Original Article

The Effect of Multimodal Exercise on the Levels of BDNF and GDNF in Patients with Parkinson's Disease

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Abstract

Background: Parkinson's disease (PD) leads to a significant decrease in brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF). This study explores the effect of 12 weeks of multimodal exercise on the levels of BDNF and GDNF in patients with PD. **Methods:** The study is a quasiexperimental study with random sampling. It was conducted in 2024 at Isfahan. Demographic data were collected using the demographic questionnaire outlined in the Methods section. Thirty patients were randomly divided into two equal groups of multimodal exercise and control, with no significant differences in age, weight, and height. The variables of BDNF and GDNF were assessed in pre- and post-tests. Multimodal exercise was performed 5 days a week for 12 weeks. Data were analyzed using covariance and *t*-test at a significant level of $P < 0.05$. **Results:** The study observed significant differences in BDNF and GDNF, among two groups of PD ($P < 0.01$). Moreover, the levels of BDNF and GDNF were significantly higher in the PD + Training group compared to the PD group ($P < 0.01$). **Conclusions:** Given that multimodal exercises are effective in increasing BDNF and GDNF in individuals with PD, it is recommended to incorporate the benefits of these exercises into physical rehabilitation programs. Therefore, the combined approach of multimodal exercises (resistance, aerobic, and balance) is recommended as the most effective complementary therapeutic strategy for PD.

Keywords: *Exercise, neurogenesis, neurogenesis factors, Parkinson's disease*

Introduction

Parkinson's disease (PD) is one of the common neurodegenerative disorders, which involves the degeneration of dopaminergic neurons in the substantia nigra of the midbrain.[1] Among the main motor symptoms associated with this disease are resting tremors, bradykinesia, difficulty in maintaining movement, stiffness in the legs, torso, and arms, and postural instability.[2] The prevalence of PD has more than doubled from 1990 to 2015, now affecting around 6.9 million people worldwide. It is estimated that by 2040, over 17.5 million people will be living with the disease globally.[3] It is estimated that by the time the first signs of PD are recognized, 30% of dopaminergic neurons in the substantia nigra and approximately 50–70% of dopaminergic neurons in the striatum have already been lost.[4] Neurotrophins are a group of proteins that play various roles, including promoting nerve survival, axon growth, synapse formation, and neurogenesis.[5] Among the most important neurotrophic factors are brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF).[6] It also supports synapse growth, neuronal differentiation, and overall nerve regeneration.[7] Additionally, GDNF promotes synapse growth, neuronal differentiation, and nerve growth.[8] The signaling pathways involved in the function of GDNF are highly complex. Because this neurotrophic factor can exert its effects through various pathways, GDNF primarily exerts its effects through the formation of the GDNF/GFRα1 complex.[9] In PD, the levels of GDNF are significantly reduced, contributing to neuronal damage and progression of the disease.[10,11] Similarly, brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin protein family that facilitates neurogenesis, neuronal growth and survival, and synaptic plasticity. BDNF also plays a significant role in long-term memory.[12] Considering that BDNF secreted in the central nervous system also distributes into the bloodstream, changes in the levels of BDNF in the

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blood may reflect changes in its secretion in the brain.[13] Studies have shown that BDNF affects neurogenesis in the brain. Additionally, BDNF can prevent the cell death of dopaminergic neurons that are damaged in PD.[14] Various research studies have indicated that in PD, the levels of BDNF are reduced, and one of the key reasons for neuronal damage and the decline in cognitive functions and memory in this disease is the decrease in BDNF.[15,16] Physical activities have been proposed as a noninvasive supportive approach to increase the levels of BDNF and GDNF in the brain.[17] Multimodal exercise, which combines strength, aerobic, balance, coordination training, as well as warm-up and cool-down phases, has shown promise in improving functional mobility, balance, and overall motor function in patients with PD.[18] Studies suggest that such exercise regimens can increase the levels of neurotrophic factors like BDNF and GDNF, potentially slowing disease progression and improving quality of life.[19,20] Previous research has primarily focused on the impact of exercise on functional factors such as balance, mobility, and motor function in patients with PD. However, there is a gap in the literature regarding the simultaneous effect of multimodal exercise interventions on neurotrophic factor levels in these patients. Most studies have explored individual exercise modalities, but fewer studies have examined the comprehensive effects of combining strength, aerobic, balance, and coordination training on disease progression and neurotrophic factors, so the present research will examine the effect of 12 weeks of multimodal exercises on BDNF and GDNF levels in patients with PD.

