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DERLEME/REVIEW

The Effect of Exercise on Myokine Levels in Multiple Sclerosis: IL-6, BDNF, Irısın and TNF- α

Egzersizin Multipl Sklerozda Miyokin Düzeylerine Etkisi: IL-6, BDNF, İrisin ve TNF- α

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ABSTRACT
Multiple Sclerosis (MS) is an autoimmune disease that causes inflammation and neurodegeneration in the central nervous system. Interleukin-6 (IL-6), brain-derived neurotrophic factor (BDNF), irisin, and tumor necrosis factor-alpha (TNF-α) are myokines that play critical roles in both the progression of the disease and in neuroprotection. Exercise is known to stimulate the release of these myokines from skeletal muscles, thereby exerting anti-inflammatory and/or neuroprotective effects. These effects contribute to the regulation of the immune system and neuroregeneration, positioning exercise as a potential complementary therapeutic strategy in MS management. The present review aims to examine alterations in myokine levels (IL-6, BDNF, irisin, and TNF-α) among patients with multiple sclerosis and to investigate the effects of exercise on these parameters. A review of the literature indicates that myokine levels in MS patients differ from those of healthy individuals, and that exercise has significant modulatory effects on these biomarkers. The findings generally demonstrate that IL-6 and TNF-α levels tend to be elevated in MS, yet decrease or stabilize following exercise interventions, whereas BDNF and irisin levels, which are often reduced in MS, increase in response to exercise. Collectively, these findings suggest that exercise may exert anti-inflammatory and neuroprotective effects, thereby contributing positively to the clinical course of the disease.
Keywords: Multiple sclerosis, myokine, exercise, inflammation, neurodegeneration

ÖZET
Multipl Skleroz (MS), merkezi sinir sisteminde inflamasyon ve nörodejenerasyona neden olan bir otoimmün hastalıktır. İnterlökin-6 (IL-6), beyin kaynaklı nörotrofik faktör (BDNF), irisin ve tümör nekroz faktörü-alfa (TNF-α) hem hastalığın ilerlemesinde hem de nöroproteksiyonda önemli roller oynayan miyokinlerdir. Egzersizin kaslardan bu miyokinlerin salınımını uyararak anti-inflamatuar ve/veya nöroprotektif etkilere sahip olduğu bilinmektedir. Bu etkiler bağışıklık sistemi düzenlenmesine ve nörorejenerasyona katkıda bulunarak egzersizi MS yönetiminde potansiyel bir tamamlayıcı tedavi stratejisi haline getirir. Bu çalışmada, multipl skleroz hastalarında miyokin (IL-6, BDNF, İrisin ve TNF- α) düzeylerinin değişimlerinin belirlenmesi ve egzersizin bu parametreler üzerindeki etkilerinin araştırılması amaçlanmıştır. Literatür incelendiğinde MS hastalarında miyokin düzeylerinin sağlıklı bireylere göre değişiklik gösterdiği ve egzersizin bu biyobelirteçler üzerinde önemli etkiler sağladığı görülmektedir. Literatürdeki bulgular, IL-6 ve TNF-α düzeylerinin MS hastalarında genellikle artış gösterdiğini, egzersiz müdahaleleri sonrasında ise bu seviyelerin azaldığını veya dengelendiğini; buna karşılık BDNF ve irisin düzeylerinin sıklıkla düşük bulunduğunu, egzersizle birlikte ise yükseldiğini ortaya koymaktadır. Bu bulgular, egzersizin antiinflamatuar ve nöroprotektif etkiler sağlayarak hastalığın seyrine olumlu katkılar sunabileceğini göstermektedir.
Anahtar kelimeler: Multipl skleroz, miyokin, egzersiz, inflamasyon, nörodejenerasyon

Introduction

Multiple Sclerosis (MS) is an autoimmune, inflammatory disease that occurs when peripheral autoreactive immune cells migrate into the central nervous system (CNS)[1]. It is known that many different types of

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immune cells play a role in the pathogenesis of MS in response to the abnormal response of the immune system. These immune cells target myelinated axons in the CNS, initiating the demyelination process, followed by axonal degeneration[2].

