Mini-Review

The importance of promoting physical activity and exercise training as adjuvant therapy for people with multiple sclerosis

Emerson Sebastião[1], Tyler Wood[1], Robert Wayne Motl[2], Felipe Balistieri Santinelli[3], Fabio Augusto Barbieri[4]

[1]Northern Illinois University, Department of Kinesiology and Physical Education, DeKalb, Illinois, United States; [2]University of Illinois at Chicago, Department of Kinesiology and Nutrition, Chicago, Illinois, United States; [3]REVAL Rehabilitation Research Center, Faculty of Rehabilitation Sciences, Hasselt University, Hasselt, Belgium; [4]Universidade Estadual Paulista "Júlio de Mesquita Filho", Faculdade de Ciências, Departamento de Educação Física, Bauru, SP, Brazil.

Associate Editor: Angelina Zanesco, [1]Universidade Metropolitana de Santos, Faculdade de Medicina, Santos, SP, Brazil; [2]Universidade Estadual Paulista "Júlio de Mesquita Filho", Departamento de Educação Física, Instituto de Biociências, Rio Claro, SP, Brazil. E-mail: angelina.zanesco@unesp.br.

Abstract - Aim: This review aimed to provide evidence and highlight the importance of including physical activity (PA) and/or exercise training (ET) as part of the comprehensive multiple sclerosis (MS) care. **Methods:** Using the current literature on the subject, we provide a brief overview of MS incorporating its definition, common symptoms, prevalence, and potential disease consequences. We further succinctly describe MS as the first line of treatment, as well as the role of PA and ET in the disease. We end the commentary highlighting important recommendations from an international initiative to improve MS-related physical activity research that we believe will help not only improve the area of study but also best practices within this population. **Results:** There is compelling evidence for the beneficial effects of PA and/or ET on MS-related symptoms and consequently health and quality of life. There is preliminary evidence suggesting the potential for a disease-modifying effect. **Conclusion:** Fomenting this discussion is timely due to the increased prevalence of MS in different regions of the globe, and people with MS report low levels of PA participation and high amounts of sedentary time. The consequences of inactivity in this population can be drastic. The current body of evidence supports the notion that PA and ET are safe health behaviors that should be adopted as an adjuvant treatment option within the comprehensive and complex MS care due to its benefits on a variety of disease-related symptoms and its potential for improving health and quality of life in this population.

Keywords: health-related quality of life, neurodegenerative disease, patient care, motor activity, rehabilitation.

Introduction

Multiple sclerosis (MS) is neurodegenerative, often disabling, unpredictable disease of the central nervous system (CNS) that disrupts the flow of information within the brain, and between the brain and the body[1]. The disease presents with a large array of symptoms that include, but are not limited to, muscle weakness, balance, mobility and cognitive impairment, depression, fatigue, pain and spasticity, vision, and sensory impairment[1]. It is estimated that 2.8 million people live with MS worldwide. In Brazil, the prevalence of MS ranges from 5 to 27 per 100,000 habitants[2]. These numbers are significantly lower compared with countries like the United States (309.2 per 100,000)[3] and Canada (240 per 100,000)[4].

The lower MS prevalence in Brazil may be partially explained by the fact that Brazil is situated close to the equator, and this probably contributes toward higher vitamin D levels. Low levels of vitamin D have been described as a potential risk factor for MS[5]. Nevertheless, MS can have devastating consequences, and therefore, should be a concern regardless of worldwide location. For example, there is evidence demonstrating that people with MS have a lower life expectancy compared with the life expectancy of the general population[6]. In addition, MS is more prevalent in women than men (2-3:1 ratio) and its onset occurs in younger adults (i.e., labor force age)[7]; this increases the chance of unemployment due to disease-related disability[8,9]. One recent study conducted in Brazil with nearly 700 MS patients with mild levels of disability

demonstrated that 95% of the participants were at working age and that roughly 50% were employed. In addition, 94% reported being affected by fatigue and approximately 64% reported cognitive difficulties[10].

