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DOES EXERCISE HAVE A NEUROPROTECTIVE FUNCTION IN MULTIPLE SCLEROSIS? A BRIEF OVERVIEW OF THE PHYSICAL TRAINING POTENTIAL EFFECTS ON CYTOKINES AND BRAIN-DERIVED NEUROTROPHIC FACTOR

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ABSTRACT

Although the advance in disease-modifying drugs has helped to stabilize the multiple sclerosis (MS) course increasing life-expectancy, physical deterioration still supervenes over time in most MS patients. In this context, physical exercise programs are considered a safe and well-tolerated tool to preserve functional independence in this population, which not only provides similar fitness improvements as usually observed in healthy general population, but it may also ameliorate some of the symptoms that this pathology entails (as fatigue, balance deficits, muscle weakness, etc.). Nowadays, the question is if exercise only aids to reverse physical deconditioning associated to the disease or it has the potential to have an impact on MS progression. In the present overview, the role of exercise as complementary therapy for modulating various physiopathological pathways related to MS disease such as inflammation and the neurotrophic support for neuronal survival was revised. Specifically, the exercise ability to modulate the immune system behaviour regulating the pro- and anti-inflammatory cytokine balance, as well as, to promote neuroprotective and neurorestorative mechanisms through the brain-derived neurotrophic factor stimulation was analysed.

Keywords: multiple sclerosis, exercise, cytokines, brain-derived neurotrophic factor, brain atrophy

¿PUEDE EL EJERCICIO FÍSICO EJERCER UNA FUNCIÓN NEUROPROTECTORA EN LA ESCLEROSIS MÚLTIPLE? UNA BREVE REVISIÓN DE LOS EFECTOS POTENCIALES DEL ENTRENAMIENTO FÍSICO SOBRE LAS CITOQUINAS Y EL FACTOR NEUROTRÓFICO DERIVADO DEL CEREBRO

RESUMEN

Aunque los avances farmacológicos han ayudado a estabilizar la evolución de la esclerosis múltiple (EM), aumentando notablemente la expectativa de vida, la mayoría de los pacientes con EM aún sufren un deterioro físico progresivo. En este contexto, los programas de ejercicio físico se consideran una herramienta segura que permite preservar la independencia funcional en esta población, proporcionando no solo las mejoras en la condición física que se observan en la población general, sino que también parecen eficaces para reducir la sintomatología asociada a la EM (como fatiga, déficit de equilibrio, debilidad muscular, etc.). Una de las preguntas actuales que existe en el ámbito científico es si el ejercicio físico sólo permite mejorar los síntomas y revertir el desacondicionamiento físico asociado con la EM o si también tiene el potencial de modular la progresión de la enfermedad. En la presente revisión se ofrece una perspectiva general del posible papel que puede jugar el ejercicio físico, como terapia complementaria en la regulación de varias

vías fisiopatológicas relacionadas con la EM, tales como la inflamación y el soporte neurotrófico para la supervivencia neuronal.
Específicamente, se analizó la capacidad que tiene el ejercicio físico para modular el comportamiento del sistema inmunitario a través de la regulación del equilibrio de citoquinas pro y anti-inflamatorias, así como para promover mecanismos neuroprotectores a través de la estimulación del factor neurotrófico derivado del cerebro.
Palabras clave: esclerosis múltiple, ejercicio, citoquinas, factor neurotrófico derivado del cerebro, atrofia cerebral