While the exact cause of MS is unknown, it is thought to develop as a result of the interplay of genetic predisposition and environmental risk factors. Various hypotheses regarding the onset of the disease have been proposed. One hypothesis suggests that inflammation is directly initiated by a viral infection in the CNS, while another suggests that inflammation occurs in the periphery and that the disease is initiated by T cell infiltration into the CNS[3]. While the precise role of inflammation in the onset of MS remains unclear, it is widely accepted that inflammation plays a significant role in disease progression.

The relationship between the peripheral immune system and CNS immune responses relies on interactions between inflammatory cells and the blood-brain barrier (BBB)[4]. The endothelial cells that form the BBB, due to their low pinocytotic activity, tightly regulate the passage of peripheral inflammatory cells and molecules from the blood into the CNS[5]. Disruption of the structural integrity of the BBB and inflammation promote leukocyte migration within the brain parenchyma, playing a central role in the pathogenesis of many neurodegenerative diseases[6]. In autoimmune diseases such as MS, T cells become auto-reactive due to the effect of an unknown antigen and enter the CNS. T cells that enter the CNS secrete various proinflammatory cytokines, causing further disruption of the BBB's permeability and facilitating the entry of macrophages, B cells, and antibodies into the CNS[7]. It has been reported that the entry of leukocytes into the CNS plays a critical role in the disruption of BBB integrity and the development of neuroinflammation[8]. Infections and other proinflammatory events have been suggested as important factors in the initiation of MS pathology and/or triggering of relapsing attacks[9]. Immune system dysregulation underlies the pathogenesis of MS, and treatment approaches focus on managing inflammatory processes. Systemic inflammation has been reported to be an important risk factor for MS relapses, and clinical symptoms have been reported to worsen following peripheral inflammation[10]. Clinical studies have found a significant relationship between infections and the progression of neurological damage; it has been noted that attacks continue even after the infection has resolved[11].

Currently, MS is a disease with no definitive cure, and disease-modifying drugs, corticosteroids, and various pharmacological approaches for symptomatic control are used. However, while there is currently no treatment method that supports remyelination or brain repair, a number of potential strategies are being intensively researched[7]. Therefore, individuals diagnosed with MS often continue to experience persistent symptoms and functional loss. In this context, alternative therapeutic strategies for symptom management, including non-pharmacological approaches for rehabilitation, are of great importance.

Exercise training is recommended for MS patients for symptom management, functional recovery, quality of life improvement, and promotion of a healthy lifestyle through daily activities. In this respect, exercise is considered an effective rehabilitation approach for disease management[12,13]. Studies have shown that regular exercise training exhibits significant anti-inflammatory effects[14]. The anti-inflammatory effects of exercise have been associated with increased hormones (cortisol and adrenaline) that reduce the production of proinflammatory cytokines by immune cells and the effects of myokines released from muscles. Furthermore, exercise promotes the activation of regulatory T (Treg) cells, natural killer cells, and immune cells that secrete the anti-inflammatory cytokine IL-10. Taken together, exercise training plays an important role in improving overall immune health by increasing antimicrobial activity and reducing systemic inflammation[15].

Myokines are defined as cytokines and other peptides produced by skeletal muscle fibers that exhibit autocrine, paracrine, or endocrine effects[16]. It has also been suggested that myokines may be used as a potential biomarker in determining the type, intensity, and frequency of exercise to be performed in the treatment of neurodegenerative diseases, cancer, and autoimmune diseases such as diabetes.

This study examines the relationship between myokines secreted as a result of exercise and the pathophysiology of MS and their possible effects on the disease mechanism. It focuses specifically on the roles of IL-6, BDNF, irisin, and TNF-α myokines in the regulation of inflammation, neuroprotection, and neuroregeneration processes. Thus, the potential benefits of exercise as a complementary, non-

pharmacological approach to MS management are being evaluated. Furthermore, by revealing the effects of exercise on disease mechanisms at the cellular level, it is intended to guide future research.

