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Original Article

Impact of a 12-week combined strength, aerobic, and balance training program on dopamine and serotonin levels in patients with Parkinson's disease: a randomized clinical trial

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Abstract

Background and aims: Serotonin and dopamine are monoamine neurotransmitters that are reduced in Parkinson's disease) (PD). This study examined the effects of the 12-week combined strength, aerobic, and balance training program on dopamine and serotonin plasma levels in patients with Parkinson's disease (PD).

Methods: This study was designed as a randomized clinical trial. A total of 30 participants were selected using convenience sampling and randomly assigned to one of two groups using block randomization, including a combined exercise group (strength, aerobic, and balance exercises) of 15 participants and a PD group with 15 participants. The study was conducted in 2024 in Isfahan, Iran. The training program lasted 12 weeks, with five weekly sessions held at a sports club. The data were analyzed using ANCOVA for between-group comparisons and a paired test for within-group changes ($P<0.05$).

Results: The results revealed significant differences in dopamine and serotonin among the two PD groups ($P<0.001$). However, there was a substantial increase in the combined exercise program group compared with the PD group ($P<0.001$). In the combined exercise group, dopamine levels increased from 0.0141 ± 0.003 at the pretest to 0.0853 ± 0.033 at the posttest ($P=0.001$). Finally, serotonin levels rose from 4.59 ± 0.56 to 6.59 ± 0.90 ($P=0.001$).

Conclusion: The combined exercise increased the dopamine and serotonin levels in PD. Accordingly, performing combined exercise can be used as a therapeutic intervention in PD prevention and treatment strategies.

Keywords: Exercise, Dopamine, Serotonin, Parkinson's disease

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Introduction

Parkinson's disease (PD) is the most widespread movement disorder related to the degeneration of neurons, impacting nearly four million older adults across the globe (1). The characteristics of this disease include motor disability, bradykinesia, postural instability, rigidity, and tremors, which ultimately lead to complete immobility (2). The pathological alterations in PD are widespread throughout the brain; however, the leading neuronal cause of the motor symptoms in PD is undeniably the degeneration of dopaminergic neurons in the substantia nigra pars compacta of the midbrain. This degeneration leads to a significant depletion of dopamine in the striatum, resulting from damage to the nigrostriatal pathway (3). Recent studies have shown a connection between various conditions, including tremor disorders and physical inactivity (4). Physical exercise helps protect the substantia nigra from damage caused by inflammation. Growing evidence indicates that physical activity and exercise delay aging, prevent chronic diseases, and enhance overall health (5). Previous research findings demonstrated that exercise improves physical function, health-related quality of life, strength, balance, and gait speed in patients with PD (6). There is a noticeable shortage of effective drugs that can preserve neurons and halt neuronal degeneration. According to reports, regular exercise and physical activity reduce the risk of future neuronal damage, such as PD and other neurodegenerative disorders (7). Additionally, exercise accelerates the healing of damage to the nigrostriatal pathway and modifies dopaminergic neurotransmission within the system (8). Dopamine transmits neural signals from the midbrain to another part of the brain called the striatum. The transmission of these signals helps maintain balance in body movements (9). When dopamine-secreting cells in the midbrain are destroyed, other centers responsible for controlling body movements become dysregulated (10). Research by

Aghasi et al revealed that voluntary resistance exercise increased the survival and longevity of dopaminergic neurons in the striatum of rats, protecting them against oxidative damage caused by 6-OHDA toxicity, indicating that exercise has a protective role against PD (11). Serotonin, a neurotransmitter, is crucial for managing various functions, including mood, sleep, appetite, memory, and cognitive activities. It is predominantly synthesized in the brain and the gastrointestinal tract (12). Both the dopaminergic and serotonergic systems are affected in PD. Serotonin can indirectly play a role in controlling movements. As a result, changes in serotonin levels can impact the motor symptoms of PD. Autopsy studies of PD have shown reduced levels of serotonin metabolites, such as 5-HIAA, in the brain. In the basal ganglia, serotonin can facilitate dopamine release from the striatum by affecting 5-HT1B receptors and inhibiting serotonin release. This mechanism has been shown to reduce motor disturbances in animal models of PD (13). The use of physical activities as a non-invasive, supportive approach to increase dopamine and serotonin levels in the brain has been proposed (14). Combined exercise programs, which incorporate strength training, aerobic activities, balance, and coordination, use essential exercise elements to promote better functional abilities in everyday tasks. Integrating these varied exercise types can lead to enhanced outcomes, such as improved walking, functional mobility, balance, postural stability, reduced muscle rigidity, increased neurotrophic markers, and a deceleration in disease progression (15). However, limited research exists on the simultaneous effects of strength, aerobic, balance, and coordination exercises on PD and neurotrophic levels. Therefore, this study investigates the effects of a 12-week combined strength, aerobic, and balance training program on dopamine and serotonin plasma levels in patients with PD.

