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The Effect of Exercise on Reducing Fatigue in Patients with Parkinson's Disease: A Systematic Review

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Abstract

Purpose/Hypothesis: Parkinson's disease (PD) is a progressive neurodegenerative disease characterized by both motor and non-motor symptoms. Fatigue is one of the most common and disabling non-motor symptoms experienced by patients. Not only does fatigue negatively affect patients' quality of life but also hinders their participation and compliance in rehabilitation. However, effective treatment of PD-fatigue is lacking. Evidence is mounting for beneficial effects of exercise for a variety of symptoms in patients with PD. The objective of this systematic review study was to evaluate the effect of exercise and physical therapy on reducing fatigue in PD. **Materials and Methods:** Databases including MEDLINE, PubMed, CINAHL Complete, and EMBASE were systematically searched. Eligibility criteria were that studies had: (1) enrolled patients with idiopathic PD, (2) administered exercise program as treatment for PD-fatigue, (3) compared the exercise intervention with usual care or conventional exercise, (4) measured fatigue, (5) used a design of randomized controlled trial, and (6) scored at least 4 out of 10 on Physiotherapy Evidence Database (PEDro) scale. **Results:** Twelve articles (N = 422) were included in this review, and all scored in the range from 4/10 to 8/10 with a mean of 6.3 (1.2) on the PEDro scale, indicating a fair to strong methodologic quality of the trials. Eight of the 12 studies showed significant improvements in fatigue scores ($p < 0.05$ to $p < 0.000$) in favor of intervention including but not limited to aerobic exercise, treadmill training, Nordic walking, exergaming, and home-based training program, as compared to controls. **Discussion and Conclusions:** Exercise and physical therapy are shown to be largely effective in reducing fatigue in patients with PD. Future studies using adequate sample sizes are needed to examine the optimal frequency, duration, and intensity of exercise to produce the most beneficial outcomes. Patients with PD may likely benefit from an integrated regimen of both PD-medication and physical therapy program. Clinical management of PD that will address both motor and non-motor symptoms is needed to maximize quality of life in people living with PD.

Keywords

Parkinson's Disease, Fatigue, Exercise, Physical Therapy

1. Introduction

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disease, and characterized by both motor and non-motor symptoms. Motor symptoms manifest as rigidity, resting tremor, bradykinesia, and postural instability while non-motor symptoms include cognitive impairments, autonomic dysfunction, sleep disorders, and fatigue etc. [1] [2]. Fatigue is one of the most common and disabling non-motor symptoms experienced by patients with PD. The prevalence of fatigue in PD ranges from 33% - 81% and approximately one third of patients report fatigue as being the most disabling symptom experienced [3].

Fatigue can be divided into two categories: peripheral fatigue and central fatigue. Peripheral fatigue is defined as a reduction in muscle strength due to repeated contractions commonly associated with physical activity. Central fatigue, related to the central nervous system, refers to the subjective experience of mental and physical exhaustion or weakness without the presence of any physical impairment [3]. Fatigue may hinder patient's adherence to and compliance with therapeutic programs as observed in persons experiencing fatigue due to multiple sclerosis [4] [5]. Thus, it is critical for clinicians to be aware of this important topic. Fatigue was voted as the leading symptom in need of research by patients with PD [6]. Treatment of PD-fatigue is among the unmet needs in clinical management of Parkinson's disease [7].

Although fatigue in PD is a common and disabling symptom that severely impacts quality of life, the underlying pathophysiology and mechanisms remain elusive and require more research. This contributes to the limitation in treatment approaches. Options for treatment of fatigue are sparse, and include medication such as antidepressants, dopaminergic and psychostimulant drugs, and non-pharmacological treatment programs (e.g., transcranial direct current stimulation, and exercise intervention). However, further investigation is required to support the use of either therapy option [3].

Ample research has been conducted to show the effect of exercise on the motor symptoms associated with PD and has shown benefits to muscular strength, endurance, gait, mobility, posture, and balance [8]. Yet, research on the effect of exercise on non-motor symptoms of PD, specifically fatigue, remains limited and demands more attention. The purpose of this systematic review was to evaluate the effects of exercise on fatigue in people with PD.

2. Methods

2.1. Data Sources and Searches

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9]. Systematic searches for pertinent articles available in English were conducted in the electronic MEDLINE, PubMed, CINAHL, and EMBASE. Search terms included Parkinson's disease (Parkinson's disease, Parkinson*, or PD*) AND fatigue (*exhaustion, tiredness, or lethargy*) AND (exercise OR physical therapy).