The Relationship Between Multiple Sclerosis, Myokines, and Exercise

Interleukin-6 (IL-6)

Interleukin-6 is produced by various cell types, including muscle cells, T and B lymphocytes, monocytes, macrophages, fibroblasts, endothelial cells, and some tumor cells[17,18]. Elevated IL-6 levels measured at rest are generally associated with pro-inflammatory properties. In contrast to IL-6 as a marker of systemic inflammation, the transient increases in IL-6 observed after exercise function as a physiological defense mechanism that protects the body against chronic low-grade inflammation. This myokine release contributes significantly to the systemic anti-inflammatory effects of exercise[19–21].

In neurodegenerative diseases such as MS, IL-6 can exhibit both protective and degenerative properties. In the CNS, IL-6 plays a role in processes such as signal transduction, neuronal protection, differentiation, growth, and survival[22]. However, in MS pathology, IL-6 triggers an increase in proinflammatory cytokines in the blood and cerebrospinal fluid (CSF), promoting the migration of immune cells to the CNS and the activation of the neuroinflammatory cascade. This process accelerates demyelination and axonal damage in the CNS[23,24]. Additionally, IL-6 induces gray and white matter degeneration by acting on astrocytes and glial cells[25]. The importance of IL-6 as a biomarker of relapses in MS has also been emphasized[26].

Several studies have reported higher IL-6 levels in the CSF, serum, or plasma of MS patients compared to healthy individuals[27–30]. Furthermore, it has been observed that CSF and serum IL-6 levels increase with increasing disease duration in MS patients, but this increase was not statistically significant[31]. Studies on the experimental autoimmune encephalitis (EAE) mouse model of MS have shown elevated IL-6 levels[32]. However, it has been reported that IL-6-deficient mice are resistant to the disease, and blockade of IL-6 suppresses disease development[23,33]. However, there are also studies showing that there is no significant difference in CSF and serum IL-6 levels between MS patients and healthy controls[34,35].

Exercise training[19] and muscle-derived IL-6[20] are known to have anti-inflammatory effects. Muscle-derived IL-6 reduces the activity of T1 cells by suppressing proinflammatory cytokines such as TNF-α, while increasing the production of anti-inflammatory cytokines such as IL-10 and IL-4[24]. Several studies have shown that plasma IL-6 levels increase during exercise[36–40]. Exercise can increase basal plasma IL-6 concentrations by up to 100-fold, and this elevation reaches its highest level shortly after or after exercise. The magnitude of the increase in IL-6 levels varies depending on the type, intensity and duration of exercise[41].

Most studies have shown that long term exercise either reduces IL-6 levels in MS patients[42–44] or does not change them[45–48]. An eight-week combined endurance, resistance, and balance exercise program has been reported to increase IL-10 levels and reduce IL-6 and CRP levels in MS patients and is a safe approach[44]. However, in the acute assessment in the study by Castellano et al., (2008), plasma IL-6 concentration in MS patients increased 30 minutes after exercise, tended to remain elevated 2 hours after exercise, and returned to baseline 3 hours after exercise[42]. Additionally, Florindo (2014) stated that regular physical activity in MS seems to promote increased IL-6 concentration[49].

In summary, a literature review reveals that chronically elevated systemic IL-6 levels in patients with Multiple Sclerosis (MS) exhibit pro-inflammatory effects. In contrast, it is reported that exercise-induced increases in IL-6, particularly those observed post-exercise, play a protective role in MS pathophysiology by supporting the anti-inflammatory response. Furthermore, it has been noted that the decrease in IL-6 following long-term exercise exerts a protective effect by reducing the systemic inflammation seen in MS. However, it should be considered that this physiological validity may vary depending on the exercise protocol applied and the stage of the disease.

Brain-derived neurotrophic factor (BDNF)

Brain-derived neurotrophic factor (BDNF) has been identified as a neurotrophin that plays an important role in neuroregeneration and neuroprotection[50]. BDNF is secreted by microglial and astrocyte cells in the central nervous system. It has also been detected in various tissues outside the CNS, such as the lung, liver, spleen, muscle cells, leukocytes, platelets, endothelial cells, and adipose tissue[51–53]. Circulating BDNF originates from both peripheral and cerebral sources due to the bidirectional permeability of the BBB[54].