Methods

The present study was a quasiexperimental, cross-sectional design with a pretest/post-test framework. Twenty patients with PD who visited the Isfahan Parkinson Association in 2024 were selected through purposive and convenience sampling. Using the Morgan table, they were randomly assigned to two equal research groups, multimodal exercise (n = 15) and control (n = 15). In other words, this was a factorial clinical trial with a 1:1 allocation ratio.

With α =0.05 and β =0.2, the sample size for each group was calculated to be 10 to achieve a statistical power of 0.8. Using Cochran's formula, the sample size for the study was calculated to be 20, which matched the previous formula.

Inclusion criteria were being a known case of PD in stage 2 or 3 according to the Hoehn and Yahr scale,[21] age between 30 and 50 years, being in the onset stage of the disease (responsive to medication), being in the moderate stage of the disease as assessed by the Unified Parkinson's Disease Rating Scale (UPDRS), and voluntary agreement to participate in the study. Exclusion criteria included a history of severe injury or surgery in the spine or lower limbs within the past year, skeletal abnormalities that would prevent participation in exercise, absence from more than 30% of the sessions, and failure to consent to participate in the study.

All pre- and post-test clinical evaluations were conducted by a single neurologist who was blinded to the study groups. The Ethics Committee of the Deputy of Research of the Islamic Azad University, Isfahan Branch, approved this study as a PhD thesis in 2024. Initially, all participants reviewed and signed the consent form, following which they were briefed on the testing procedures. The study was approved by the Ethics Committee of the Deputy of Research at the Islamic Azad University, Isfahan Branch, as a PhD thesis (IR.IAU.KHUISF.REC.1403.264).

Demographic data for each participant were collected, including age, height, and weight. The mean age of the participants in the multimodal exercise group was 60.1 ± 7.6 years, and in the control group, it was 60.4 ± 8.2 years. The mean height of participants in the multimodal exercise group was 161.3 ± 5.49 cm, and in the control group, it was 160.1 ± 4.55 cm. Regarding weight, the multimodal exercise group had a mean weight of 67.94 ± 8.82 kg, and the control group had a mean weight of 68.54 ± 9.82 kg. All pretest and post-test assessments were conducted in the specialized gym and laboratory.

Blood samples from the participants were collected 24 hours before the first session and 24 hours after the last exercise session, following approximately 10 hours of overnight fasting. Plasma levels of GDNF were measured using the ELISA method with a specific kit manufactured by obcam in USA, with a sensitivity of <4 pg/mL Similarly, plasma levels of BDNF were determined using the ELISA method with a specific kit, also manufactured by obcam in USA, with a sensitivity of 2.48 pg/mL. Participants in the multimodal physical exercise program attended 3 sessions per week, each lasting 60 minutes, for a total of 12 weeks. The control group, on the other hand, received standard care and did not participate in any exercise activities during this period.[22] The components of this program included aerobic resistance, muscular strength, balance, motor coordination, agility, and flexibility. The design of the current research program adhered to the principles of physical exercise, such as individuality, overload, and variety, while also considering the needs of the target sample. Overload was achieved through movement challenges and task complexities, ranging from simple to complex movement sequences, and from single-task to dual-task exercises [Table 1].

Exercise intensity was monitored using both heart rate and the Borg Scale to ensure participants were working within an appropriate intensity range. All exercises were conducted in a fitness club under the supervision of a trained specialist, ensuring proper guidance and safety throughout the program. Movements related to daily tasks with a wide range of motions were used during transitions. Large muscle groups and multijoint exercises

were prioritized during resistance training. Visual cues and unstable surfaces were incorporated for walking and dynamic balance exercises. Motor and cognitive learning were stimulated through variations in stimuli, different materials, and games. During the exercise, the training load was controlled by the coach.[19]

Statistical analysis

Data collected from the SPSS software (version 22, IBM Corp., Armonk, NY, USA) were analyzed. To assess the normal distribution of the data in both groups, the Shapiro–Wilk test was used. For comparing variables within and between groups at a significance level of less than 0.05, the *t*-test and repeated measures ANOVA were employed.

Results

Twenty patients in two equal groups were enrolled in this study. The two study groups were not statistically different in age, height, and weight [Table 2]. Table 3 shows the mean and standard deviation of GDNF and BDNF in two groups in the pre- and post-tests. The within-group changes in the GDNF (t = 90.215, P = 0.001) and BDNF (t = 14.706, P = 0.001) variables were significant, as determined by the paired *t*-test, with multimodal exercise resulting in a significant increase in these factors. The between-group comparison using analysis of covariance (ANCOVA) revealed that multimodal exercise significantly increased GDNF (F (1, 28) = 170.128, P = 0.001, partial eta squared = 0.86) and BDNF (F (12, 65) = 45.724, P = 0.001, partial eta squared = 0.62) levels compared to the control group.

