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The Effect of Exercise Volume on Depressive-Related Behaviors and Levels of Brain-Derived Neurotrophic Factor and Serum Testosterone Levels

Farnaz Torabi[1*], Reza Ahmadi[2]

[1] Associated Professor. Department of Physical Education and Sport Sciences, Payame Noor University, Tehran, Iran
[2] MS. Department of Physical Education and Sport Sciences, Payame Noor University, Tehran, Iran

*** Corresponding author email address**: F.torabi@pnu.ac.ir

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ABSTRACT

Objective: The aim of the present study was to investigate the effect of training volume on depression-related behaviors and serum levels of brain-derived neurotrophic factor (BDNF) and testosterone in mice. Male NMRI mice, approximately 80 days old and weighing 20 to 23 grams, were used in this study.
Methods and Materials: They were kept under a 12-hour light/12-hour dark cycle at a temperature of 23±1°C, with adequate food and water provided. The male NMRI mice, approximately 80 days old and weighing 20 to 23 grams, were kept under a 12-hour light/12-hour dark cycle at a temperature of 23±1°C, with adequate food and water provided. From 90 days old to 118 days old, the animals underwent swimming exercise for 4 weeks. They were divided into two groups: long-term training volume and short-term training volume. The short-term swimming group included one session of short-term training, while the long-term group included three sessions of long-term training with 10-minute swimming periods and 15-minute rest intervals between each session. The water depth and swimming duration gradually increased from 5 to 15 centimeters (second to fourth week) and from 20 (second to third week) to 30 (fourth week) minutes per day. The non-exercised animals were placed in a round tank without water for a duration similar to that of the exercised animals.
Results: The results showed a significant difference in immobility duration between the control group and the two training groups, as well as between the two training groups ($P \leq 0.05$). There was also a significant difference in depression levels between the two training groups and between the long-term training group and the control group ($P \leq 0.05$). However, there was no significant difference between the short-term training group and the control group ($P \geq 0.05$). Post hoc test results indicated a significant difference in BDNF levels between the control group and the long-term training group ($P \leq 0.05$). Furthermore, there was a significant difference in testosterone levels between the control group and both the short-term and long-term training groups ($P \leq 0.05$), but no difference between the two training groups ($P \geq 0.05$).
Conclusion: Based on the overall results of the study, different training volumes have varying effects on depression and BDNF levels, with long-term training producing greater effects.

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1. Introduction

In recent years, depression has increased as the second most common disabling disease globally. One of the examined methods to improve the condition of patients with depression is exercise and physical activity (1, 2). Physical activity improves depression symptoms through the involvement of growth factors such as BDNF (3), insulin-like growth factor 1 (Won), and vascular endothelial growth factor (4), as well as by increasing testosterone levels. Meanwhile, among various exercises, aerobic exercises such as swimming, cycling, and hiking have a more significant effect on mood and depression treatment (5, 6). In contrast, the effect of anaerobic exercises like bodybuilding in this regard is minimal (Krog, 2009). However, it is believed that swimming is one of the most influential physical activities for improving depression symptoms (7, 8). Kaya and colleagues (2020) found in a study titled "The Effect of Swimming Exercise on Hopelessness and Depression Levels in Older Adults" that a 12-week swimming protocol had a very positive and significant impact on reducing depression symptoms (7). Park et al. (2020) also found that swimming improves mood and memory disorders in socially isolated mice during adolescence by increasing neurogenesis, serotonin expression, and inhibiting apoptosis (8).

Testosterone is one of the hormones affected by depression and mood states. Chen et al. (2020) found in their studies that testosterone levels in individuals with depression are lower than in normal individuals (9). Meanwhile, many studies support that physical activity increases testosterone levels in the body (10). Chen et al. (2020) showed in a study titled "The Relationship of Testosterone with Depression Symptoms in Adult Men" that the average levels of testosterone, sex hormone-binding globulin, and luteinizing hormone in the depressive symptom group were significantly higher than in the non-depressed group. The average levels of free serum testosterone and the free testosterone index in the depressive symptom group were significantly lower than in the non-depressed group. Furthermore, the average free testosterone had a negative relationship with the Beck Depression Inventory scale score in a multiple linear regression model. There is no consensus on the amount and intensity of exercise duration (11, 12).

Exercise is increasingly recognized as a cost-effective and accessible intervention that can complement traditional pharmacological and psychological therapies (13). Various forms of exercise, including aerobic and anaerobic activities, have been shown to alleviate symptoms of depression by modulating neurobiological pathways and improving physical health. Aerobic exercises, in particular, have been associated with enhanced mood and reduced depressive symptoms through the release of endorphins and other neurochemicals that promote feelings of well-being (14). The benefits of exercise are not limited to mood improvement but also include enhanced cognitive function, reduced anxiety, and better overall physical health (6).

