Sport and Fitness Journal
E-ISSN: 2654-9182 Volume 12, No.1, January 2024: 27-36

AEROBIC EXERCISE TRAINING AS A POTENTIAL THERAPY FOR PARKINSON'S DISEASE PATIENTS: A LITERATURE REVIEW

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ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disorder that exhibits motor and non-motor symptoms. The management of PD consists of pharmacotherapy and surgical management. However, the clinical improvement of pharmacotherapy is still inconsistent. Aerobic exercise provides a restorative and protective benefit by supporting synaptogenesis and angiogenesis, oxidative stress inhibition, and increasing mitochondrial function. It can be a complementary treatment to pharmacotherapy management. We aimed to describe the effect of aerobic exercise on Parkinson's disease through a literature review. Literature searching was performed using the keywords (aerobic exercise) AND (Parkinson's disease) to obtain eligible articles. The literature search was performed in the PubMed database. The findings in the included articles were reviewed and described narratively. Aerobic exercise has a protective effect on the nigrostriatal dopaminergic system and could improve symptoms of PD including somatomotor and non-motor symptoms. The mechanism of aerobic exercise and its effect on neuroprotection includes the increased release of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and glial cell-derived neurotrophic factor (GDNF), increased serum urate, regulating turnover of dopamine, and upregulating the transcriptional regulator peroxisome proliferator-activated receptor gamma (PPARγ) coactivator 1α (PGC1α). Aerobic exercise can improve balance, gait velocity, stride/step length, and other motor functions in patients with PD. Improvement of cadence and quality of life is still inconclusive following aerobic exercise in patients with PD.

Keywords: aerobic exercise; motor symptoms; Parkinson's disease; quality of life

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder that progressively affects older people[1]. Approximately 0.3% of the general population was affected by this disease and 1 – 3% was more than 65 years old. It is estimated that in 2030, there will be 8.7 to 9.3 million patients with PD[2,3]. The clinical manifestation of PD mainly affects the somatomotor system which consists of tremor, rigidity, akinesia or bradykinesia, postural instability, and gait dysfunction[4,5]. Besides somatomotor symptoms, the clinical manifestation also exhibits non-motor symptoms which include dementia, hyposmia, and gastrointestinal disturbance[6-8]. The daily life activities and the independence of patients with PD are disturbed due to these dysfunctions[9].

The management of PD usually consists of medication and surgery. The medication given to treat PD includes levodopa and dopamine agonists. The surgical management includes deep brain stimulation[10]. Pharmacotherapy is a first-line treatment by optimizing the levodopa and adjusting the dose of multiple drugs. The worsening of motor symptoms leads to shorter and limited responses to treatment. In the advanced stage, more frequent doses of levodopa and

its agonist are required. Surgical management is also required in the advanced stage. The clinical improvement after pharmacotherapy management is still inconsistent. Severe motor and cognitive impairment are still experienced by most of the patients[11]. The reduction of balance and walking ability can occur following the administration of conventional pharmacotherapy which leads to an increased risk of falls[12].

Exercise is an alternative treatment that does not require medication. This complementary and alternative treatment gained popularity because it has benefits on neuroplasticity and self-repair[13]. Exercise also exhibits a protective effect on the onset of symptoms in animal studies[14]. The most studied exercise is aerobic exercise and it is considered the best option for improving health throughout life[15]. Aerobic exercise provides a restorative and protective benefit by supporting synaptogenesis and angiogenesis, oxidative stress inhibition, and increasing mitochondrial function. All of these possibly occur due to the regulation of neurotrophic factors by performing aerobic exercise[16]. The motor function along with gaits, balance, and quality of life in moderate to severe PD are improved by performing treadmill training, walking, and dancing[17-19].

Aerobic exercise can be a complementary treatment to pharmacotherapy management. It is still debated about the benefits of aerobic exercise to the improvement of Parkinson's disease. Some reviews reported an improvement in motor and non-motor symptoms in Parkinson's disease following exercise. Many studies reported a mixed exercise involved in improving Parkinson's disease. However, no review analyzes the effectiveness of aerobic exercise specifically for the improvement of Parkinson's disease. Therefore, we aimed to describe the effect of aerobic exercise on Parkinson's disease through a literature review.