Multiple sclerosis: first line of treatment

Currently, there is no cure for MS. The first line of treatment for the disease is the use of disease-modifying therapies (DMTs), and these are commonly prescribed following disease diagnosis. There are 17 approved DMTs for the treatment of relapsing forms of MS (i.e., CIS, RRMS, and SPMS), and one for the PPMS (Figure 1). These drugs focus on reducing both the number and severity of relapses (exacerbations) by targeting latent immune dysregulation of cytokines and lymphocytes and, therefore, slowing the progression of the disease[11,12]. However, DMTs are not appropriate for treating the disease symptoms or curing MS. For instance, these medications seem to not positively affect common disease symptoms such as fatigue and cognition[13,14]. In addition, DMTs may cause significant side effects[15]; which may compromise medication adherence. For symptoms management, people with MS are often prescribed numerous medications for alleviating the numerous symptoms and therefore improving their quality of life[16]. Consequently, polypharmacy may have serious side effects, such as the increased risk of adverse drug events, drug interactions, reduced functional capacity, and medication non-adherence[17,18]. To this end, non-pharmacological therapies that engender minimal side-effects are of particular interest for the MS population. A non-pharmacological therapy with potential beneficial effects in a wide-array of MS symptoms with minimal to no almost no side-effects is physical activity (PA) or exercise training[19-21]. In fact, the idea of prescribing PA/exercise training as a potential treatment for disease symptoms and progression in people with MS corroborates the global exercise is medicine movement[22].

Multiple sclerosis: physical activity and exercise training as adjuvant therapy

Researchers and health professionals have agreed that wellness should be a priority for people with MS, and can be achieved through health behaviors including PA and exercise training[23,24]. In fact, PA - particularly exercise training, represents an adjuvant therapy for managing symptoms of MS. In the past, partaking in exercise training was controversial for people with MS. It was believed that such practice would cause an exacerbation of the symptoms[25]. However, studies conducted in the United States, Canada, and across European countries, where the prevalence of MS is high, have demonstrated that both PA and exercise training is safe and yield beneficial effects in this population, including improvements in fitness, fatigue, depression, balance, function, and walking performance, and those collectively improve quality of life[19,26,27] (Figure 1). Although isolated studies have observed improvements in cognition, results from a recent meta-analysis do not support the efficacy of exercise training on global or domain-specific (e.g., attention, processing speed) cognitive performance in people with MS[28].

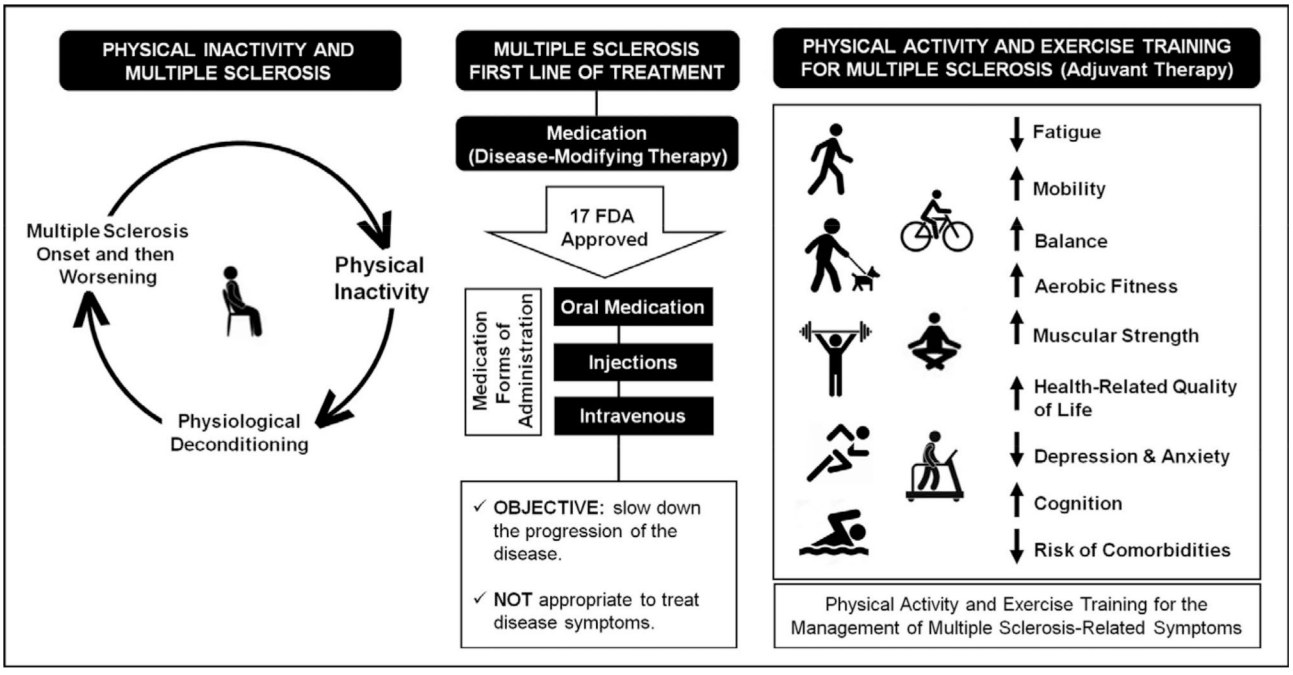

Figure 1 - Overview of the multiple sclerosis treatment and the health benefits of physical activity and exercise training in this population.