BDNF plays numerous critical roles in the CNS. It plays a crucial role in maintaining brain function by participating in synaptic plasticity, neuronal growth, development, differentiation, and synapse formation[52,55]. BDNF supports the survival and maintenance of function of sensory neurons, retinal ganglia, certain cholinergic neurons, spinal motor neurons, and some dopaminergic neurons[56]. Experimental studies have shown that increasing BDNF levels derived from sympathetic neurons by 2-4 fold leads to hypertrophy of preganglionic cell bodies and axons and increases synaptic innervation to sympathetic neurons[57]. Furthermore, decreases in BDNF levels have been reported to negatively affect oligodendrocyte progenitor cells and myelin proteins[58]. BDNF is also known to have anti-inflammatory effects[59]. Overexpression of BDNF has been shown to reduce elevated levels of inflammatory factors TNF-α and IL-6[60].

Many studies have indicated that BDNF levels are significantly lower in the serum[61–64], plasma[65–67] and cerebrospinal fluid[68,69] of MS patients compared to healthy individuals. However, there are also studies reporting higher BDNF levels in MS patients[70]. Yoshimura et al. (2010) observed higher serum BDNF levels in MS patients compared to healthy controls and individuals with other neurological diseases; They also reported that MS patients with higher BDNF levels were younger and had fewer relapses compared to patients with lower BDNF levels[71].

Some studies have reported higher BDNF levels in patients with relapsing MS compared to patients with remission MS or controls[66,72–75]. For example, Oraby et al. (2021) reported that BDNF was significantly higher in relapsed patients than in remission patients, while no statistically significant difference was found between relapsed patients and controls or between remission patients and controls[74].

A study in animal models reported that mice deficient in BDNF in immune cells exhibited a weakened immune response in the acute phase of Experimental autoimmune encephalomyelitis (EAE) and developed progressive disability with increased axon loss in the chronic phase of the disease[76]. Similarly, Lee et al. (2012) demonstrated that clinical symptoms and structural damage increased when BDNF was deficient in the initial phase of clinical EAE[77]. Makar et al. (2009) reported that BDNF treatment delivered to the CNS significantly delayed the onset of EAE, reduced overall clinical severity, reduced demyelination, and increased remyelination. Moreover, this treatment inhibited the expression of proinflammatory cytokines TNF-α and IFN-γ in CNS tissues, while increasing the expression of anti-inflammatory cytokines IL-4, IL-10 and IL-11[78].

Various studies have shown that physical exercise increases serum, plasma, or CSF BDNF levels in healthy and various diseases individuals[79–83]. Uysal et al. (2015) reported that exercise promotes an increase in BDNF in the prefrontal cortex[84]. A large body of literature indicates that exercise increases BDNF levels in MS patients[45,46,85–90]. Gold et al. (2003) reported that BDNF levels were similar in MS patients and healthy individuals, and that exercise increased BDNF levels to similar extents in both groups[91]. Ozkul et al. (2018) reported that pre-exercise BDNF levels were similar between the two groups, but exercise increased BDNF levels only in the MS group[92]. However, there are also studies showing that exercise does not alter BDNF levels in MS patients[27,93,94].

In summary, although studies suggesting the opposite are rare in the literature, BDNF levels are often found to be lower in MS patients compared to healthy individuals, and exercise increases BDNF levels in these patients. Through its anti-inflammatory and neuroprotective properties, BDNF stands out as an important biomarker for MS. Therefore, exercise may play a critical role in increasing BDNF levels in MS patients.

Irisin

In 2012, Pontus Boström and colleagues discovered a new exercise-induced myokine and named it "irisin" after the Greek messenger goddess Iris, due to its ability to transmit signals from muscles to other tissues[95]. Subsequent research revealed that the irisin molecule functions as both an adipokine and a potential neurokine[96]. Furthermore, irisin expression has been shown to occur in skeletal muscle cells, cardiomyocytes, and Purkinje cells in the cerebellum [97].

Studies show that the irisin molecule in the CNS supports synaptic plasticity, improves learning and memory processes, reduces neuroinflammation, and prevents cognitive decline[98–101]. Furthermore, irisin contributes to the neurogenesis process and supports neuronal cell survival[102]. Exercise induces muscle contraction, stimulating Irisin secretion from skeletal muscle. This situation suggests that exercise-induced irisin may play an indirect role in neuroplasticity and anti-inflammatory processes.