METHODS

This was a narrative literature review study. The eligibility criteria are determined based on the PICO framework. The population in this review was patients with PD; the interest was aerobic exercise; the comparator was none; and the outcomes were improvement of motor symptoms and quality of life. The PICO framework then can be used to create keywords to perform literature searching in the database. The keywords to perform the literature review were (Parkinson's disease) AND (aerobic exercise). The online database that has been used was the PubMed database. Articles that have been written in English that describe the effect of aerobic exercise on Parkinson's disease were included in this review. We restrict the year of publication to the past 10 years. The included studies were reviewed further and narratively elaborated. In this literature review, we included 14 articles that describe the effect of aerobic exercise on Parkinson's disease. The literature-searching process can be seen in **Table 1**.

Table 1. The literature-searching process

Process	Articles
Identification using keywords	3,014 articles included
Screening by inclusion criteria	126 articles included
Screening by exclusion criteria	16 articles included
Included articles	14 articles included

RESULTS

As can be seen in **Table 2**, we provided a summary of the findings of the included articles.

Table 2. Summary of findings of included articles

Author	Sample	Intervention	Result

Ganesan *et al.*[20], 2014	I = 20; C = 20	I = Treadmill training with a duration of 30 minutes per session, four sessions per week for 4 weeks C = Stable dosage	UPDRS-III I = -6.85 ± 4.55; C = 0,2 ± 3,8 BBS I = 4.1 ± 7.25; C = 0 ± 2.62
Nadeau *et al.*[21], 2014	I = 23; C = 11	I = Treadmill walking with a duration of 60 minutes per session, 60 – 80% VO_2peak, and three sessions per week for 24 weeks C = Normal physical activity	UPDRS-III I = -7 ± 10.83; C = -4.4 ± 6.41 6 MWT I = 43.5 ± 107.21; C = 22.1 ± 80.31 PDQ-39 I = -9 ± 12.32; C = 0 ± 15.26
Cugusi *et al.*[22], 2015	I = 10; C = 10	I = Walking with a duration of 60 minutes per session, 60 – 80% of heart rate reserve, and two sessions per week for 12 weeks C = Conventional care	UPDRS-III I = -6.3 ± 11.75; C = 1 ± 11.85 BBS I = 6.6 ± 6.85; C = -3 ± 7.39 TUG I = -0.7 ± 2.48; C = 0.9 ± 2.3 6 MWT I = 64.7 ± 71.91; C = 1.2 ± 57.51
Hashimoto *et al.*[23], 2015	I = 15; C = 14	I = Dance with a duration of 60 minutes per session and one session per week for 12 weeks C = Normal lives	BBS I = 4 ± 3.03; C = 0 ± 3.91 TUG I = -2.65 ± 3.87; C = -0.7 ± 4.39
Altmann *et al.*[24], 2016	I = 11; C = 10	I = Aerobic exercise with a duration of 20 – 45 minutes per session, 50 – 75% of heart rate reserve, and three sessions per week for 16 weeks C = Normal activities	UPDRS-III I = -0.9 ± 8.33; C = 2.1 ± 7.47
Schenknman *et al.*[25], 2017	I = 81; C = 38	I = Treadmill exercise with a duration of 40 – 50 minutes per session, 40 – 85% of heart rate max, and four sessions per week for 24 weeks C = Wait list	UPDRS-III I = 0.3 ± 6.3; C = 3.2 ± 5.6
Lee *et al.*[26], 2018	I = 25; C = 16	I = Dance with a duration of 60 minutes per session, 60 – 75% of heart rate max, and two sessions per week for 8 weeks C = Normal lives	UPDRS-III I = -0.9 ± 1.2; C = 0.2 ± 2.6 BBS I = 0.8 ± 3.55; C = -0.7 ± 5.64
Arfa-Fatollahkhani *et al*.[27], 2019	I = 9; C = 9	I = Treadmill walking with a duration of 30 minutes per session, 60% of heart rate max, two sessions per week for 10 weeks C = Usual care	TUG I = -3.92 ± 7.64; C = -2.56 ± 11.18 6 MWT I = 84.77 ± 68.42; C = 13.78 ± 141.82
Sacheli *et al.*[28], 2019	I = 20; C = 15	I = Aerobic with a duration of 40 – 60 minutes per session, 60 – 80% VO_2 max, and three sessions per week for 12 weeks C = Control	UPDRS-III I = 0.65 ± 10.99; C = -1.69 ± 13.76 TUG I = 0.45 ± 2.62; C = 3.19 ± 12.72
Solla *et al.*[29], 2019	I = 10; C = 10	I = Dance with a duration of 90 minutes per session and two sessions per week for 12 week C = Usual care	UPDRS-III I = -5.3 ± 6.98; C = 0.88 ± 6.67 BBS I = 6.9 ± 3.55; C = -0.7 ± 5.64 TUG I = -1.82 ± 0.94; C = -0.48 ± 1.19 Stride/step length I = 0.06 ± 0.09; C = 0.07 ± 0.19 Gait velocity I = 0.1 ± 0.12; C = 0.01 ± 0.22 Cadence I = 6.89 ± 10.96; C = 5.67 ± 10.95