Furthermore, the neurobiological mechanisms underlying the antidepressant effects of exercise have garnered significant attention. Studies have demonstrated that exercise induces neuroplastic changes in the brain, including increased neurogenesis, synaptogenesis, and the expression of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) (3, 12). BDNF plays a crucial role in supporting the survival, growth, and maintenance of neurons and is implicated in the pathophysiology of depression (11). Elevated levels of BDNF following exercise have been linked to improvements in mood and cognitive function, suggesting a potential therapeutic mechanism (6). Additionally, exercise has been shown to influence hormonal levels, such as testosterone, which can affect mood and behavior (5). Understanding these underlying mechanisms is essential for developing targeted exercise interventions that can effectively mitigate depressive symptoms and improve mental health outcomes. Therefore, in this study, we aim to investigate the effect of swimming exercise volume on depression-related behaviors and levels of brain-derived neurotrophic factor (BDNF) and serum testosterone in mice, and hence, we seek to answer the question of whether exercise volume affects depression-related behaviors and levels of BDNF and serum testosterone in mice.

2. Methods and Materials

2.1 Study Design and Participants

From 90 days old to 118 days old, the animals underwent swimming exercise for 4 weeks (28 days). Exercise was performed 5 days a week as follows. The animals were placed in a round tank (diameter: 80 cm; height: 30 cm) filled with water (temperature: 32 ± 1°C). To prevent the animals from floating, a wave maker motor was placed at different angles of the tank. In this method, there are two stages (adaptation stage and swimming exercise stage). In the adaptation period, to reduce water-induced stress, the animals were placed in shallow water (5 cm) for 20 minutes for the first 3 days of the first week to adapt to the procedure. The swimming stage included one (low volume) or three sessions (high volume) of 10-minute swimming exercises with a 15-minute rest interval between each session. The water depth and swimming duration gradually increased from 5 to 15 cm (second to fourth week) and from 20 (second to third week) to 30 (fourth week) minutes per day. Non-exercised animals were placed in a round tank without water for a duration similar to that of the exercised animals.

2.2 Measurements

2.2.1 Depression

On the first day after completing the exercise, the sucrose consumption level was examined. This test was conducted over 12 hours. Two bottles, one with 2% sucrose and the other with plain water, were placed in the test group's cage. The amount of water consumed from each bottle was immediately calculated after the test. Reluctance to consume the sucrose bottle was determined as a depressive behavior.

2.2.2 Suspension

Pregnant mice on day 18 of pregnancy and other mice on day 7 postpartum were examined. Each mouse was individually suspended by the tail using a clip, 2 cm from the end, in a gray wooden compartment (20 × 30 × 40 cm). The immobility duration within 4 minutes was recorded as a depression indicator.

2.2.3 Serum and Brain Isolation and Factors

After completing the behavioral tests, the mice were deeply anesthetized with ketamine (50 mg/kg) and xylazine (5 mg/kg). Blood was then collected from the heart, and perfusion with cold saline was performed to remove blood from the brain, followed by euthanasia and brain extraction. To separate serum from blood, the blood was placed on a cold surface for 15 minutes, then centrifuged at 3000 rpm for 10 minutes. The serum was collected into sterile microtubes and stored at -70°C for testosterone measurement. The brain was immediately stored in liquid nitrogen after extraction. Testosterone and brain-derived neurotrophic factor were measured using ELISA kits from Abcam.

2.3 Data Analysis

All data were expressed as mean ± standard deviation (SD). Initially, the Shapiro-Wilk test was used to determine normal distribution, and the Levene test was used to assess variance equality. Next, one-way analysis of variance (ANOVA) and Tukey's post hoc test were used to test the research hypotheses. A significance level of $P < 0.05$ was considered for all calculations, and all computations were performed using SPSS 21 software.

3. Findings and Results

The variables of the subjects (mean ± standard deviation) in the three research groups (control, short-term exercise, and long-term exercise) and in two conditions (pre-test and post-test) are presented in Table 1.

Table 1. Variables of Subjects (Mean ± Standard Deviation) in Research Groups

Variables	Groups	Mean ± SD
Tail Suspension Test (TST)	Control	149.80 ± 18.89
	Short-term Exercise	131.50 ± 12.22
	Long-term Exercise	111.80 ± 12.399
Sucrose Preference Test (SPT)	Control	66.20 ± 11.32
	Short-term Exercise	74.10 ± 12.32
	Long-term Exercise	75.67 ± 13.87
Brain-derived Neurotrophic Factor (BDNF) (pg/ml)	Control	40.00 ± 12.25
	Short-term Exercise	46.80 ± 13.61
	Long-term Exercise	58.20 ± 15.18
Testosterone (ng/dl)	Control	672.70 ± 111.54
	Short-term Exercise	858.80 ± 112.09
	Long-term Exercise	902.70 ± 133.81

The data related to all variables in the research groups had a normal distribution; therefore, parametric tests can be used. Levene's test results also confirmed the homogeneity of variances for all four conditions of the two variables TST, SPT, and BDNF ($P \geq 0.05$).

To test the present hypothesis, given the normal distribution of the data, an analysis of variance (ANOVA) test was used, and the results are summarized in the following table.