Irisin contributes to BDNF transcription, and BDNF deficiency or reduction plays an important role in neurodegenerative processes. Both irisin and BDNF levels in human serum have been shown to increase with physical exercise, making exercise and irisin potentially important in preventing degenerative brain diseases[103]. Physical exercise has been reported to support hippocampal cell proliferation, neuronal differentiation, and cell survival by increasing irisin levels in the hippocampus[104]. Altaş et al. (2022) reported that irisin levels are low in patients with Relapsing-Remitting MS, and this may contribute to inflammation, oxidative stress, and apoptosis, triggering demyelination, axonal damage, neuronal loss, and gliosis[96].

In a study conducted on patients with progressive MS, Briken et al. (2013) demonstrated that 9 weeks of endurance exercise improved various cognitive functions and that exercise may have positive effects on brain functions and neuroplasticity in MS[105]. However, in their subsequent study, they stated that although acute endurance exercise increased BDNF levels, there was no change in baseline irisin and BDNF levels after 22 sessions of exercise training[86]. Bilek et al. (2022) observed that irisin serum levels increased significantly in a study group of patients with Relapsing-Remitting MS who underwent aerobic exercise and Frenkel coordination exercise for 6 weeks, while there was no change in these levels in the control group who received only coordination exercise. Furthermore, significant improvements were noted in depression, cognitive performance, and fatigue in the study group[103].

In summary, while irisin, a relatively newly identified myokine, has not yet been studied as frequently as other myokines in MS, it has attracted attention for its anti-inflammatory and neuroprotective effects. Studies in the literature indicate that irisin levels are low in MS patients and increase with exercise. Therefore, exercise may play an important role by supporting irisin levels in these patients.

Tumor Necrosis Factor-Alpha (TNF-α)

Tumor Necrosis Factor-Alpha has a versatile signaling mechanism that can cause cell death through apoptosis or necrosis, or conversely, promote cell survival or inflammation[106]. In the CNS, TNF-α plays a role in regulating homeostatic processes such as neurogenesis, myelination, BBB permeability, and synaptic plasticity under normal conditions. However, in pathological conditions, it can trigger neuronal excitotoxicity, demyelination, apoptosis, and neurological damage[107,108]. Although monocytes and macrophage-lineage cells are the primary sources of TNF-α, T lymphocytes, neutrophils, mast cells, and endothelial cells also contribute to TNF-α production under various conditions[109,110]. The effects of TNF-α are mediated through the two main TNF receptors in the CNS, TNFR1 and TNFR2. TNFR1 generally exerts neurotoxic effects by triggering demyelination and apoptosis, while TNFR2 provides neuroprotection by promoting remyelination and neuroprotection[111,112]. Neuroprotection is thought to be mediated through activation of the p75 receptor pathway, which promotes cell growth and proliferation[113].

T lymphocytes and macrophages in newly formed plaques in the CNS of MS patients increase inflammation by secreting tumor necrosis factor-α (TNF-α), which plays a key role in inflammatory processes. In MS patients, TNF-α causes oligodendrocyte apoptosis, damages myelin sheaths, and accelerates demyelination[114,115].

TNF-α is generally undetectable in healthy individuals; however, serum and tissue levels increase significantly under inflammatory and infectious conditions[116]. Many studies have reported elevated TNF-α levels in the serum, mRNA, CSF, and active lesion sites of MS patients[115,117–124]. In particular, there are studies reporting that CSF TNF-α levels are associated with disease severity and progression[115]. Serum TNF-α levels are higher in patients with relapsing MS compared to patients with MS in remission[125]. However, some studies reported that TNF-α levels were unchanged or showed no significant difference in MS patients[126–128]. Studies on EAE, an experimental mouse model of MS, have found elevated TNF-α production, consistent with human studies[129]. Studies in TNF-α-deficient mice have shown a significantly delayed disease onset, and TNF-α deficiency, once demyelination has occurred, leads to a significant delay in remyelination[130,131]. Therefore, it appears that TNF-α accelerates the acute demyelinating process, but its presence in the CNS is also necessary for remyelination to occur[113]. The effects of various exercises on TNF-α levels in MS patients have been investigated. In the vast majority of studies, TNF-α levels remained unchanged[45,47,48,90,132–135] or decreased[87,136–139]. Castellano et al. (2008) showed that resting plasma TNF-α levels were higher in MS patients compared to controls, and increased in MS patients after 8 weeks of exercise, while remaining unchanged in controls[42].