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INTRODUCTION

Multiple sclerosis (MS) is an immune-mediated chronic disease of the central nervous system (CNS) characterized by a breakdown of the blood-brain barrier (BBB), multifocal inflammation, demyelination, oligodendrocyte loss, reactive gliosis, and axonal degeneration (Baecher-Allan, Kaskow, & Weiner, 2018; Craig, Young, Ennis, Baker, & Boggild, 2003; Hohlfeld, 1997). MS neurodegeneration entails several physical symptoms such as balance disorders, muscular weakness, spasticity and fatigue (Gandhi, Laroni, & Weiner, 2010). Nowadays, MS is the most common neurological condition and it is among the most common causes of neurological disability in young adults in developed countries (Koch-Henriksen & Sorensen, 2010), with a much higher incidence (i.e. 3:1 ratio) among women (Orton et al., 2006). In Spain, its prevalence in the last 40 years has grown, affecting over 100 patients/100.000 people (Fernandez et al., 2012). Although the precise aetiology of the disease is unclear, the immune dysregulation seems to be prompted by an interaction between environmental and genetic factors (Hohlfeld, 1997; Koch-Henriksen & Sorensen, 2010). In individuals with a genetic predisposition to develop autoimmunity, MS is probably triggered by an environmental antigen (i.e. viral or bacterial infection), which auto-reactive T cells (Th1 and Th17), in a process identified as molecular mimicry, targets myelin antigens in the CNS (Garg & Smith, 2015; O'Connor, Bar-Or, & Hafler, 2001). The different pathophysiological mechanisms of the disease contribute to a brain volume loss, which seems to be accelerated in patients with MS [annual rate: 0.5–1.35% per year in patients with relapsing-remitting MS (RRMS)] compared to the healthy general population (annual rate: 0.1%–0.3%) (Calabrese et al., 2007; De Stefano et al., 2014; De Stefano et al., 2010; Hardmeier et al., 2005; Narayana et al., 2012; Rudick, Fisher, Lee, Simon, & Jacobs, 1999; Simon, 2006). Brain atrophy is a prominent feature of MS that advances inexorably throughout the disease course, with a rate that seems to be mostly independent of the MS subtype (De Stefano et al., 2014; De Stefano et al., 2010).

Although the improvement in disease-modifying drugs has helped to stabilize the disease progression increasing life-expectancy (Scalfari et al., 2013), physical deterioration still ensues over time in most MS patients (Filippini et al., 2013). In this context, rehabilitation programs become a key tool to preserve functional independence and quality of life (Dalgas, 2011). Among different complementary therapies, exercise, understood as a planned, structured and repetitive physical activity undertaken over a prolonged period (Caspersen, Powell, & Christenson, 1985), has shown to promote relevant, not only physical but also psychological and cognitive, improvements in MS patients (Aidar et al., 2018; Pilutti, Greenlee, Motl, Nickrent, & Petruzzello, 2013; Platta, Ensari, Motl, & Pilutti, 2016). Years ago, MS individuals were advised not

to perform any vigorous physical activity because it could worsen their neurological status (Giesser, 2015; Sutherland & Andersen, 2001). This is known as Uhthoff's phenomenon, in which some MS individuals show symptom exacerbations such as balance perturbations and increased spasticity when they become overheated during exercises (Dalgas, 2011; Giesser, 2015; Opara, Brola, Wylegala, & Wylegala, 2016). In addition, because patients generally experience symptoms of fatigue, they were also advised to avoid exercise in order to preserve their energy for activities of daily living. Both concerns usually made MS individuals be less active (Motl, McAuley, & Snook, 2005; Nortvedt, Riise, & Maeland, 2005), fostering physical deconditioning and potentially creating additional comorbidities such as obesity, osteoporosis or vascular diseases (Giesser, 2015). Nevertheless, it has already been shown that physical exercise does not increase the risk of relapse or adverse events in this population (Giesser, 2015; Pilutti, Platta, Motl, & Latimer-Cheung, 2014); conversely, exercise appears to be safe, well-tolerated and not only provides similar health and fitness improvements as usually observed in healthy individuals, but it also may ameliorate some of the symptoms that this pathology entails such as fatigue, balance deficits, muscle weakness, etc. (Cruickshank, Reyes, & Ziman, 2015; Giesser, 2015; Heine, van de Port, Rietberg, van Wegen, & Kwakkel, 2015; Latimer-Cheung et al., 2013; Motl & Pilutti, 2012; Motl & Sandroff, 2015).

An important question related to the impact of physical training in MS individuals' status is whether exercise only reverses physical deconditioning associated to the disease or it has a neuroprotective effect, which could attenuate the disease progression (Dalgas & Stenager, 2012). The data from the last decade reinforce the second approach, suggesting that physical activity could modulate to some extent various physiopathological pathways related to MS disease, like inflammation and the neurotrophic support for neuronal survival and regeneration.

