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Investigation of the effect of six weeks of swimming on the caspase-1, TGF-β1, and IFN- γ protein content in the hippocampal tissue of rats with multiple sclerosis

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Abstract

Background: Performing exercise training with various protocols, especially aquatic exercises, can be effective against the harmful effects of Multiple Sclerosis. Therefore, the present study aimed to investigate the effect of six weeks of swimming training on the Caspase-1, TGF-β1, and IFN-γ protein content in the hippocampal tissue of rats with Multiple Sclerosis.

Methods: Twenty-one Wistar rats were divided into three equal groups: (1) Healthy control, (2) Multiple Sclerosis control, and (3) Multiple Sclerosis swimming. After two weeks of adaptation to the laboratory environment, the Multiple Sclerosis groups were induced by adding cuprizone to their diet. Six weeks of swimming training were then performed. Forty-eight hours after the last session, hippocampal tissue was isolated to examine Caspase-1, TGF-β1, and IFN-γ protein content. To analyze the data, one-way analysis of variance was used with a significance level of 0.05.

Results: Findings showed that the induction of Multiple Sclerosis in rats caused a significant increase in TGF-β1 and Caspase-1 protein content (P-Value=0.001) and a significant decrease in IFN-γ (P-Value =0.001). After six weeks of swimming, there was a significant decrease in Caspase-1 (P-Value =0.001) and a significant increase in IFN-γ (P-Value =0.001) protein content; however, there was no significant decrease in TGF-β1 protein content (P-Value =0.1).

Conclusion: Based on the findings of this study, it can be concluded that swimming, as a non-pharmacological intervention, has a protective effect on nerves by reducing factors related to inflammation and cell death, which may have beneficial effects on memory information processing in Multiple Sclerosis disease.

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Keywords

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Hippocampus
Multiple sclerosis

Highlights

What is current knowledge?

- Studies have shown a significant relationship between severe clinical symptoms of the disease and inflammation.
- According to the literature, there is apparently no study that has examined the effect of swimming on the Caspase-1, TGF-β1, and IFN-γ protein content in the hippocampal tissue of MS patients.

What is new here?

- Exercise has been shown to enhance organization and connectivity in neural networks, which can have beneficial effects on memory information processing.
- Apparently, six weeks of swimming caused an increase in IFN-γ and a decrease in Caspase-1 protein content in the hippocampal tissue of rats.
- Inflammation in response to swimming could possibly be related to an increase in structural proteins and the myelin sheath radius in hippocampal tissue.

Introduction

Multiple Sclerosis (MS) is a chronic neurological disorder that causes the loss or damage of the myelin sheath in various parts of the central nervous system (1). This disease is pathologically characterized by demyelination and inflammation (2). Episodic memory loss, caused by hippocampal and thalamic atrophy, is one of the most common cognitive symptoms in patients with MS (3). At least some of the clinical manifestations of MS, including depression and memory loss, are linked to hippocampal involvement. Advances in magnetic resonance imaging technology have made it possible to evaluate hippocampal involvement in vivo in new ways, and pathological studies have revealed widespread demyelination, neuronal destruction, and synaptic abnormalities in the hippocampus of people with MS (4). It is widely acknowledged that hippocampus-related clinical symptoms result from both focal hippocampal injury and the hippocampus's disconnection from many brain networks (5).

There is evidence that various hippocampal subfields are anatomically and functionally specialized, leading to regional differences in the degree of damage and repair (6). Several studies have shown a significant relationship between the severe clinical symptoms of this disease and inflammation (7). In particular, the demyelinating inflammatory process that occurs during MS, as well as systemic inflammatory stimuli, can lead to abnormal production of inflammatory mediators at synaptic sites, and consequently to disruption of synaptic homeostasis (5). Among the markers involved in inflammation, Caspase-1, TGF-β1, and IFN-γ have attracted attention. Caspase-1, a key indicator of inflammation, initiates inflammatory processes and is associated with the induction of apoptosis (8). TGF-β1 causes cerebrovascular dysfunction and neuroinflammation (9). Clinical studies have reported an increase in blood levels of TGF-β1 in MS patients with both relapsing and progressive forms of the disease, but the role of this cytokine remains unclear (9). Another important protein in the inflammatory process is IFN-γ, which exhibits antiproliferative, immunoregulatory, and proinflammatory activity, thereby playing a role in defense and inflammatory mechanisms (10). IFN-γ has both inflammatory and aggravating effects in MS, and compelling evidence suggests that it has dual effects in autoimmune diseases (11).