In summary, TNF-α, like IL-6, is a myokine that can exhibit opposing effects. It can exert both neuroprotective and neurodegenerative and inflammatory effects through various receptors. Despite findings to the contrary in the literature, most studies have shown that TNF-α levels increase in MS patients, while levels decrease or remain unchanged with exercise. While the findings do not constitute a consensus, it is believed that exercise can provide significant benefits for these patients when tailored programs are developed, taking into account variables such as the type, intensity, and duration of exercise, as well as the stage of the disease. Figure 1 summarizes "how myokines change in MS compared to healthy individuals and the effect of exercise on these myokines in MS" as described in the subheadings IL-6, BDNF, IRISIN, and TNF-α. The literature studies mentioned in this review are summarized in Table 1.

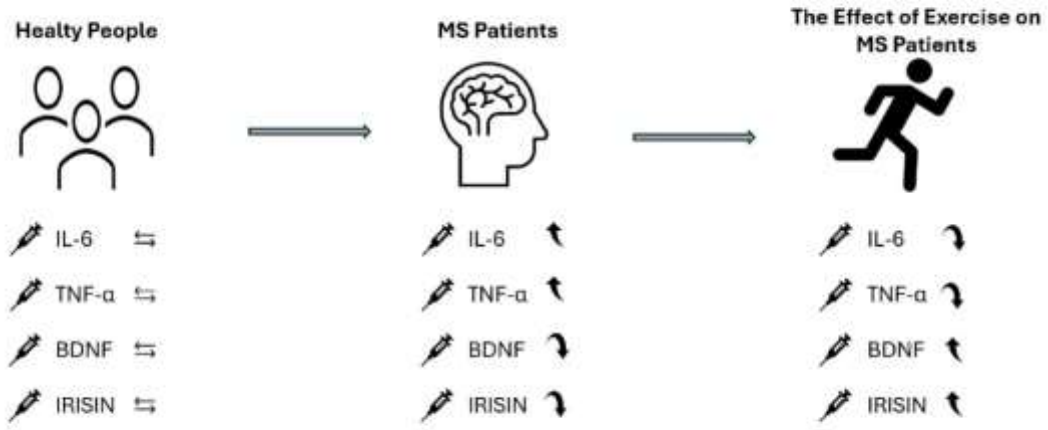

Figure 1. Changes in Myokine Levels in Multiple Sclerosis and the Effects of Long-term Exercise ⇆: normal range, ↴:decrease, ↾:increase, BDNF: Brain-derived neurotrophic factor, IL-6:Interleukin 6, MS: Multiple sclerosis, TNF- α: Tumor necrosis factor.

Table 1. Summary of Controlled Studies Examining the Effects of Long-term Exercise on Myokine Levels in Individuals with Multiple Sclerosis