CNS inflammation in MS: the potential effect of exercise on pro- and anti-inflammatory cytokines

According to McDonald's criteria (Thompson et al., 2018), most MS patients suffer the RRMS form of the disease, which is initially characterized by relapses of focal neurological deficits followed by a variable degree of recovery (Compston & Coles, 2008). During the early stage of the RRMS, CNS inflammation seems to be the primary cause of damage (Loma & Heyman, 2011). This phase is probably driven by a systemic immune response, in which there is a myelin-specific autoreactive lymphocyte infiltration of the BBB that leads to the formation of inflammatory demyelinating lesions (Ciccarelli et al., 2014; Olsson, 1995). Cytokines are proteins that regulate the immune system

function (Alexander, 2002) playing an important role in the pathogenic events that characterize MS progression (Ozenci, Kouwenhoven, & Link, 2002). Commonly, in healthy individuals, due to a cross-inhibitory effect, there is a homeostatic balance between pro-and anti-inflammatory cytokines. In presence of pathogens this balance changes, resulting in an increase of pro-inflammatory cytokines [i.e. interleukin (IL)-1, IL-6, IL-12, IL-17, IL-23 tumor necrosis factor (TNF)-α, interferon (INF)-γ] and a decrease of the anti-inflammatory ones (i.e. IL-4, IL-10, IL-13) which induces, through different pathways, a local inflammatory and immunological response (i.e. immune cell differentiation, growth, proliferation and activation) (Ozenci et al., 2002). However, as the immune cells are sensitized to the myelin antigen in MS, the pro-inflammatory imbalance is self-sustained over time which induces the cascade of inflammatory and demyelination processes observed in the illness pathogenesis (Pilli, Zou, Tea, Dale, & Brilot, 2017): 1) Pro-inflammatory cytokines IL-12 and IL-23 participate in the peripheral immune activation (differentiation of CD4+ T cell into Th1 or Th17 phenotypes) regulating the interaction between T lymphocytes and the antigen presenting cells such as B cells, dendritic cells, microglia and macrophages (Loma & Heyman, 2011); 2) Cytokines also facilitate the migration of those activated T cells into the CNS disrupting the BBB through TNF-α, INFγ, IL-1β, IL-17 and IL-22 (Kebir et al., 2007; Minagar & Alexander, 2003); 3) Once activated immune cells have crossed the BBB, they release several pro-inflammatory cytokines stimulating microglia, macrophages, astrocytes, and recruit B cells, which, in turn, damage myelin, oligodendrocytes and axons (Rivera-Quinones et al., 1998; Zamvil & Steinman, 2003). It must be noted that the release of pro-inflammatory cytokines such as TNF-α and INFγ promotes inflammation, also suppressing the differentiation of T-regulatory cells (Th2), which release anti-inflammatory cytokines (Minty et al., 1993; Zhu & Paul, 2008).

Due to the role of cytokines in MS pathogenesis, the balance regulation of the pro- and anti-inflammatory cytokines is a major issue, not only for disease-modifying drugs therapies (Motl et al., 2017) but for any complementary treatment trying to slow-down the disease progression. In this sense, as regular exercise has shown to chronically reduce the basal levels of inflammatory markers (Petersen & Pedersen, 2005), it may be expected that exercise could be used as an anti-inflammatory and complementary therapy in MS patients (Dalgas & Stenager, 2012). Physical activity seems to reduce Th1 cell production, but not Th2 cells production (Gleeson, 2007; Sharif et al., 2018; Steensberg et al., 2001), promoting a long-term immune regulation characterized by a post-exercise transient anti-inflammatory state (Gleeson et al., 2011). During and after exercise, IL-6 is released from muscles, which, in this case, acts as a myokine, inducing an anti-inflammatory response (Brandt &