Given the role of different exercise protocols in reducing MS symptoms and improving patients' conditions, there is much debate about prescribing appropriate exercise programs for these patients. Aerobic exercise represents a cost-effective, widely available, natural,

and self-administered treatment with no adverse side effects that may serve as an effective intervention for improving memory in MS patients. Aquatic exercise is particularly beneficial for patients who have difficulty bearing weight on land, as floating in water reduces the forces required for movement and prevents joint stress (12). Swimming has been shown to improve memory function by inhibiting signaling pathways that lead to cell death in MS models (13). According to the literature, there is apparently no study that has examined the effect of swimming on the Caspase-1, TGF-β1, and IFN-γ protein content in the hippocampal tissue of MS patients. Therefore, the aim of the present study was to investigate the effect of six weeks of swimming on the Caspase-1, TGF-β1, and IFN-γ protein content in the hippocampal tissue of rats with MS.

Methods

The present study was an experimental and applied investigation conducted in a laboratory setting using a post-test design with control groups (Healthy and MS). Accordingly, 21 male Wistar rats (Weight = 225 ± 17 g; age = 12 weeks) were obtained from the animal house of Shahid Chamran University of Ahvaz. The rats were then transferred to the laboratory and kept in transparent polycarbonate cages (Two to three rats per cage) under a 12:12 light-dark cycle at a temperature of 20-23°C, with free access to water and food according to standard animal care protocols. During the adaptation period, active and inactive rats were identified. Inactive rats were placed in the control group, and active rats were selected for MS induction. To induce MS, cuprizone was added to the rat food powder at a weight ratio of 0.5%. After complete mixing with water, the mixture was converted into uniform food pellets. This diet was provided to the rats in the MS groups for six weeks (14). Rats were randomly divided into three groups: healthy control group (HC), MS control group (MC), and MS training group (MT). The intervention period lasted six weeks, during which the rats in the training group underwent swimming sessions. The animals had access to food up to three hours before training, but water was always available.

Method of speed and disease induction

At the end of six weeks, the Rotarod test was used to confirm the induction of MS. All experiments were conducted during the light period of animal activity (Between 9:00 a.m. and 12:00 p.m.). The Rotarod test measures coordination and balance in rodents. Given that cuprizone induces demyelination, oligodendrocyte death, and motor defects, observing motor dysfunction in this test serves as an indicator of successful MS induction, as frequently reported in studies using the cuprizone model (15). The Rotarod device consists of a rotating horizontal rod divided into four separate sections by spherical plates, approximately 20 cm above the ground. The rotation speed was set at 7 rpm (About 10-11 revolutions per minute). To assess balance, rats were placed on the rotating wheel, which increased in speed from 5 rpm to 45 rpm over five minutes, and the time they maintained balance was recorded. Initially, each rat was placed on the rotating bar twice to learn the movement and adapt to the device. Then, each rat underwent three test trials (Five minutes each, with 15-minute intervals). The average time spent on the bar across trials was recorded in seconds (16).

Swimming training protocol

After confirming disease induction, a voluntary swimming training program (Without waves or weights) was carried out for six weeks in a rodent pool (Water temperature = 26-30°C; depth = 50 cm). The MS training group performed one swimming session per day for six weeks. The duration of each session gradually increased from 10 minutes on the first day to 30 minutes by the sixth week (17) (Table 1).