In addition, as shown in Figures 1 and 2, it is clearly seen that the multimodal exercises were significantly higher than the control group and were significantly higher in both studied variables. This shows that multimodal exercises had a significant effect on these variables in patients with PD.

Table 1: Multimodal exercise training program

Exercise Type	Training Program
Warm-up 5 to 10 minutes	During this time, they participated in playful activities to develop joint mobility, activate the neural-muscular muscles that would be used in the training program, and enhance functional movements (transitions).
Resistance training	Targeted exercises for different body parts, including facial muscles, shoulders, chest, arms, back, hips, calves, and thighs. For each exercise, perform 2 sets with 10 repetitions per set.
Balance exercises	Exercises involving specific movements, such as seated balance exercises, standing balance exercises (with eyes open and closed), and dynamic balance exercises. Each exercise is performed for 10 to 15 seconds, with 2 sets for each movement.
Walking exercises	Steady Walking Exercises: 1 to 2 sets, with 30 to 50 steps per set. – Walking and turning exercises: 1 to 2 rounds per set, for a total of 2 sets – Obstacle crossing exercises: 5 to 10 steps in each direction, for a total of 2 sets.

Table 2: Participant demographics (Mean±SD)

Variable group	Intervention	Control	*t*	*P*
Age (year)	60.1±7.6	60.4±8.2	0.162	0.67
Height (cm)	161.3±5.49	160.1±4.55	0.667	0.51
Weight (kg)	67.94±8.82	68.54±9.82	0.670	0.41

Discussion

PD is a degenerative disorder of the central nervous system that leads to difficulties in standing and movement in affected individuals. Additionally, the correlation between PD and aging results in immobility and a decrease in brain neurotrophins.[23] According to the results of this study, after a 12-week training period, GDNF levels significantly improved in the multimodal exercise group compared to the control group. However, this improvement was greater in the "multimodal exercise" group after 12 weeks. PD is associated with the loss of dopaminergic neurons, and this neuronal degeneration is progressive. This progression occurs because the mitochondrial content of these neurons diminishes, leading to a decline in the function of the substantia nigra in the brain.[24] In the past 3 decades, GDNF has been identified as a neurotrophic factor, with its role established not only in the survival and plasticity of neurons but also in the proliferation, differentiation, and protection of dopaminergic neurons.[25] GDNF protects dopaminergic neurons against neurotoxins during PD and supports the survival of these neurons by increasing transcription factors such as Nurr1 and PITX3. Additionally, GDNF exerts its trophic effects by forming the GDNF/GFRα1 complex, which subsequently activates the RET receptor.[10] With the formation of the RET/GDNF/GFRα1 complex, a series of reactions involving ERK, PI3K, Akt, JNK, and MAPK pathways occurs, ultimately leading to the survival of dopaminergic neurons.[26] Consistent with the findings

Table 3: Results of paired *t*-test and analysis of covariance (ANCOVA) for the research variables

Factor	Group	Pretest Mean±SD	Posttest Mean±SD	*t*	F	Eta
GDNF	Intervention	32.16±8.82	46.12±8.82	90/215 *P*=0/001	170.128 *P*=0/001	0/86
	Control	34.65±8.82	36.28±8.82	3/713 *P*=0/002		
BDNF	Intervention	3429.2143±47.35	4189.6636±38.50	14/706 *P*=0/001	45.764 *P*=0/001	0/62
	Control	3478.4489±53.51	3709.9714±60.16	1/377 *P*=0/19		

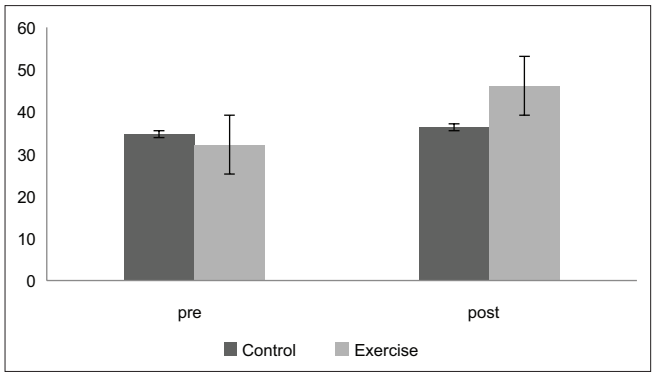

Figure 1: Changes in the scores of the variable of GDNF in two study groups in pretest and post-test