Pedersen, 2010; Sharif et al., 2018). Commonly, IL-6 works together with TNF-α as a pro-inflammatory cytokine against a pathogen, promoting the proliferation and activation of Th1 cells (Sharif et al., 2018). Nevertheless, after exercise, IL-6 is released from muscles without TNF-α secretion, working as a myokine. In this condition, IL-6 promotes the secretion of IL-10 and the reduction of TNF-α, reducing inflammation and inhibiting Th1-cells (de Vries, 1995). Conversely, IL-6 from monocytes, which acts as a pro-inflammatory cytokine, as well as IL-2 from Th1 lymphocytes, are inhibited during and after exercise, contributing to the inflammatory reduction (Lancaster et al., 2004). The decrease of Th1 following exercise is also attributed to the increase in hormonal levels of cortisol and adrenaline in response to physical activity, which inhibits the production of IL-12 from antigen presenting cells (Elenkov & Chrousos, 1999; Pedersen & Hoffman-Goetz, 2000) and reduces TNF-α produced by Th1 cells (Bergmann et al., 1999). Although changes in circulating lymphocytes normally return to baseline levels in no more than 24 h (Gleeson, 2007), systematic changes in IL-6, cortisol and adrenaline caused by regular bouts of exercise could offer protection against auto-immune disease (Gleeson, 2007; Lancaster et al., 2004).

While the effectiveness of regular exercise to modulate the cytokine profile and the progression of inflammatory-related diseases has been proven (Bilski et al., 2016; Leal, Lopes, & Batista, 2018; Pearson, Mungovan, & Smart, 2018; Pedersen, 2017), experimental studies on MS have shown limited and contradictory results. In a recent systematic review of the experimental studies conducted by Negaresh et al. (2018), no systematic cytokine changes in serum associated to regular exercise were found, which, according to the authors, would not support the idea that the cytokine modifications caused by exercise are a regulator of the disease progression. Nevertheless, the real effect of exercise on cytokine in MS must still be elucidated because, as the aforementioned authors pointed out, the few experimental studies present several methodological limitations, which hinder the generalization of the results: small samples, only female population, different MS types in the same experimental group, cytokines monitored using a variety of methods and taken from different body fluids, etc. For example, the fact that cytokine levels in plasma and serum did not change towards a more anti-inflammatory profile can be attributed to a lower BBB permeability caused by exercise (Mokhtarzade et al., 2018) which would limit the immune cell infiltration into the CNS.

Among those limitations, from the point of view of physical exercise prescription, one of the most important ones that could explain the current disparity of cytokine findings was the high heterogeneity observed in the exercise programs. Acute and chronic cytokine modifications caused by exercise depend on several parameters as, for example, the type of exercise (i.e.

aerobic training, resistance training, combined training, etc.), the intensity and volume of training, program duration, participant training status, age, type of the disorder, etc. (Gleeson, 2007). For instance, focusing on the secretion of IL-6 induced by exercise, it has been observed that the higher duration, intensity and greater number of muscles involved in the exercise are, the greater the release of this cytokine after exercise is (Gokhale, Chandrashekara, & Vasanthakumar, 2007; Pedersen & Febbraio, 2005). Probably, longer and more intense training implies higher energy demands and consequently, a greater carbohydrate depletion associated to a higher acute IL-6 production from muscles (Keller et al., 2001) which, in turn, could chronically modify pro- and anti-inflammatory cytokine profile. This rationale could explain why some studies found significant changes in the cytokine levels after training in RRMS individuals (Deckx et al., 2016; Golzari, Shabkhiz, Soudi, Kordi, & Hashemi, 2010; Kierkegaard et al., 2016; Mokhtarzade, Ranjbar, Majdinasab, Patel, & Molanouri Shamsi, 2017). For instance, Kierkegaard et al. (2016) found a significant reduction in the basal level of several pro-inflammatory cytokines in serum in RRMS after a high-intensity resistance training performed at 80% of one repetition maximum test involving several muscle groups (8 exercises) during three months (24 sessions). Golzari et al. (2010) observed a significant reduction in plasma INFγ and IL-17 after a combined endurance and resistance training of 3 sessions per week for 2 months (24 sessions). Similarly, Deckx et al. (2016) found a significant reduction in plasma TNF-α when faced with lipopolysaccharide and IFN-γ stimulation after a combined endurance and resistance training of 5 sessions per 2 weeks for 3 months (30 sessions). Overall, these findings suggest that the higher the duration, intensity and energy demand are, the greater the cytokine activity is. However, as individuals with higher fitness level show a reduced response to exercise (Gokhale et al., 2007; Pedersen & Febbraio, 2005), a continuous and individualized modulation of training parameters seems to be required to elicit cytokine adaptations along time. In spite of these potential implications, nowadays, the small number of experimental studies carried out on MS, the heterogeneity of the experimental design and the inconsistent reporting of their training parameters hinder the dose-response characterization of the exercise effect on cytokines in this population (Negaresh et al., 2018).