Table 1. Swimming training overload

Weeks	One	Two	Three	Four	Five	Six
Time (Minutes)	10	15	20	25	30	30

Methods of measurement

The protein content of Caspase-1 was measured using the western blot method. Initially, for each 200 mg of tissue, 100 µL of cold lysing buffer was added (Lysis buffer containing: Tris-HCl [0.3 g, 50 mmol/L], Triton X-100 [0.02 g, 0.1%], calcium dioxide sodium [0.05 g, 0.25%], sodium chloride [NaCl, 0.43 g, 150 mmol/L], SDS [0.02 g, 0.1%], and ethylenediamine tetraacetic acid [EDTA, 5.84 g], dissolved in 20 mL of distilled water, pH = 7.4). The hippocampal tissue samples were homogenized using a homogenizer at 25,000 rpm (Speed Mill Plus, Analytikjena, Germany). Next, the samples were centrifuged at 14,000 rpm for 10 minutes, and the supernatant was transferred to new microtubes. One tablet of protease inhibitor was used per 10 mL (10X). The supernatant concentration was analyzed using the Bradford kit. Before electrophoresis, protein samples were mixed 1:1 with 2× loading buffer based on concentrations obtained from the Bradford method and boiled for 5 minutes to linearize the proteins. Samples (30 µg each) were loaded into electrophoresis wells, and an electric current was applied-first at 60 V for 15 minutes, then at 100 V for one hour. In each electrophoresis run, one well was dedicated to a protein marker (Ladder). After protein separation using the SDS-PAGE method (12% polyacrylamide gel), the gel was placed in a transfer buffer for 10-15 minutes. A five-layer sandwich was prepared consisting of two layers of sponge and two layers of Whatman paper on each side, along with one layer of PVDF paper and one layer of gel. All components were soaked in the transfer buffer for 15 minutes before assembly. After ensuring that no bubbles were trapped in the gel, the sandwich was placed in the blotting tank filled with transfer buffer, with the blotting paper on the cathode side and the gel on the anode side. The transfer was carried out at 60 V for 105 minutes. Following transfer, the PVDF paper was rinsed three times with PBS, each for 5 minutes. Blocking was performed using a blocking buffer (Skim milk) overnight at 4°C. After blocking, the PVDF membrane was rinsed three times with PBS (5 minutes each). The membrane was then incubated with primary antibodies-Caspase-1 (Anti-Caspase-1 antibody, ab286125: Abcam) and GAPDH (Anti-GAPDH antibody [G-9]: sc-365062, Santa Cruz)-diluted 1:2000 to 1:5000 in PBS buffer for one hour at room temperature on a shaker at 65 rpm. Blotting was done separately for each protein. After incubation, the membrane was washed three times with PBS (5 minutes each), followed by incubation with secondary antibodies (Mouse anti-rabbit IgG-HRP, sc-2357, Santa Cruz) prepared at a 1:2000 dilution in PBS buffer for one hour. After washing three times with PBS (5 minutes each), two solutions of the ECL kit (Abcam, 133408, USA) were mixed in a 1:1 ratio (250 µL total) and poured onto the PVDF paper using a 1000 sampler. The membrane was soaked for one minute under red light in a dark room. The papers were then dried and placed inside a plastic protective cassette containing a photosensitive film, and the bands were developed using an X-RAY processor (LD-14, China). The photosensitive papers were digitized using a JS 2000 scanner (BonninTech, China), and the density of the bands was measured. The density of each protein band relative to the calibrator protein in the studied groups was compared to that of the control group, and data were analyzed using JS 2000 software.

The ELISA method was used to measure TGF-β1 (Human/Mouse/Rat TGF-β1 One-Step ELISA Kit: One-EK008Mt, Sunlong Medical, Size: 48 or 96 tests) and IFN-γ (IFN-γ High Sensitivity ELISA Kit: HS-EL0014Ra, Sunlong Medical, Size: 96 tests) levels. The ELISA (Enzyme-Linked Immunosorbent Assay) protocol began with preparing all reagents, standards, samples, and the microplate. Standards, assay buffer, and samples were added to the respective wells and incubated at room temperature on a microplate shaker for one hour. After incubation, the plate was washed four times to remove unbound materials. Substrate solution was added and incubated for 10 ± 5 minutes, protected from light. The reaction was stopped by adding stop solution, resulting in a color change to yellow. The optical density was then measured at 450 nm using a microplate reader within 30 minutes, with wavelength adjustments at 570 or 630 nm recommended for precision. To prepare a 5% blocking buffer, 0.5 g of skim milk was mixed with 10 mL of distilled water and shaken until completely dissolved. After the blocking step and following incubation with primary and secondary antibodies, the PVDF membrane was washed three times for 5 minutes each with PBS.

Statistical analysis

The Shapiro-Wilk and Levene's tests were used to confirm the normality and homogeneity of variances, respectively. A one-way analysis of variance (ANOVA) was used to compare the mean protein content of Caspase-1, TGF-β1, and IFN-γ among the different groups after six weeks of intervention. Pairwise comparisons of protein content averages were analyzed using Tukey's post-hoc test. All statistical analyses were performed using SPSS software (Version 19). Statistical significance level was 0.05.