Research	Participants	Recruitment Criteria	Exercise Type	Exercise	Main Outcome	Conclusion
Castellano, V.[42]	Patient group: 11 Control group: 11	P: RRMS EDSS (0-5,5) C: matched healthy individuals	Aerobic	8-week cycle ergometer three times per week for 30 min at 60% peak O2 uptake	P: IL-6 ↓ TNF- α ↑ C: IL-6 ↓ TNF- α ↔	Individuals with MS may respond to physical stress similarly to matched healthy controls.
Faramarzi, M [43]	Exercise group: 43 Low disability:22 Moderate disability:13 High disability: 8 Control group: 46 Low disability:23 Moderate disability:13 High disability: 10	For all group -RRMS -women -18-50 EDSS (0-4): Low disability EDSS (4,5-6): Moderate disability EDSS (6,5-8): High disability	Combined exercise (stretching, balance, pilates, resistance and endurance exercises)	12-week combined exercise, three times per week.	IL-6 ↓	Combined exercise training intervention improved inflammatory mediators (decreased IL-6) independent of disability status. There is a clear correlation between some inflammatory mediators change with increasing walking ability and strength.
Tadayon Zadeh, F. [44]	Exercise group:15 Control group: 15	For all group: -women -25-40 years EDSS<6	Combined endurance, resistance, and balance exercise	8- week at a frequency of 3 sessions per week.	Exercise group: IL-6 ↓ Control group: IL-6 ↔	8-weeks exercise training is safe in MS patients. Decreased levels of IL-6 in patients with MS following the 8-week combined endurance, resistance, and balance exercise training program.
Bansi, J. [45]	ELG:28 EWG:24	For all group: Being diagnosed with MS EDSS=1-6	Endurance training	3 week, cycling at 50–60 rounds per minutes (rpm) at the lactate threshold (equal to 70% of HRmax or 60% VO2max).	ELG: -BDNF ↔ -TNF-α ↔ -IL6 ↔ -sIL-6r ↔ EWG: -BDNF ↑ -TNF-α ↔ -IL6 ↔ -sIL-6r ↔	Longterm effects only in EWG with significantly higher BDNF serum levels, indicating that training produced an adaption of the immune system.
Schulz, K.[46]	Training group: 15 Control group:13	For all group: Being diagnosed with MS EDSS<6	Aerobic	8 weeks, twice a week for 30 min at a maximal intensity of 75% of the maximal watts taken from the ergometry results.	IL-6 ↔ BDNF ↔	Some indication that some biological parameters such as sIL-6R and neurotrophines may be affected by such training interventions
Deckx, N [48]	Exercise intervention group: 29	-Aged >18 years -EDSS<6	Combined exercise training	12 weeks (5 sessions per 2 weeks)	IL-6 ↔ TNF- α ↔	Overall, the 12-week exercise programme reduced the secretion

	Sedentary control group 16					of inflammatory mediators and promoted immunoregulatory function, suggesting a positive effect of exercise on the underlying immunopathogenesis of MS.
Banitalebi, E. [85]	Exercise group: 43 Low disability:22 Moderate disability:13 High disability: 8 Control group: 46 Low disability:23 Moderate disability:13 High disability: 10	For all group -RRMS -women -18-50 EDSS (0-4): Low disability EDSS(4,5-6): Moderate disability EDSS(6,5-8): High disability	Combined exercise (stretching and PNF, balance, pilates, resistance and endurance exercises)	12 weeks, 3sessions/week	BDNF ↑	Overall, the current trial demonstrated that 12 weeks, 3 session per week, of combined exercise training can stimulate neurotrophics production and secretion include BDNF in women with MS.
Mokhtarzade, M[90]	Normal weight participants Exercise group: 17 Control group: 14 Overweight Exercise group: 17 Control group: 13	EDSS ≤ 4, age > 22 year	Upper- and lower-body interval-training	8 weeks (three sessions per week)	BDNF ↑ TNF- α ↔	8 weeks of exercise training can stimulate BDNF production and secretion in normal weight multiple sclerosis subjects.
Ozkul, Ç. [92]	MS-Excersie: 18 MS-Control:18 Healthy Control: 18	18–60 years old EDSS<5	MS-EX: combined exercise training MS-C: relaxation exercise	3 times per week for 8 weeks (in total 24 sessions)	BDNF ↑	Combined exercise training improved BDNF, and physical performance in patients with MS
Abbaspoor, E. [93]	Combined functional training group: 8 Control group: 8	-RRMS -EDSS<5	Combined functional training	8 weeks (3 days per week)	BDNF ↔	The CFT had not been significant effects on BDNF levels.
Jørgensen, M. [94]	Training group: 16 Control group: 14	-Age: 18–60 -MS diagnosis -EDSS: 2.5–5.5 (pyramidal subscore ≥2) -ongoing interferon treatment	Progressive high intensity resistance training	2 times per week for 24 weeks	BDNF ↔	24 weeks of progressive high-intense RT did not affect acute or chronic circulating levels of BDNF, whereas neuromuscular activity and muscle strength increased.
Briken, S. [86]	Intervention group: 32 Control group: 10	Progressive MS EDSS: 4–6	Endurance exercise training	9 weeks (2-3 days per week)	Irisin ↔ BDNF ↔ IL-6 ↔	Long-term effects of exercise programmes on biological parameters (Irisin, BDNF, IL-6) are not pronounced.