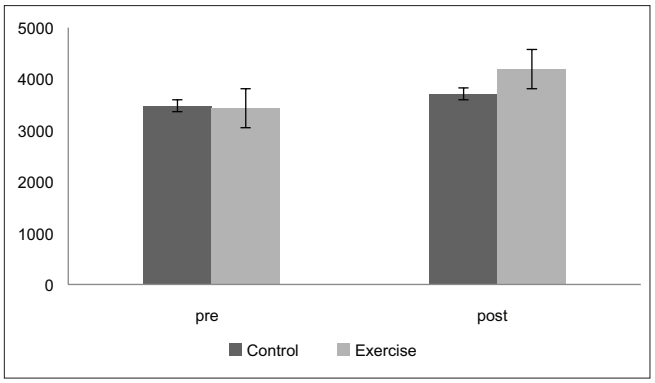

Figure 2: Changes in the scores of the variable of BDNF in two study groups in pretest and post-test

of this study, previous research has also shown that levels of GDNF and RET decrease in PD. This reduction in these two proteins leads, on one hand, to decreased survival of dopaminergic neurons and, on the other hand, to an increase in cellular death mechanisms.[9] Exercise has been suggested as a noninvasive method to increase the levels of neurotrophins in the brain as well as to promote neurogenesis and angiogenesis.[27] Consistent with the results of the current study, our findings indicate that the expression of the GDNF gene in the hippocampus of male Wistar rats increases after 12 weeks of wheel-running activity.[28] Salehpoor and colleagues demonstrated that 6 weeks of TRX training had a significant impact on the GDNF protein levels and upper and lower body strength in elderly women, and it may potentially be effective in reducing or delaying sarcopenia.[29] Contrary to the results of the present study, Shibani and colleagues showed that internal attention during dribbling exercise had no significant effect on serum GDNF levels and cognitive performance.[30] The discrepancy in the results is likely due to differences in the duration of the exercise, the intensity of the training, and the type of subjects used. Multimodal exercise, by modulating the immune response and reducing the inflammatory environment, can protect dopaminergic neurons and enhance the effects of GDNF. Multimodal exercises exert antioxidant effects in the body and reduce oxidative stress. Therefore, another potential mechanism for the increase in GDNF in the present study may be the increase of antioxidant factors and the reduction of oxidative stress factors in the brain.[28]

Moreover, according to the results of this study, the training protocol has improved BDNF in both training groups, with this variable showing a greater improvement in the multimodal exercise therapy group. Neurotrophic factors, such as BDNF, play crucial roles in supporting and promoting the growth of various brain neurons. It has been reported that exercise can indirectly influence the expression of neurotrophic factor genes by affecting the release of neurotransmitters such as acetylcholine, gamma-aminobutyric acid (GABA), and monoamines, leading to increased levels of BDNF mRNA in the hippocampus. High levels of BDNF in the hippocampus and cortex reflect its essential role in maintaining proper brain function.[31] BDNF has a clear neuroprotective role, and exercise enhances cholinergic activity, which is involved in neuronal plasticity induced by physical activity. Luo and colleagues demonstrated that exercise increases neurogenesis in rats and also enhances the production of BDNF mRNA, contributing to improved brain function and better learning and memory. Intense physical activity increases cerebral blood flow, which may play a role in boosting neuronal cell formation, new blood vessel growth, synapse formation, and neurotransmitter synthesis in various brain regions.[32] Osali *et al*.[33] found that BDNF levels and memory improved after 12 weeks of aerobic exercise. Ganji and colleagues[34] demonstrated that combined exercise led to an increase in BDNF levels in patients with PD. These findings do not align with studies by Nakhzari *et al*.,[35] which reported decreased or unchanged BDNF levels following endurance exercise.[36] This discrepancy may be due to differences in the subjects or exercise programs used. Another potential mechanism for the increased BDNF following multimodal exercise in PD could be the regulation of Trk receptors in brain tissue. In the present study, multimodal exercise significantly increased BDNF levels in PD.

Conclusions

Limitations of the present study included nutrition, lack of control over physical activity outside of training sessions, and sleep and psychological states. The results suggest that multimodal exercise may help enhance brain neurogenesis in AD by increasing levels of BDNF and GDNF. Notably, multimodal exercise has a more significant effect. Therefore, the combined approach of multimodal exercises (resistance, aerobic, and balance) is recommended as the most effective complementary therapeutic strategy for AD. However, further and more comprehensive studies are needed to validate and expand upon these findings.

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Conflicts of interest

There are no conflicts of interest

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