Results

The results of the one-way ANOVA showed a significant difference between groups (P-Value = 0.001, df = 2). The results of Tukey's post-hoc test indicated that the protein content of Caspase-1 increased significantly due to MS induction (P-Value = 0.001), as shown by comparing the MC group with the HC group. Swimming training significantly decreased Caspase-1 protein content (P-Value = 0.001), as shown by comparing the MT group with the MC group (Figure 1).

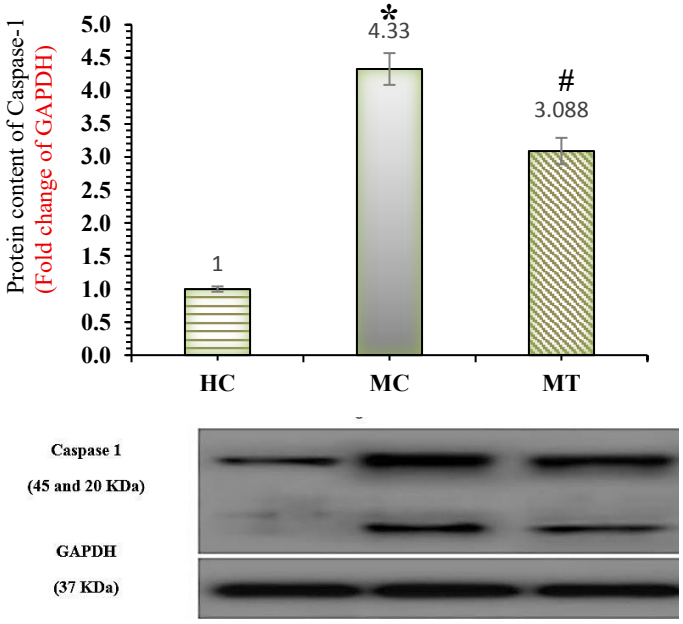

Figure 1. Protein content of Caspase-1 in training and control groups
* Indicates a significant increase in the MC group compared to the HC group. # Indicates a significant decrease in the MT group compared to the MC group. Abbreviations: HC: Healthy Control group; MC: MS Control group; MT: MS Training group

The one-way ANOVA also showed a significant difference between groups (P-Value = 0.001, df = 2). The results of Tukey's post-hoc test indicated that the protein content of TGF-β1 increased significantly due to MS (P-Value = 0.001), as shown by comparing the MC group with the HC group. However, there was no significant decrease between the MC and MT groups (P-Value = 0.1) (Figure 2).

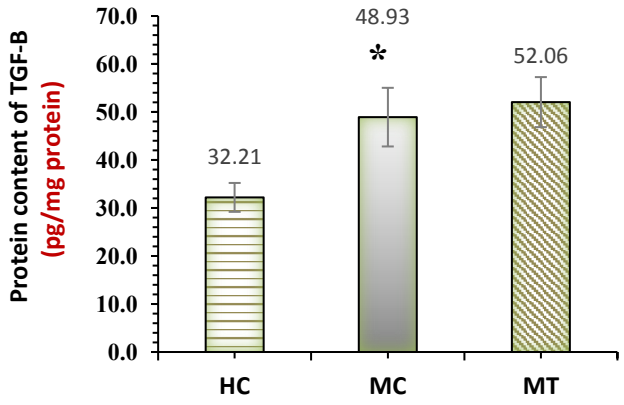

Figure 2. Protein content of TGF-β1 in training and control groups
* Indicates a significant increase in the MC group compared to the HC group. Abbreviations: HC: Healthy Control group; MC: MS Control group; MT: MS Training group

The one-way ANOVA further showed a significant difference between groups (P-Value = 0.001, df = 2). The results of Tukey's post-hoc test indicated that the protein content of IFN-γ decreased significantly due to MS (P-Value = 0.001), as shown by comparing the MC group with the HC group. Swimming training significantly increased IFN-γ protein content (P-Value = 0.001), as shown by comparing the MT group with the MC group (Figure 3).