Additionally, another limitation related to the exercise program design was whether the training protocols were enough to induce weight loss (Mokhtarzade et al., 2017; Negaresh et al., 2018), which is an important tool to regulate the secretion of the cytokines by the adipose tissue, i.e., adipokines (Gleeson et al., 2011). An important adipokine related to the MS pathology is leptin, which promotes the secretion of pro-inflammatory cytokines TNF-α, IL-2, and IL-6 and the activation of Th1 cells (Matarese, Procaccini, & De Rosa, 2008).

In this sense, Mokhtarzade et al. (2017) observed that weight loss in RRMS induced by an exercise program was significantly related with a reduction in leptin together with TNF-α, which, in turn, were related with greater fatigue improvements. These authors also observed an increase in the adiponectin hormone which increases the production of the anti-inflammatory cytokine IL-10 (Kraszula et al., 2012). Although these preliminary findings suggest that exercise programs on MS should also focus on weight loss in order to maximize their effects on the cytokine and adipokine profile, further research is necessary to clarify the role of weight loss after training on the immune system in MS.

CNS integrity in MS: the potential effect of exercise on brain-derived neurotrophic factor

Although white matter infiltration by immune cells and subsequent demyelination are commonly considered the most recognizable signs of MS, demyelination of the cortical gray matter, axonal deterioration and CNS atrophy have been detected in MS patients even in early stages of the disease (Baecher-Allan et al., 2018; Bevan et al., 2018; Kutzelnigg et al., 2005; Lucchinetti et al., 2011; Siffrin, Vogt, Radbruch, Nitsch, & Zipp, 2010; Trapp & Nave, 2008). In MS patients, brain atrophy, mainly assessed through magnetic resonance imaging techniques, progresses at a faster rate than in healthy individuals (Vollmer et al., 2015). Importantly, neurodegenerative rather than demyelination processes seem to be more related with the degree of disability in MS (Lemus, Warrington, & Rodriguez, 2018; Wujek et al., 2002). In rodent models, no motor impairment has been observed in presence of demyelination if the axonal integrity was preserved (Rivera-Quinones et al., 1998), but long-lasting neurological disability was found in presence of axonal loss (Wujek et al., 2002). These findings have also been observed in MS patients, in whom the cortical and gray matter atrophy was the best predictor of the disease progression and motor disability (Fisniku et al., 2008) as well as of the degree of cognitive impairment (Sacco et al., 2015). In this sense, it has been suggested that the evolution from RRMS to a progressive form of the disease materializes when the CNS is not able to compensate the axonal injuries (Ksiazek-Winiarek, Szpakowski, & Glabinski, 2015; Nave & Trapp, 2008). This explains why there is a higher rate of axonal loss and brain atrophy in later stages of the disease (Simon, 2006). All these reasons justify that therapeutic interventions aim at not only reducing relapse events, inflammation and demyelination but also at enhancing neuroprotection and neurorestoration of the CNS (Luhder, Gold, Flugel, & Linker, 2013).

