chapter was guided by the ICF model for classifying the evidence regarding exercise training effects on outcomes in MS. The existing evidence demonstrated a pattern of smaller effects of exercise on outcomes when moving from body structure and function through

activity performance. This is logical as body structure and function represent more proximal outcomes associated with adaptations as a result of exercise itself, whereas activity performances (i.e., participation) are more distal outcomes that are likely not the direct result of exercise training. This is consistent with models of exercise and physical activity effects on QOL in aging [42, 43]. There is obviously a need for considerable work in the areas of disease pathogenesis, activities, and participation within the ICF framework for providing a complete picture of exercise in MS.

22.3 Safety of Exercise in MS

The safety profile of exercise has been described in a recent review of exercise in persons with MS [7], and this is critical for informing decisions and recommendations regarding its safety. To that end, the systematic review focused on adverse events (AEs) reported in RCTs of exercise training in MS. We searched electronic databases for RCTs of exercise training in MS. We calculated the rate of AEs and the relative risk of AEs for exercise training versus control. Twenty-six studies were reviewed that included 1295 participants. We determined that the rate of AEs was 1.2% and 2.0% for control and exercise, respectively. The relative risk of AEs for exercise training was 1.67, and the risk of AEs was no different when compared with evidence from the general population of adults who participate in exercise. The most common AEs involved musculoskeletal issues (e.g., low back and joint pain) associated with resistance exercise training. This evidence should reduce uncertainty regarding the safety profile of exercise training in MS.

22.4 Prescription of Exercise in MS

There are two primary resources on the prescription of exercise in people with MS [44, 45]. One set of guidelines [45] were developed based on a systematic literature review of exercise training interventions in MS [40]. The resulting guidelines suggest that persons with MS who have mild or moderate disability should engage in at least 30 min of moderate-intensity aerobic activity two times per week and strength training exercises for major muscle groups two times per week. The aerobic and resistance exercise training can be performed on the same day, but should be separated by 24 hours (i.e., not performed on consecutive days). This prescription should yield fitness benefits and possibly reduce fatigue, improve mobility, and improve components of HRQOL. Importantly, these guidelines have not been formally tested and require evaluation before broad application, particularly among those with advanced disability with MS.

Another set of guidelines was developed through a scoping review of existing resources on exercise prescriptions in persons with MS, stroke, and Parkinson's disease for the provision of resources that are uniformly recognizable by healthcare practitioners and patients/clients with these diseases [44]. This paper, in particular, synthesized resources that reported aerobic and resistance training guidelines for people with MS, stroke, and PD. Regarding MS, the systematic search yielded ten eligible resources from electronic databases and textbooks or websites of major organizations. Data were extracted (exercise frequency, intensity, time, and type) and synthesized into recommendations per disease. Exercise guidelines for MS consistently recommended 2–3 days/week of aerobic training (10–30 min at moderate intensity per session) and 2–3 days/week of resistance training (1–3 sets between 8–15 repetitions maximum per session). The frequency ranges between 2 and 3 days per week and should generally start with 2 days per week and progress toward 3 days per week over time. The duration of the exercise bouts ranges between 10 and 30 min and should gradually progress from 10 to 30 min over time. The intensity should be moderate and range between 11 and 13 on the 20-point rating of perceived exertion scale, or between 40 and 60% peak oxygen consumption or peak heart rate. The overall progression should start with increases in either duration or frequency. Progressions in intensity

should be based on the tolerability of the individual with MS, only after duration and frequency are well tolerated. This harmonizing of exercise guidelines provides a prescriptive basis for healthcare providers, exercise professionals, and people living with MS regarding disease-specific exercise programming. Importantly, these guidelines still require verification for benefits and safety before broad application, particularly among those with advanced MS disability.

22.5 Next Steps Regarding Exercise in MS

There is an abundance of evidence supporting the benefits of exercise in MS. Nevertheless, we still observe low rates of participation in physical activity among persons with MS, particularly when compared with the general population [46]. This is, in part, associated with major gaps in research that require remediation [9]. Some of the necessary steps for guiding future research include identifying a minimally effective dose of exercise for benefits, focusing on exercise and neuroplasticity, and understanding exercise benefits, safety, and prescription in advanced stages of MS.