Tollar *et al.*[30], 2019	I = 25; C = 24	I = Cycling with a duration of 60 minutes per session, 80% of heart rate max, and five sessions per week for 5 weeks C = Usual care	BBS I = 4.2 ± 4.17; C = -1.4 ± 5.91 6 MWT I = 41.6 ± 51.53; C = -16.3 ± 81.61
Van der Kolk *et al.*[31], 2019	I = 65; C = 11	I = Aerobic exercise with a duration of 30 – 45 minutes per session, 50 – 80% of heart rate max, and three sessions per week for 24 weeks C = Active control	UPDRS-III I = 1.5 ± 6.45; C = 2.8 ± 6.45 TUG I = 0.5 ± 3.22; C = 0.7 ± 3.22 6 MWT I = -11.3 ± 95.14; C = -15.6 ± 98.36 PDQ-39 I = -0.2 ± 15.32; C = 0 ± 15.32
Wan *et al.*[32], 2021	I = 20, C = 20	I = Qigong exercise with a duration of 60 minutes per session, 70 – 80% of heart rate max, and four sessions per week for 12 weeks C = Reguler medicine	TUG I = -2.21 ± 4.09; C = 0.94 ± 5.79 Stride/step length I = 0.12 ± 0.15; C = 0.03 ± 0.31 Gait velocity I = 0.28 ± 0.24; C = -0.01 ± 0.18 Cadence I = 2.08 ± 14.23; C = 3.57 ± 10.67
Li *et al.*[33], 2022	I = 20; C = 20	I = Wuqinxi Qigong exercise with a duration of 90 minutes per session, 60 – 70% of heart rate max or 6 – 12 on Brog scale, and two sessions per week for 24 weeks C = Active control	UPDRS-III I = -8.68 ± 14.96; C = -2.6 ± 5.58 TUG I = -1.38 ± 1.98; C = 1.95 ± 3.71 PDQ-39 I = -7.63 ± 15.3; C = -4.37 ± 13.26

6MWT: 6-minute walking test; BBS: Berg balance scale; C: Control; I: Intervention; TUG: Timed up and go test; UPDRS-III: Unified Parkinson's disease rating scale part-III; VO_2max: maximal oxygen consumption

DISCUSSION

Parkinson's disease is a neurodegenerative disease that is caused by progressive loss of neurons and deposition of protein in the brain. Progressive loss of neurons and protein cause disturbance of physicochemical properties[34-36]. Aerobic exercise has a protective effect on the nigrostriatal dopaminergic system. Therefore, aerobic exercise could improve symptoms of PD including somatomotor and non-motor symptoms. The mechanism of aerobic exercise and its effect on neuroprotection includes increased release of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and glial cell-derived neurotrophic factor (GDNF), increased serum urate, regulating turnover of dopamine, and upregulating the transcriptional regulator peroxisome proliferator-activated receptor gamma (PPARγ) coactivator 1α (PGC1α)[37].

Brain-derived neurotrophic factor (BDNF) is the indicator of neurogenesis in the peripheral. BDNF has a role in supporting the growth of neurons and their survival[34-36]. In PD, the level of neurotrophic factors such as BDNF and its receptors are decreased[38-40]. Aerobic exercise has been reported to increase the level of BDNF and dopaminergic neurons. Therefore, it has a role also in the recovery of motor function in patients with PD[41,42]. Furthermore, another study also reported that the duration of aerobic exercise that provided the most effective increase in BDNF levels was 40 minutes for 12 weeks[43]. A meta-analysis study reported that aerobic exercise was able to increase BDNF levels in patients with neurological disorders. The upregulation of BDNF is important because it can increase neurogenesis, dendritic growth, and potentiation of neurons. All of these are the parameters of neuroplasticity[44].