A therapeutic target for preserving CNS integrity are the neurotrophins, which are proteins involved in neural regeneration, preservation and

remyelination processes (Azoulay, Vachapova, Shihman, Miler, & Karni, 2005; Begni, Riva, & Cattaneo, 2017; Ceni, Unsain, Zeinieh, & Barker, 2014; Ebadi et al., 1997; Huang & Reichardt, 2001; Kelamangalath & Smith, 2013; Linker, Gold, & Luhder, 2009; Vacaras, Major, & Buzoianu, 2017). One of the most important neurotrophins is the brain-derived neurotrophic factor (BDNF) which, in healthy subjects, has been associated with age-related volume reduction in white matter (Driscoll et al., 2012) and brain volume, mostly the hippocampus and the amygdala (Erickson, Prakash, et al., 2010; Manna et al., 2015). BDNF is also involved in the pathogenesis of several neurological diseases such as Huntington's disease (Ferrer, Goutan, Marin, Rey, & Ribalta, 2000; Zuccato & Cattaneo, 2007), Alzheimer's disease (Ye, Tai, & Zhang, 2012) and Parkinson's disease (Howells et al., 2000). Mature BDNF functions are related to several neuroplasticity mechanisms as neuronal protection and survival, axonal and dendritic remodeling, neuronal differentiation, synaptogenesis in axon terminals and synaptic transmission efficacy (Alsina, Vu, & Cohen-Cory, 2001; Barde, 1994; Knaepen, Goekint, Heyman, & Meeusen, 2010). The major source of circulating BDNF (70–80%) is the brain, mainly the cortex and hippocampus (Rasmussen et al., 2009). Commonly, serum and plasma levels of BDNF, which are highly correlated to BDNF in the CNS (Pan, Banks, Fasold, Bluth, & Kastin, 1998), are reduced in MS patients compared to healthy controls (Azoulay et al., 2005; Tongiorgi et al., 2012). However, during periods of higher inflammatory activity, especially after MS relapses (Frota et al., 2009), BDNF levels rise (Weinstock-Guttman et al., 2007) being observed not only in plasma but also in immune and CNS cells of demyelinating lesions (Stadelmann et al., 2002). This transitory increase of BDNF associated to active stages of the disease is produced not only by neurons but also by immune cells (T lymphocyte, microglia and astrocytes) (Kerschensteiner et al., 1999), which has been interpreted as a neuroprotective mechanism in response to CNS injuries. The neuroprotective role of the BDNF in MS would also be supported by correlational results, which have showed that the greater the BDNF release is, the higher the white matter volume in MS patients is (Weinstock-Guttman et al., 2007). Thus, a lower BDNF secreted by neuron and immune cells linked to the disease progression would indicate an exhaustion of the CNS restoration ability (Azoulay, Urshansky, & Karni, 2008; Azoulay et al., 2005).

It is currently well recognized that exercise elicits molecular and cellular processes that promote neural plasticity in aging and disease (White & Castellano, 2008). Interestingly, among the potential pathways for CNS preservation, BDNF seems to be the most susceptible neurotrophin to be modulated by exercise (Knaepen et al., 2010). Commonly, BDNF circulating levels from several brain areas such as the hippocampus, amygdala, prefrontal and motor cortex, cerebellum, etc. (Fang et al., 2013; S. Gustafsson, Liang, &

Hilke, 2011; Koo et al., 2013; Liu et al., 2009; Marais, Stein, & Daniels, 2009; Neeper, Gomez-Pinilla, Choi, & Cotman, 1996) rise after a single bout of exercise (Ferris, Williams, & Shen, 2007; G. Gustafsson et al., 2009; Rojas Vega et al., 2006) and they generally return back to baseline values in less than 1 h (Knaepen et al., 2010). As various meta-analyses have confirmed (Dinoff et al., 2016; Szuhany, Bugatti, & Otto, 2015), exercise training programs chronically increase resting concentrations of BDNF in peripheral blood in healthy adults and, to higher extent, in individuals with neurological disorders as Parkinson's disease (Hirsch, van Wegen, Newman, & Heyn, 2018). It must be noted that aerobic rather than resistance training programs seem to be more effective to increase resting BDNF concentrations in peripheral blood (Dinoff et al., 2016), but probably BDNF modulation depends on the type of exercise, number of muscles involved, intensity and duration of the exercise bouts as wells as the participants' physical status. BDNF changes caused by regular exercise could explain why higher fitness levels and physical activity are associated with greater brain volume. Cross-sectional studies (Colcombe et al., 2003; Erickson et al., 2009; Floel et al., 2010; Verstynen et al., 2012) but more importantly longitudinal works (Erickson, Raji, et al., 2010) as well as randomized control trials (Colcombe et al., 2006; Erickson et al., 2011; Ruscheweyh et al., 2011) have shown how physical fitness and exercise are linked with brain volume and gray matter preservation in older adults (Erickson, Leckie, & Weinstein, 2014). Interestingly, as Erickson et al. (2011) showed, higher serum BDNF changes caused by an aerobic training program were correlated with changes in the hippocampal volume, which would confirm the neuroprotective role of BDNF as a physiological mediator of exercise effects on CNS preservation. It is important to note that a similar association has been found between physical fitness and white matter volumes, not only in older adults (Sexton et al., 2016), but also in children (Chaddock-Heyman et al., 2014).