Materials and Methods

Subjects

The current research was a randomized clinical trial utilizing a pretest/posttest design. A total of 30 participants with PD were referred to the Isfahan PD Association. These participants were randomly divided into a combined exercise group (n = 15) and a PD control group (n = 15), using block randomization to ensure equal distribution. To minimize bias, the study employed a double-masked design, meaning that the participants and the evaluators were unaware of the group. The sample size was determined based on clinical trial guidelines and power analysis using G*Power software. Considering a power of 80%, an alpha level of 0.05, and an expected effect size based on (16), 30 participants were required for this study. The current study received approval from the Islamic Azad University Ethics Committee, Isfahan Branch, and informed consent was obtained from all participants. Moreover, the participants' demographic details, such as name, age, gender, and pertinent medical history, were documented. The inclusion criteria for the study were "having a confirmed diagnosis of PD at stages 2 or 3 based on the Hoehn and Yahr scale, being in the early stage of the disease (responsive to medication), being in the moderate stage according to the Unified PD Rating Scale, and having no history of major spinal or lower limb surgery or injury in the past year. The other criteria for inclusion included having no significant musculoskeletal deformities limiting exercise participation, having no cognitive impairments (Mini-Mental State Examination) score < 24), having no severe cardiovascular or neurological conditions other than PD, and giving voluntary consent to participate in the study. All PD patients included in this study were under standard treatment with PD medications, such as levodopa and dopamine agonists. These patients did not change their medication regimen during the study period. However, patients were excluded from the study if they had any changes in their PD medication regimen during the study period and missed more than 30% of the sessions. The study population flow is outlined in the CONSORT diagram (Figure 1).

All clinical assessments, conducted before and after the intervention, were performed by a neurologist blinded to the study groups. Blood samples were taken from participants 24 hours before the first exercise session and 24 hours after the final session, following an overnight fast of approximately 10 hours. Plasma serotonin levels were measured using the enzyme-linked immunosorbent assay method with a specific kit from the United States, which had a sensitivity of 0.293 ng/mL. Similarly, plasma dopamine levels were assessed using the enzyme-linked immunosorbent assay method with a specific kit from France, with a sensitivity of 0.25 ng/mL.

Exercise Training Protocol

Participants in this combined exercise engaged in three sessions per week, each lasting 60 minutes, over 12 weeks. The program included various components, such as aerobic resistance, muscular strength, balance, motor coordination, agility, and flexibility (17), the details of which are provided in Table 1.

Statistical analysis

The collected data were analyzed using SPSS software (version 22, IBM Corporation, Armonk, NY, USA). The Shapiro-Wilk test was utilized to assess the normal data distribution in both groups. The t-test and repeated measures analysis of variance were used to compare variables within and between groups at a significance level of less than 0.05.

Results

A total of 30 patients were enrolled in the study and divided into two equal groups. There were no statistically significant differences between the two groups regarding age, height, and weight (Table 2).