Bilek, F [103]	Study group: 16 Control group: 16	RRMS Age: 19–65 EDSS: 1–5,5	Combined exercise training	Three sessions per week for 6 weeks	Irisin ↑	The aerobic exercise revealed significant changes in depression, fatigue and irisin serum levels in MS patients.
Kjølhede, T [134]	Training group: 16 Control group: 16	RRMS Age: 18–60 EDSS: 2–5,5 (pyramidal functions" subscore ≥ 2 and receiving IFN-β 1a or 1b)	Resistance training	24 weeks (2 days per week)	TNF- α ↔	Little acute and chronic effect of PRT on cytokine levels in IFN-treated PwMS.
Heesen, C [135]	MS naive:13 MS training:15 Control group: 20	-EDSS<5	Aerobic exercise	8 weeks (2 days per week)	TNF- α ↔	Endocrine and proinflammatory immune responses to physical exercise are not significantly altered in MS.
Alvarenga-Filho, H [136]	MS trained:8 MS untrained:10 Control:10	-RRMS -EDSS≤2	Combined exercise training	12 weeks (2 h per week).	IL-6 ↔ TNF- α ↔	Physical activity has beneficial effects on management of fatigue in MS patients, and it could be related, at least in part, to its ability in regulating neuroimmune parameters into T cell compartment.
Mokhtarzade, M. [138]	Training group: 22 Control group: 18	-RRMS EDSS<3 Age = 20–40 years	Upperlimb and lower-limb aerobic interval training	8 weeks (24 sessions, 3 days per week)	TNF- α ↓	Aerobic interval training is lowering the levels of TNF-α as pro-inflammatory factors and increasing adiponectin.
Rezaee, S [139]	Training group: 10 Control group: 10	RRMS -EDSS 0-4	Aerobic exercise	Approximately 60% of VO_2 max in 30-min sessions 3 times a week for six weeks.	TNF- α ↓	While a single bout of exercise reduces the amount of TNF-α in MS patients, the baseline TNF- α level also decreases after six weeks of training

↑: increase , ↓: decrease, ↔: no difference, BDNF: Brain-derived neurotrophic factor, EDSS: expanded disability status scale, IFN-γ: Interferon gamma, IL-6: Interleukin 6, RRMS: Relapsing remitting multiple sclerosis, sIL-6R: soluble form of the IL-6R, TNF-α: Tumor necrosis factor.

Limitations and Future Research

The focus of this study has been to generally evaluate how myokines change in MS and how exercise affects them. Due to the lack of a sufficient number of studies in the literature, differences in results across MS subtypes could not be separately evaluated and synthesized. Similarly, the results obtained in exercise studies could not be disaggregated by exercise type, intensity, and duration. This heterogeneity in the literature makes it difficult to directly translate the findings to clinical practice. In addition, the extent to which exercise-induced peripheral BDNF and Irisin crosses into the CSF and influences the CNS remains unclear, thereby constituting a limitation in the interpretation of the findings. Therefore, more randomized controlled trials, standardized exercise protocols, and research specific to MS subtypes are needed in the future.

Conclusion

Exercise stands out as an important complementary strategy in MS management. This review examines the effects of exercise on the biomarkers IL-6, BDNF, irisin, and TNF-α, demonstrating its potential to regulate inflammation and support neuroprotective mechanisms. Current findings suggest that biomarkers such as BDNF and irisin, which play a crucial role in MS due to their anti-inflammatory and neuroprotective effects, but are typically low, can increase with exercise. However, uncertainty regarding the effects of peripheral BDNF and Irisin on the CNS should be considered when interpreting the results. Biomarkers such as IL-6 and TNF-α, which are undesirable in MS due to their pro-inflammatory, neurodegenerative, and demyelinating effects and are often elevated, may decrease with exercise. Thus, exercise has been shown to potentially slow disease progression and have beneficial effects on disease-related symptoms. However, it should be noted that the effects of exercise may vary depending on the stage, duration, and severity of the disease. Therefore, further clinical research and studies on individualized exercise protocols are needed.

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