Maintaining balance and stable posture are problems for most patients with PD. Unable to maintain stability and balance leads to increased fall incidence and can be dangerous. The incidence of falls affects half of patients with PD[45,46]. Assessment of postural balance and

control can be obtained using BBS and TUG[47,48]. In this review, we found that aerobic exercise could improve BBS and TUG in patients with PD. Aerobic exercise can increase physical control and therefore reduce the risk of falls in daily activities. This review is consistent with another study that reports improvement of upper and lower limb coordination after performing Nordic walking lie. Improvement of coordination between upper and lower limbs leads to balance improvement in performing complex daily living activities[49].

Patients with PD have been known to have slow velocity during walking. Therefore, it increases the risk of falls and its complications.[45] Preventing falls in patients with PD can be achieved by improving gait also. This review showed that aerobic exercise improves the gait velocity and stride/step length in patients with PD. This result is similar to other studies that reported improvement in gait velocity and stride/step length in patients with PD after performing aerobic exercise for 4 to 24 weeks[46-49]. Aerobic exercise can reduce axial stiffness by decoupling the movement of the shoulder girdle and pelvis and promoting postural response. Therefore, an increase in control of the trunk can improve posture, balance, and gait[50,51]. The evidence of the effect of aerobic exercise on cadence is still little. A study reported the duration of aerobic exercise has an important role in improving cadence where longer duration gives better improvement[47].

The UPDRS-III is a tool to assess the severity of motor symptoms of PD such as tremors, bradykinesia, akinesia, postural instability, and gait disturbance[52]. UPDRS-III is considered as the gold standard for assessing motor symptoms to determine the effect of aerobic intervention[53]. In this review, we found that aerobic exercise provides a reduction of UPDRS-III in patients with PD. This is consistent with other studies that also reported similar results[54,55]. Aerobic exercise is reported as safe and well-tolerated training that improves the fitness, function of somatomotor, and quality of life of patients with mild and moderate PD[56,57].

The 6MWT is a parameter to determine walking endurance which is assessed by instructing the participant to walk as fast as possible in a 100-m-long corridor for six minutes. The walking distance in meters is measured by the assessor[58]. This review found that aerobic exercise increases the distance during the 6MWT test in patients with PD. This result is consistent with another study that showed improvement in walking ability regardless of the aerobic exercise duration[57]. The improvement of balance function and ability to perform complex motoric tasks were also reported following aerobic exercise in patients with PD[57-59].

The PDQ-39 is a scale to assess the quality of life of patients with PD[60]. PDQ-39 consists of 39 items with higher scores showing a lower quality of life. This scale is divided into eight subscales which are mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and discomfort[60-63]. In this review, we found no significant improvement in quality of life in patients with PD following aerobic exercise. This is consistent with another study that reported no improvement in the PDQ-39 scale following aerobic exercise compared to the usual care or placebo group[64]. However, aerobic exercise is reported to improve the quality of life by using another scale such as Parkinson's disease quality of life questionnaire (PDQL) and EuroQol (EQ-5D)[65]. It is also reported that following aerobic exercise, the ability to concentrate, remember, and recall information was improved[66].

Aerobic exercise is an effective non-pharmacotherapy management that improves physical fitness and motor symptoms in daily activities[67]. This improvement is thought of as increasing the neurogenesis, neuroplasticity, and neuroprotective benefit to various cortical regions[68-71]. Aerobic exercise is reported to modulate cognition, altered signaling pathways in the central nervous system, and modulate olfaction sense in patients with PD[72]. Besides as a non-pharmacotherapy treatment, aerobic exercise also can prevent the occurrence of PD[73,74].

CONCLUSION

Aerobic exercise can improve balance, gait velocity, stride/step length, and other motor functions in patients with PD. Improvement of cadence and quality of life is still inconclusive following aerobic exercise in patients with PD. Therefore future studies should assess the effect of aerobic exercise on cadence and quality of life in patients with PD.

CONFLICT OF INTEREST

The authors declared the absence of a conflict of interest regarding the preparation of this manuscript.

FUNDING

The authors declare received no funding to sponsor the process of the preparation of this manuscript.

AUTHOR CONTRIBUTION

All the authors had equal contributions during the preparation of this manuscript and agree to accept equal responsibility regarding the content of the article.

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