The results of the Rotarod behavioral test are presented in Figures 4 and 5. Based on the open-field test, both the distance traveled and movement speed in the MC group were significantly reduced compared to the HC group (P-Value = 0.001). However, in the MT group, both parameters significantly increased compared to the MC group (P-Value = 0.001). A summary of the schematic design of the research protocol is depicted in Figure 6.

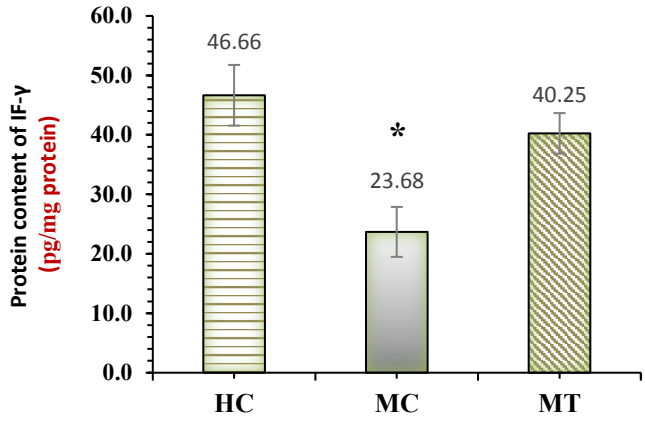

Figure 3. Protein content of IFN-γ in training and control groups
* Indicates a significant decrease in the MC group compared to the HC group. # Indicates a significant increase in the MT group compared to the MC group. Abbreviations: HC: Healthy Control group; MC: MS Control group; MT: MS Training group

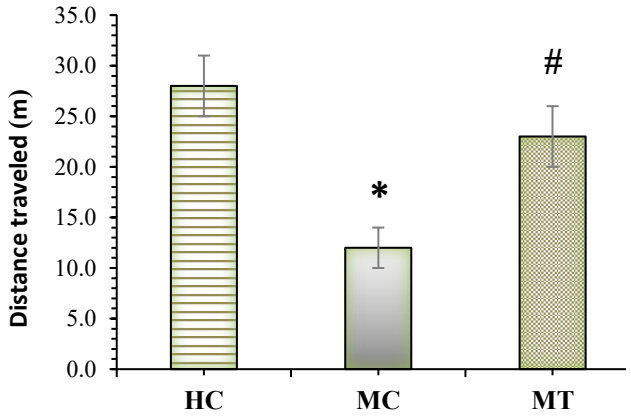

Figure 4. Results of the Rotarod behavioral test (Open-field test: distance traveled)
* Indicates a significant decrease in the MC group compared to the HC group. # Indicates a significant increase in the MT group compared to the MC group. Abbreviations: HC: Healthy Control group; MC: MS Control group; MTL: MS Training group

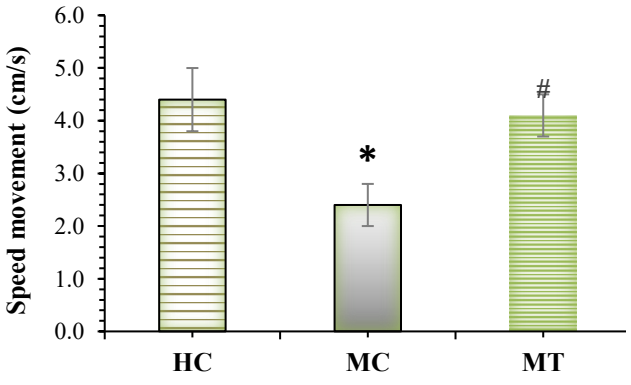

Figure 5. Results of the Rotarod behavioral test (Open-field test: movement speed)
* Indicates a significant decrease in the MC group compared to the HC group. # Indicates a significant increase in the MT group compared to the MC group. Abbreviations: HC: Healthy Control group; MC: MS Control group; MT: MS Training group