22.5.1 Minimal Dose of Exercise

The promotion of exercise in MS requires identifying the "minimally" effective dose of exercise for benefits; this has not been uniformly established for any of the outcomes identified in this chapter. Such research could be guided by recent guidelines for the prescription of exercise in MS [44, 45]. Importantly, these guidelines have not been formally tested and require evaluation before broad application, particularly among those with advanced MS disability. There further is a need for focal research on the dose-response association between exercise parameters and outcomes of MS. Such studies might focus on the dose of exercise based on manipulations of the intensity, frequency, and duration of exercise bouts and the associated outcomes for persons with MS. This will assist in the promotion of exercise by clearly identifying the dose of exercise necessary for benefits as a target for persons with MS.

22.5.2 Exercise and Neuroplasticity

Exercise can improve the structure of the CNS [47]—this is based on a wealth of evidence from animal studies and human research involving older adults. For example, RCTs of exercise training in older adults consistently demonstrate improvements in the volume of the hippocampus based on magnetic resonance imaging, and this translates into better learning and memory [48]. There is a growing body of research indicating that physical fitness and physical activity are associated with volumes of the basal ganglia, hippocampus, and thalamus in persons with MS [49–51]. Such cross-sectional research has informed the design of a recent pilot RCT wherein aerobic exercise training yielded improvements in the viscoelastic properties of the hippocampus that were associated with changes in learning and memory in persons with MS [52]. This research is exciting, as it provides a possible basis for exercise as a countermeasure for CNS decline in MS, yet the evidence derives from a small number of cross-sectional studies and only one RCT. This is an obvious area of future research for extending our knowledge of the pleotropic benefits of exercise in MS.

22.5.3 Exercise in More Advanced Stages of MS

The evidence for the benefits of exercise in persons with MS primarily has been established in those with mild-to-moderate disability. Nevertheless, mobility impairment (e.g., use of assistive device for ambulation) is common in MS, and those with more severe disability have greater detriments in aerobic fitness, muscular function, and balance than those with lower disability. Those persons with MS who have more severe disability may in fact represent the people

who are most in need of exercise programs. To that end, a recent systematic review was conducted of the current literature regarding exercise training in those with severe MS mobility disability (i.e., Expanded Disability Status Scale (EDSS) ≥ 6.0) [53]. This systematic review identified 19 relevant papers from 18 studies overall; 5 studies involved aerobic and/or resistance exercise training and 13 studies involved adapted exercise methods (i.e., body-weight support treadmill training, total-body recumbent stepper training, and electrical stimulation cycling). Of the five studies that examined exercise, two reported that resistance exercise training yielded significant improvements in muscle endurance; there were no significant improvements in any outcomes from the three studies of aerobic exercise training. Of the 13 studies that examined adapted exercise training, 9 reported significant improvements in disability, physical fitness, physical function, and/or symptomatic and participation outcomes. Collectively, the evidence is promising for beneficial effects of exercise in persons with severe MS disability, yet there is a lack of high-quality evidence regarding exercise for managing disability accumulation and associated outcomes in persons with severe MS disability. There further is limited research on the safety and prescription of exercise in this segment of MS. This highlights the importance of future research for optimizing the safety, prescription, and efficacy of exercise training in persons with MS who have severe disability.

22.6 Summary

Overall, there is increasing evidence for the role of exercise in managing the MS-disease pathophysiology, functions, and symptoms and optimizing QOL and participation outcomes. There further is evidence for the safety and prescription of exercise in MS. Nevertheless, there are exciting opportunities for research on exercise and neuroplasticity in MS and a need for developing a strong knowledge base regarding exercise in persons with advanced stages of MS. Such research will provide a comprehensive knowledge base for the promotion of exercise by healthcare providers as an approach for managing MS itself and the many consequences of this disease [54].

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