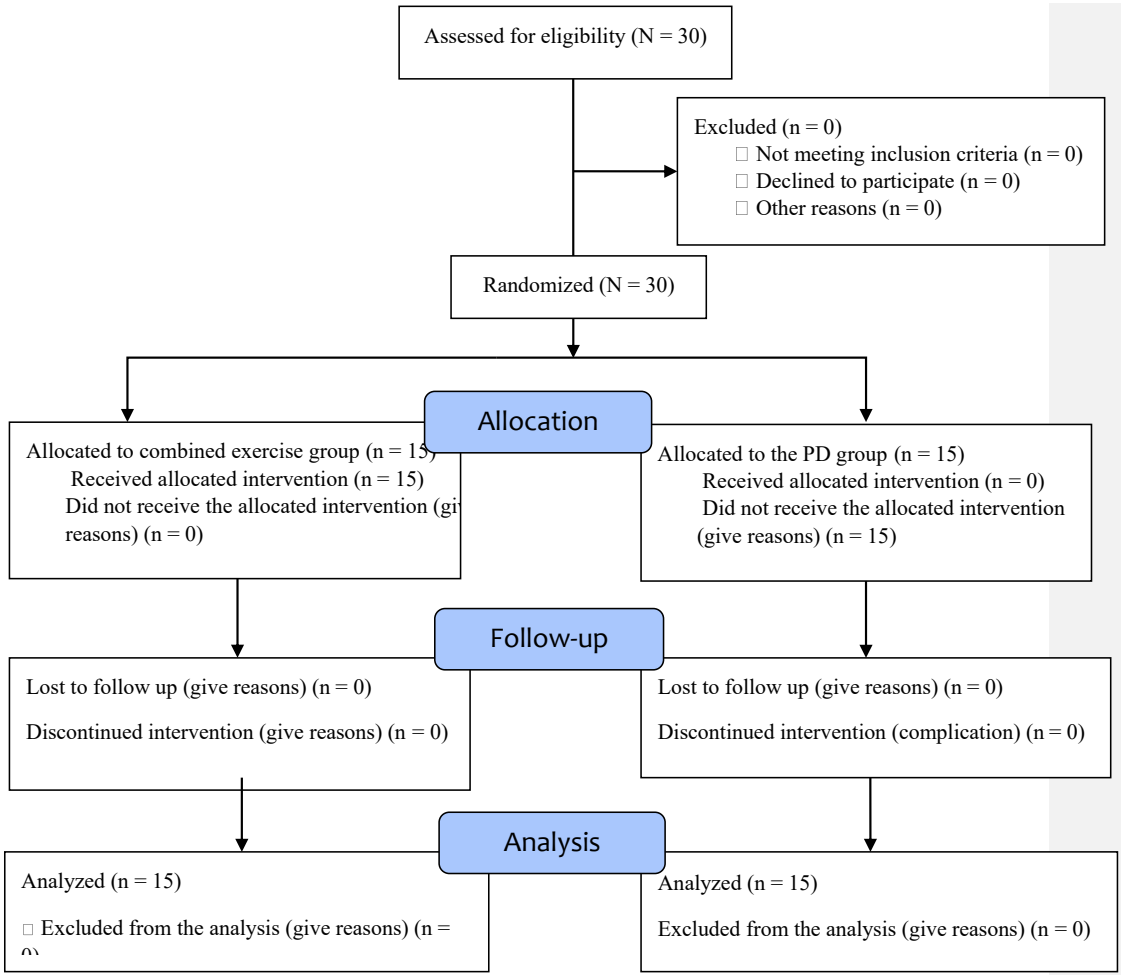

Figure 1. CONSORT Flow Diagram of the Study Population. *Note*. CONSORT: Consolidated Standards of Reporting Trials; PD: Parkinson's disease

Table 1. Implementation Elements of the Combined Exercise

Elements	Definition
Warm-up for 5 to 10 minutes	Throughout this period, I participated in playful activities that improved joint mobility, activated the neuromuscular muscles involved in the training program, and enhanced functional movements (transitions).
Resistance training	The targeted exercises for different body parts included facial muscles, shoulders, chest, arms, back, hips, calves, and thighs. For each exercise, two sets were performed, with 10 repetitions per set.
Balance exercises	Exercises involved specific movements, such as seated balance exercises, standing balance exercises (with eyes open and closed), and dynamic balance exercises. Each exercise was 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 2 sets - Obstacle crossing exercises: 5 to 10 steps in each direction, for a total of 2 sets

Table 2. Demographic Data of the Subjects (Mean ± SD)

Variable	Combined exercises (Mean ± SD)	PD (Mean ± SD)	t	*P* value
Age (years)	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

Note. SD: Standard deviation; PD: Parkinson's disease.