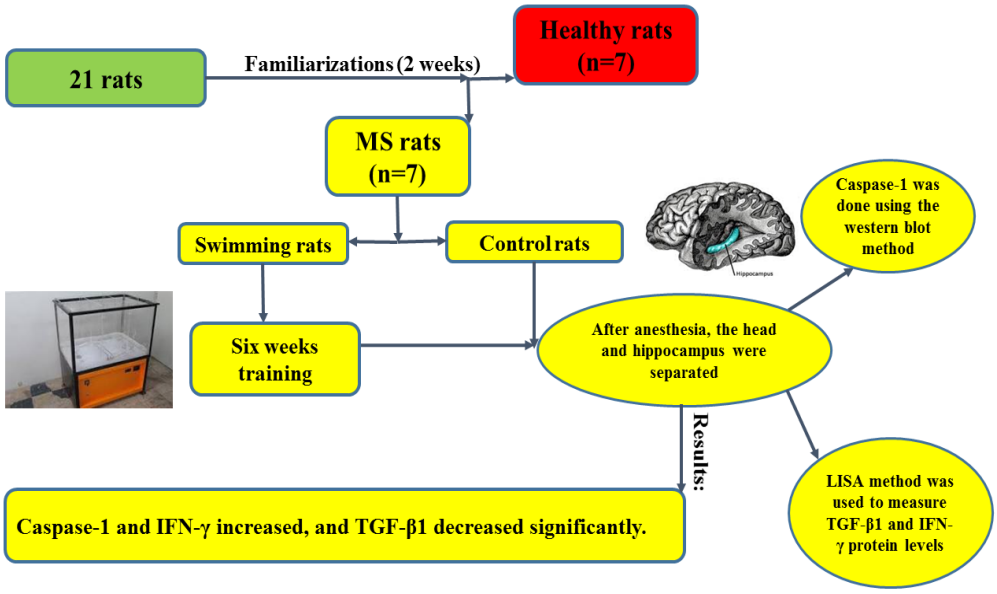

Figure 6. Graphical abstract

Discussion

Recent research has examined the effects of training with different protocols on the outcomes of MS (18,19). The findings of these studies have shown that exercise, particularly aquatic training, can be effective against the harmful effects of MS (19). For example, exercise reduces apoptosis-related factors and can delay cell death. The aim of the present study was to investigate the effect of six weeks of swimming training on Caspase-1, TGF-β1, and IFN-γ protein content in the hippocampal tissue of rats with MS. According to the data obtained in this study, induction of MS in rats caused a significant increase in Caspase-1 and TGF-β1 protein content, and a significant decrease in IFN-γ protein content. However, six weeks of swimming in the MS training group caused a significant decrease in Caspase-1, a significant increase in IFN-γ, and no significant change in TGF-β1 protein content. Caspase-1 is one of the key indicators of inflammation, initiating inflammatory processes. According to the current findings, after MS induction, Caspase-1 protein content in the MS control group increased significantly compared to the healthy control group. This finding aligns with those of Shao et al. (2021) (20), Yu et al. (2018) (21), and Liu et al. (2021) (22). Similarly, Beheshti et al. (2020) (18) reported an increase in serum Caspase-1 levels in humans with relapsing MS. In the present study, swimming training significantly reduced Caspase-1 protein content in the MS swimming group compared to the MS control group. This is consistent with the findings of Hajivand et al. (2024) (19), who showed that swimming reduced Caspase-1 protein content in the hippocampus of healthy rats. In the study by Khakroo et al. (2019) (23), moderate-intensity exercise reduced levels of inflammatory markers, whereas high-intensity exercise had the opposite effect (23). Therefore, variations in exercise intensity likely account for inconsistencies among studies examining the effects of exercise training on inflammatory markers. Most research indicates that moderate-intensity exercise can reduce inflammation (19,23). Caspase-1 stimulates immune cells and accelerates apoptosis by converting inactive forms of IL-18 and IL-1β into their active forms. Exercise appears to prevent these processes by reducing Caspase-1 levels. Although IL-18 and IL-1β levels were not measured in this study, previous research has shown a relationship between these cytokines and Caspase-1 levels (24).