Table 1 - Exercise Training and Physical Activity Recommendations for People with MS.

1. Persons with MS should be encouraged to undertake 150 minutes or more per week of physical activity and/or exercise training.
2. Progression in volume per week should be gradual and based on a person's abilities, preferences, and safety.
3. Early evaluation by an exercise specialist with knowledge in MS is recommended for an individualized physical activity/exercise training plan.
4. Patients presenting with disability levels where physical activity and exercise training become more challenging should be referred to specialists for safety and appropriate prescription.
5. Exercise for patients with limiting physical mobility should be facilitated by a trained specialist.

Adapted from: Kalb and colleagues [26].

There is further positive evidence of the benefits of PA/exercise training in "preventing" (i.e. risk reduction) MS, MS pathogenesis, relapses, central nervous system structures, and participation outcomes as well as risk for comorbidities[19,29,30]. Collectively, the current body of knowledge in this area supports meaningful consequences of PA and exercise training in people with MS; which underscores its important role in both primary (i.e., prevent disease before it develops) and secondary (i.e., reduce the impact of the disease that has already developed) prevention.

The multitude of clinical trials in this area yielded a recent publication on recommendations for exercise training and lifestyle PA for people with MS across the disability spectrum[26]. This initiative led and sponsored by the National MS Society of the United States brought together renowned researchers from different parts of the globe and underscores the important role of PA and exercise training as a treatment for people with MS. Major points described in the referred manuscript are summarized in Table 1.

Nevertheless, those with MS engage in lower levels of PA than counterparts from the general population[31]. This is a concern because inactivity can place people with MS in a vicious cycle whereby physical deconditioning due to inactivity worsens symptoms and accelerates disease progression, which in turn increases inactivity levels due to increased disability[32]. The current body of evidence regarding the benefits of PA and/or exercise for people with MS supports the notion that PA and exercise training are safe health behaviors that should be adopted as an adjuvant treatment option within the comprehensive and complex MS care due to its benefits on a variety of disease-related symptoms. This is especially important in countries where the prevalence of MS is relatively low such as Brazil. For instance, in consensus guidelines for MS treatment in Brazil published by the Neuroimmunology Scientific Department of the Brazilian Academy of Neurology, the only treatment discussed was pharmacological[33,34]. The high-cost medications (MS drugs included) in Brazil are financed by the Universal Health System (SUS in Portuguese). According to Comini-Frota et al.[33], the distribution of MS-specific medications follows the protocol from the Ministry of Health, which is based upon "bureaucratic rules and pharmacoeconomics", posing a challenge to a neurologist, as it is inflexible. Such a model does not consider the complexity and individual heterogeneity of the disease and its treatment. Thus, given the numerous benefits of PA and/or exercise training for people with MS, supporting and promoting such behavior along with standard treatment (i.e., DMT) seems to be paramount.

Final considerations

There is solid evidence that PA and exercise training are important components in the management of MS due to its plethora of benefits for this population. The number of studies using exercise as a treatment effect in people with MS is increasing exponentially. However, a recent international initiative urged for the necessity for the development of consensus within the MS-related exercise research in several different aspects (i.e., definitions and terminologies, studies methodologies, reporting and outcomes, adherence and compliance to exercise, and mechanisms of action)[35]. According to this initiative, achieving consensus in the highlighted areas will better equip researchers to conduct large, international multicenter efforts that would target the most pressing research questions in this area, with a positive impact on those who need the most of best practices - the MS patients. Altogether, PA or exercise training are powerful tools in managing MS-related symptoms and are essential for general health and well-being. Of note, PA or exercise training does not have to be a high-intensity type of activity for benefits, and general activities that can normally be at home or in the community can result in positive physical and mental health outcomes[21]. PA and exercise training do not increase the number of relapses or exacerbate symptoms[25], but rather improve quality of life and well-being, and promote participation[36].

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Corresponding author

Emerson Sebastião. Department of Kinesiology and Physical Education, Northern Illinois University, DeKalb, Illinois, United States.
E-mail: esebastiao@niu.edu.

Manuscript received on November 1, 2021
Manuscript accepted on November 8, 2021