The paired t-test results indicated a substantial increase in dopamine and serotonin levels in the combined exercise group ($P = 0.001$). In contrast, no significant change was observed in the control group ($P = 0.90$ for dopamine, $P = 0.09$ for serotonin). Additionally, the ANCOVA results showed a significant difference between the two groups, with a greater increase in dopamine and serotonin levels found in the exercise group compared to the control group ($F = 66.530$, $P = 0.001$, $(\eta^2) = 0.71$ for dopamine, $F = 3161.964$, $P = 0.001$, $(\eta^2) = 0.62$ for serotonin). For serotonin plasma levels, the results revealed that the intervention significantly influenced dopamine and serotonin levels, with notable differences between the groups. The significant interaction effects imply that the observed changes were group-dependent (Table 3).

Discussion

This study examined the simultaneous effects of strength,

Table 3. Results of Paired t-Test and ANCOVA for Research Variables

Factor	Group	Pretest (Mean ± SD)	Posttest (Mean ± SD)	Within-group (t-Test)	Between-group (ANCOVA)	Effect size (η^2)
Dopamine (ng/mL)	Combined	0.0141 ± 0.003	0.0853 ± 0.033	$t=8.270$, $P=0.001$	$F=66.530$, $P=0.001$	0.71
	PD	0.0140 ± 0.002	0.0141 ± 0.002	$t=0.118$, $P=0.90$		
Serotonin (ng/mL)	Combined	4.59 ± 0.56	6.59 ± 0.90	$t=9.034$, $P=0.001$	$F=3161.964$, $P=0.001$	0.62
	PD	4.53 ± 0.88	4.65 ± 0.87	$t=1.805$, $P=0.09$		

Note. ANCOVA: Analysis of covariance; PD: Parkinson's disease; SD: Standard deviation.

aerobic, and balance exercises on brain dopamine and serotonin levels. Our findings demonstrated that the combined exercise program could significantly and positively impact dopamine levels in patients with PD. In contrast, no significant changes in this parameter were observed in the PD group. Therefore, the results obtained from this study, alongside similar findings, confirm the importance of physical activity in improving dopamine levels in patients with PD (1,18). The present study's findings are consistent with the results of research conducted by Aghasi et al, Tsai et al, Smith et al, Tajiri et al, and Hou et al (11,12,19-21). Smith et al investigated the effects of treadmill exercise on 8-10-week-old PD mice induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. The treadmill exercises improved walking performance and increased physical activity. Moreover, they enhanced dopamine levels and tyrosine hydroxylase activity in the striatum (19). The findings of Hou et al revealed that appropriately prescribed physical activity and exercise can be essential in lowering the risk of developing PD in at-risk populations while also offering substantial benefits for individuals already diagnosed with PD. These benefits include the protection of the remaining dopamine neurons and the restoration of the cortico-basal ganglia motor circuit that is impaired due to the disease. These effects are probably mediated by the activation of neuroprotective neurotrophic molecules generated through exercise. Therefore, exercise can be viewed as a universal, side-effect-free treatment that should be recommended as a preventive measure for at-risk individuals and included in the therapeutic plan for patients with PD (21). The results of the study by Aghasi et al confirmed that voluntary resistance exercises enhance the lifespan of dopaminergic neurons in the striatum of rats, protecting them against oxidative damage induced by 6-OHDA (6-hydroxydopamine) toxicity. These exercises play a protective role against PD (11). Physical activity stimulates dopaminergic cells and can increase dopamine release in the brain. This effect is particularly observed in regions such as the striatum, which plays a significant role in motor control (22). Additionally, physical activity enhances the production of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) (23), which can strengthen dopaminergic cells and protect them against oxidative damage. In human subjects with PD, a reduction in mitochondrial complex I activity in the nervous system was observed, along with a correlation between mitochondrial dysfunction and neurodegenerative diseases in laboratory settings and genetic studies on animal models. Physical activity is likely effective in preventing PD through mitochondrial biogenesis (24). Furthermore, exercise prevents the destruction of dopaminergic neurons by reducing free radicals and enhancing the activity of antioxidant enzymes (10). Evidence indicates that exercise can increase the number of dopamine receptors in areas associated with motor control, which improves the brain's response to dopamine (1). The results of the present study showed that multi-modal strength, aerobic, and balance exercises increased dopamine levels in patients with PD. It was found that combined strength, aerobic, and balance exercises increased serotonin levels in patients with PD. The present study's findings are in line with the results of research conducted by Tsai et al, Hoghooghizadeh et al, Nourolapour et al, and Shin et al (12,25-27). Hoghooghizadeh et al reported that performing 4 weeks of mandatory aerobic exercise (treadmill), despite increasing serotonin neurotransmitter levels in the hippocampal tissue of male rats, does not affect gamma-aminobutyric acid neurotransmitter levels. In addition, voluntary aerobic exercise (swimming) did not cause significant changes in serotonin or gamma-aminobutyric acid neurotransmitter levels in the hippocampal tissue of male rats. Therefore, a mandatory aerobic treadmill can increase serotonin neurotransmitter levels in male rats (25). Nourolapour et al demonstrated that methamphetamine use was linked to a reduction in the expression of neural factor genes in the cerebral cortex tissue. Furthermore, 8 weeks of aerobic training, combined with crocin supplementation, or aerobic exercise plus crocin, exhibited neuroprotective effects in rats treated with methamphetamine. This intervention increased the expression of BDNF, tropomyosin receptor kinase B, dopamine, and serotonin genes in the cerebral cortex of the rats (26). Tsai et al studied the immediate effects of aerobic exercise at different intensities on executive control related to eye movements and the concentrations of dopamine, serotonin, and norepinephrine metabolites in individuals with PD. The findings revealed that both types of exercise had unique positive effects on executive performance and brain neurotransmitter levels in individuals with PD (12).