Table 2. Results of Analysis of Variance (ANOVA) for Comparison of Indices in Control and Experimental Groups

Indices	Conditions	Sum of Squares	df	Mean Square	F	Sig
TST	Between Groups	7223.267	2	3611.633	16.412	.001
	Within Groups	5941.700	27	220.063		
	Total	13164.967	29			
SPT	Between Groups	2138.067	2	1069.033	8.384	.001
	Within Groups	3442.600	27	127.504		
	Total	5580.667	29			
BDNF	Between Groups	1691.467	2	845.733	4.482	.021
	Within Groups	5095.200	27	188.711		
	Total	6786.667	29			
Testosterone	Between Groups	298201.400	2	149100.700	10.424	.001
	Within Groups	386209.800	27	14304.067		
	Total	684411.200	29			

The results of the analysis of variance (ANOVA) test showed a significant difference between groups for both depression-related variables (TST and SPT) ($P \leq 0.05$). To determine the differences between the groups, Tukey's post hoc test was used.

The results of the post hoc test showed a significant difference in the TST variable between the control group and the two exercise groups, as well as between the two exercise groups ($P \leq 0.05$). In the SPT variable, there was a significant difference between the two exercise groups and between the long-term exercise group and the control group ($P \leq 0.05$). However, there was no significant difference between the short-term exercise group and the control group ($P \geq 0.05$). Additionally, the results of the post hoc test showed a significant difference in the BDNF variable between the control group and the long-term exercise group ($P \leq 0.05$), but no difference between the other two groups ($P \geq 0.05$).

4. Discussion and Conclusion

The research findings showed a significant difference between the groups for both depression-related variables (TST and SPT) ($P \leq 0.05$). The post hoc test results showed a significant difference in the TST variable between the control group and the two exercise groups, as well as between the two exercise groups ($P \leq 0.05$). In the SPT variable, there was a significant difference between the two exercise groups and between the long-term exercise group and the control group ($P \leq 0.05$). However, there was no significant difference between the short-term exercise group and the control group ($P \geq 0.05$).

Recent clinical and experimental studies have shown that swimming can be a potential treatment for cognitive and behavioral disorders. It appears that neurogenesis in the hippocampus also plays an important role in treating psychiatric disorders such as depression. Neurogenesis may involve hippocampal volumization and synaptogenesis (9) and has been observed to be associated with exercise. BDNF levels showed a significant difference between the control group and the long-term exercise group ($P \leq 0.05$), but no difference between the other two groups ($P \geq 0.05$).

Aerobic activity can lead to increased BDNF gene expression through two different pathways by releasing glutamate and BDNF from presynaptic terminals. Glutamate, by binding to NMDA and increasing calcium flow, activates the MAP kinase pathway via calmodulin kinase 4. The activated MAP kinase can act on the nuclear target and cause CREB transcription (15). Contrary to the present research, Lou et al. (2008) stated that high-intensity running on a treadmill leads to a decrease in BDNF gene expression in the hippocampus (11). They also observed that five weeks of running on a treadmill at an intensity of less than 11 meters per minute increased BDNF gene expression in the hippocampus of mice, whereas running on a treadmill at an intensity of 20 meters per minute decreased BDNF expression in the hippocampus compared to the control group. They reported that the decrease in BDNF gene expression is due to a reverse U-shaped dose response to exercise intensity and BDNF gene expression. They also stated that the decrease in BDNF gene expression during high-intensity exercise may be partly due to glucose uptake or lactate production during exercise. It has also been reported that high-intensity exercise leads to a reduction in overall brain glucose uptake and an increase in lactate production in humans. High-intensity activity leads to increased lactate in the body, and it has recently been reported that lactate in the body plays an effective role in increasing BDNF gene expression due to the enhancement of the glutamate, NMDA pathway (11).

The results showed a significant difference in the testosterone variable between the control group and both the short-term and long-term exercise groups ($P \leq 0.05$), but no difference between the short-term and long-term exercise groups ($P \geq 0.05$).

Numerous studies have reported an increase in serum testosterone levels following strength training exercises. Meanwhile, testosterone is one of the hormones affected by depression and mood states. The testosterone levels of individuals with depression are lower than those of normal individuals (9). Many studies support that physical activity increases testosterone levels in the body (10, 13). Overall, past studies have shown that increasing BDNF and testosterone has antidepressant effects. Therefore, since physical activity, especially swimming, leads to an increase in these factors, it may reduce depression through these mechanisms. Physical activity is considered one of the strategies to reduce depression (2, 16).

Authors' Contributions

F.T. conceptualized the study, designed the research methodology, and supervised the overall project implementation. R.A. conducted the experimental procedures, including the animal training sessions, and contributed to data collection. F.T. performed the data analysis, interpreted the results, and led the drafting and revising of the manuscript. Both authors participated in discussing the findings, critically reviewed the manuscript for important intellectual content, and approved the final version for publication.

Declaration

In order to correct and improve the academic writing of our paper, we have used the language model ChatGPT.

Transparency Statement

Data are available for research purposes upon reasonable request to the corresponding author.

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Declaration of Interest

The authors report no conflict of interest.

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Ethics Considerations

The study protocol adhered to the principles outlined in the Helsinki Declaration, which provides guidelines for ethical research involving human participants.

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