Based on these findings, recent works have tried to elucidate if exercise can work in a similar way in MS patients, helping to slow-down demyelination and axonal deterioration caused by the disease. To the best of the authors' knowledge, the first study which observed the link between exercise and MS progression was carried out by Prakash, Snook, Motl, and Kramer (2010). In this study, a significant relationship between aerobic fitness and both, gray matter volume and white matter integrity in RRMS patients was found. Subsequent cross-sectional studies have confirmed these results finding significant associations between the physical activity level and the volume of some brain areas (Klaren et al., 2015; Schwartz et al., 2016). These results, although promising, can be biased by confounding variables, especially the stage of the disease in which each patient is. Thus, longitudinal studies and randomized trials are needed to reduce the influence of confounding

parameters. To the best of the authors' knowledge, only three intervention studies have analysed the effect of exercise programs on brain volume parameters in MS. The first one was a case study (Leavitt et al., 2014), in which an RRMS patient, who was involved in a 3-month aerobic training program, showed an important increase of the hippocampal volume (+16.5%), while another RRMS patient, who underwent a stretching program, did not show any noticeable change (+2.8%). Later, a very recent pilot study found a lower but non-significant ($p < 0.1$) brain atrophy in a group of RRMS patients who carried out a 6-month resistance training program compared with a control group (Kjolhede et al., 2018). Finally, the first randomized control trial analysing exercise and brain atrophy found that RRMS patients involved in a community-located running training program presented an increase in brain volume compared with a control group; however, these changes were only significant in the pallidum (Feys et al., 2017).

In spite of these promising results suggesting that exercise is not only helpful to reverse physical deconditioning associated to the MS disease but that it also has neuroprotective effects, from the authors' point of view, it is too early to assert that exercise is able to reduce the brain atrophy caused by MS progression. It is even more difficult to perform any recommendations about which type of training would be the most appropriate to achieve this goal. Many more experimental studies with a larger sample size and longer training duration are needed to clarify all these questions. Until that happens, sport science professionals, exercise physiologists and physiotherapists should base their physical exercise interventions on the general recommendations and precautions developed for this population (Dalgas, Stenager, & Ingemann-Hansen, 2008; Halabchi, Alizadeh, Sahraian, & Abolhasani, 2017), which ensure that exercise is well-tolerated and focuses on the improvement of the most prominent symptoms of each patient.

CONCLUSIONS

Overall, the results from the last decade presented in this overview suggest that physical exercise might be a complementary but powerful therapy to regulate the immune system behaviour in MS through the modulation of pro- and anti-inflammatory cytokine balance, as well as to promote neuroprotective and neurorestorative mechanisms through BDNF stimulation. Therefore, although exercise does not make the front pages of the main scientific journals as frequently as drug research does, these findings on exercise reinforce the idea that more randomized controlled trials, supervised by a multidisciplinary group (neurologists, practitioners, sport science professionals, etc.), should be carried out to confirm if exercise can play a neuroprotective role capable to

slow-down MS course, and to quantify their dose-response association in both, the relapse-remitting and the progressive forms of the disease.

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