The results of the study performed by Shin et al indicated that the increased expression of the 5-HT1A receptor and levels of serotonin and TPH in the dorsal raphe reflect the positive effect of exercise on the serotonergic system in

PD (27). Exercise increases the synthesis of tryptophan in the brain, and tryptophan is the primary precursor of serotonin. Elevating its levels due to physical activity can enhance serotonin production in PD patients (13). Additionally, exercise can reduce the serotonin reuptake by neurons, allowing more significant amounts of serotonin to remain in the synaptic cleft (28). Another possible mechanism for increased serotonin levels following exercise is the enhanced firing of serotonergic neurons. This increased neuronal firing increases serotonin release and promotes serotonin synthesis (29).

Exercise can increase the number of serotonin receptors (receptor density) in brain regions associated with movement and mood. This change helps PD, who often face reduced serotonin receptor functionality, to improve their symptoms (30). Regular physical activity increases BDNF levels. This protein supports the survival, growth, and function of neurons and positively affects serotonin receptor function (30,31). The results of this study confirmed that combined exercise (including strength, aerobic, and balance training) led to an increase in serotonin levels in PD.

Conclusion

The current study's findings indicated that 12 weeks of combined exercise (including strength, aerobic, and balance training) increased brain serotonin and dopamine levels in individuals with PD. Consequently, incorporating these exercises in conjunction with treatments can effectively improve and prevent PD.

Authors' Contribution

Conceptualization: Khosro Jalali Dehkordi.
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Project administration: Khosro Jalali Dehkordi.
Software: Abbas Abdulameer Naser, Khosro Jalali Dehkordi.
Supervision: Khosro Jalali Dehkordi.
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Writing-review & editing: Khosro Jalali Dehkordi, Mahmoud Nasser Radhi, Farzaneh Taghian, Ahmad Chitsaz.

Competing Interests

The authors declare that there is no conflict of interests.

Ethical Approval

This study was derived from an exercise physiology thesis (No. IR.IAU.KHUISF.REC.1403.264) approved by the Physical Education and Sport Sciences Department of Isfahan Islamic Azad University (Khorasgan Branch), Isfahan, Iran, in October 2024. It was registered on the Iranian Registry of Clinical Trials website (identifier: IRCT20241008063289N1). The authors of this article express their gratitude to the dear friends and colleagues who helped us in conducting this research.

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