TGF-β1 was another protein measured in this study. Apparently, six weeks of training did not cause significant changes in its protein content, and the mechanism by which exercise affects this protein remains unclear. The findings of this study are inconsistent with those of Habibian et al. (2023) (8), Golbashi et al. (2017) (25). Golbashi et al. (2017) (25) found that exercise reduced TGF-β1 levels in aged and ischemic rats, while Habibian et al. (2023) (8) showed that eight weeks of swimming training reduced cardiac TGF-β1 levels in diabetic rats. In contrast, Xiang et al. (2023) (26) and Li et al. (2016) (27) reported increased TGF-β1 following exercise. Li et al. (2016) investigated factors involved in ventricular hypertrophy and found that exercise increased TGF-β1 levels (27). Possible reasons for the differences between studies include the timing of tissue collection, the severity of MS induction, methodological variations, the type of subjects, and the specific tissues used for measurement. For example, Li et al. (2016) examined healthy rats and cardiac tissue, whereas the present study examined hippocampal tissue in MS-induced rats. Clinical studies have reported elevated blood TGF-β1 levels in both relapsing and progressive MS patients, though its role remains unclear. Evidence suggests that TGF-β1 may play a dual role in MS progression (27). For example, TGF-β1 can induce astrogliosis and defective oligodendrocyte gene expression in MS patients (9). Conversely, it can reduce neuroinflammation and B-lymphocyte activation in MS models (28). Although swimming reduced TGF-β1 levels in the present study, further research is needed to clarify this cytokine's role in MS-related neuroinflammation.

Another protein measured in this study was IFN-γ, which exhibits antiproliferative, immunoregulatory, and proinflammatory activity. Thus, it plays an important role in both defense and inflammatory mechanisms (10) and has a key proinflammatory role in MS (29). In animal models, stable expression of IFN-γ and IL-1β in the hippocampus can activate microglia and astrocytes, leading to severe inflammation, neuronal death, and hippocampal-dependent memory impairment (30). Low levels of IFN-γ influence the adaptive immune response by guiding microglia to act as antigen-presenting cells (31). In the present study, MS significantly decreased IFN-γ protein content, while six weeks of swimming significantly increased it in the hippocampal tissue of diseased and healthy rats. However, the literature shows inconsistent findings regarding IFN-γ responses to exercise. For example, Smith et al. (2012) reported that six months of exercise (Two and a half hours per week, 70 minutes per session) decreased IFN-γ levels in middle-aged adults (32), which contradicts the present study. Another study found that plasma IFN-γ increased 30 minutes after cycling at 80% of maximal oxygen consumption, while Choi et al. (2018) reported that high-intensity interval training had no effect on IFN-γ levels in the spleen tissue of rats (33). These discrepancies may arise from differences in training protocols, exercise intensity, nutritional status, genetic factors, physical condition, psychological state, and laboratory methods. The type of subject (Obese vs. MS-induced rats), sex (Female vs. male), exercise duration, exercise type (Treadmill vs. swimming), and tissue studied (Heart vs. hippocampus) also influence outcomes. An appropriate concentration of IFN-γ in the hippocampus appears to be essential, as it can have both neuroprotective and inflammatory effects (31). Future research is needed to clarify these contradictions. One possible reason for discrepancies is disease condition: during chronic MS, IFN-γ may have protective effects. For instance, one study found that IFN-γ signaling in regional astrocytes induces immunoproteasome expression and enhances CNS protection

during chronic autoimmunity (34). A limitation of this study was the lack of measurement of other MS-related complications, including additional inflammatory and oxidative factors.

Conclusion

Considering the available evidence and the known benefits of exercise, especially swimming, on factors related to inflammation, apoptosis, and neurogenesis, it can be stated that physical activity in the form of aquatic training, possibly due to its anti-inflammatory properties, may have beneficial effects in preventing nerve degeneration during the progression of MS. Therefore, swimming could be considered a promising non-pharmacological strategy for controlling complications associated with MS. Apparently, six weeks of swimming led to an increase in IFN-γ and a decrease in Caspase-1 protein content in the hippocampal tissue of rats. The reduction in inflammation in response to swimming could be related to an increase in structural proteins and the radius of the myelin sheath in hippocampal tissue. It is suggested that future studies investigate the optimal exercise parameters for MS patients and further explore the underlying mechanisms of swimming-induced neuroprotection.

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Ethical statement

The Ethics Committee of Shahid Chamran University of Ahvaz approved this study's protocol (SCU. EC.SS. 403.1106).

Conflicts of interest

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Author contributions

Ali Esmaeili played pivotal roles in data collection, statistical population management, and laboratory coordination. Ali Esmaeili, Abdolhamid Habibi, Mohammad Rami, and Mehrzad Shabani made key contributions to developing the research background; their expertise and insights were crucial to the success of this study.

Data availability statement

All data used in this study are available in the text of the article and do not require separate access.

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