2.2. Eligibility Criteria and Study Selection

Eligible studies included in this review must have met the following criteria: (1) enrolled patients with idiopathic PD, (2) administered exercise program as treatment for PD-fatigue, (3) compared the exercise intervention with usual care or conventional exercise, (4) measured fatigue, (5) used a design of randomized controlled trial (RCT), and (6) scored at least 4 out of 10 on Physiotherapy Evidence Database (PEDro) scale [10]. After eliminating the duplicate articles from different databases, two independent reviewers (C.Z., E.B.) screened titles and abstracts of the studies for possible inclusion based on eligibility criteria. Full texts of potentially relevant studies were obtained and independently assessed to determine the status of eligibility. If disagreements arose, a third reviewer (R.P.) was consulted to make the final decisions.

2.3. Data Extraction and Quality Assessment

Data were extracted from the eligible studies by one reviewer (C.Z.) and cross-checked by a second independent reviewer (E.B.). Disagreements were resolved through discussion or by including a third reviewer (R.X.). The data items extracted from the included studies were: first author's name, study design, number of participants, intervention program, comparative program, outcome measures and the PEDro score of each included study as presented in (**Table 1**).

Table 1. Characteristics of the included studies.

Authors	Design # of subjects	Intervention	Comparison	Outcome Measure	PEDro scale
Atan *et al.* 2019	RCT N = 37	Body weight supported treadmill training	Unsupported treadmill training	Fatigue Impact Scale; Fatigue Severity Scale	7
Canning *et al.* 2012	RCT N = 20	Home-based treadmill walking	Usual care	Fatigue VAS	8
Cugusi *et al.* 2015	RCT N = 20	Nordic walking	Conventional care	Parkinson's Fatigue Scale	4
Dishtipour *et al.* 2015	RCT N = 11	LSVT BIG	General exercise program	Modified Fatigue Impact Scale	5

Continued

Granziera *et al.* 2020	RCT N = 32	Nordic walking	Walking	Parkinson's Fatigue Scale	6
Landers *et al.* 2019	RCT N = 27	High-intensity exercise boot camp	Low-intensity exercise program	Piper Fatigue Scale	6
Ortiz-Rubio *et al.* 2018	RCT N = 46	Resistance training	Usual care	Revised Piper Fatigue Scale	8
Ribas *et al.* 2017	RCT N = 20	Exergaming	Conventional exercise	Fatigue Severity Scale	7
Rios Romenets *et al.* 2019	RCT N = 33	Tango classes	Self-directed exercise	Fatigue Severity Scale	6
Solla *et al.* 2019	RCT N = 20	Sardinian folk dance	Usual care	Parkinson's Fatigue Scale	6
Uc *et al.* 2014	RCT N = 60	Continuous aerobic exercise	Interval aerobic exercise	Fatigue Severity Scale	6
Wu *et al.* 2021	RCT N = 98	Home-based exercise	Usual care	Fatigue Severity Scale	6

Abbreviation: LSVT BIG: Lee Silver Voice Training BIG; PEDro: Physiotherapy Evidence Database; RCT: randomized controlled trial.

Methodological quality of individual trials was assessed using the PEDro scale which contains 10 items evaluating internal and statistical validities and one assessing external validity of clinical trials. Only those items for internal and statistical validities participated in calculation of the scale. The greater the PEDro scale was, the higher quality the study design. The scores between 0 - 3 are considered "poor", 4 - 5 "fair", 6 - 8 "good", and 9 - 10 "excellent" quality in study designs. Reviewers (C.Z., E.B.) independently assessed methodological quality of included trials, with disagreements resolved by a third independent reviewer (B.Z.).

2.4. Data Syntheses and Analyses

There was a high degree of heterogeneity among the included trials. No meta-analysis was performed. Findings of included studies were qualitatively aggregated.

3. Results

3.1. Study Characteristics of Included Trials

Of the 603 studies identified in the original search, 29 were selected as potentially relevant studies and further assessed for their eligibility. After reviewing full text, 17 studies were deemed not eligible and thus excluded from this review study. Ultimately, twelve RCTs with a total of 422 patients were reviewed in this study (**Figure 1**). The included studies were published between 2012 and 2021, and trials were conducted in Italy, Australia, the United States, China, Sweden, Spain, Turkey, Brazil and other region.

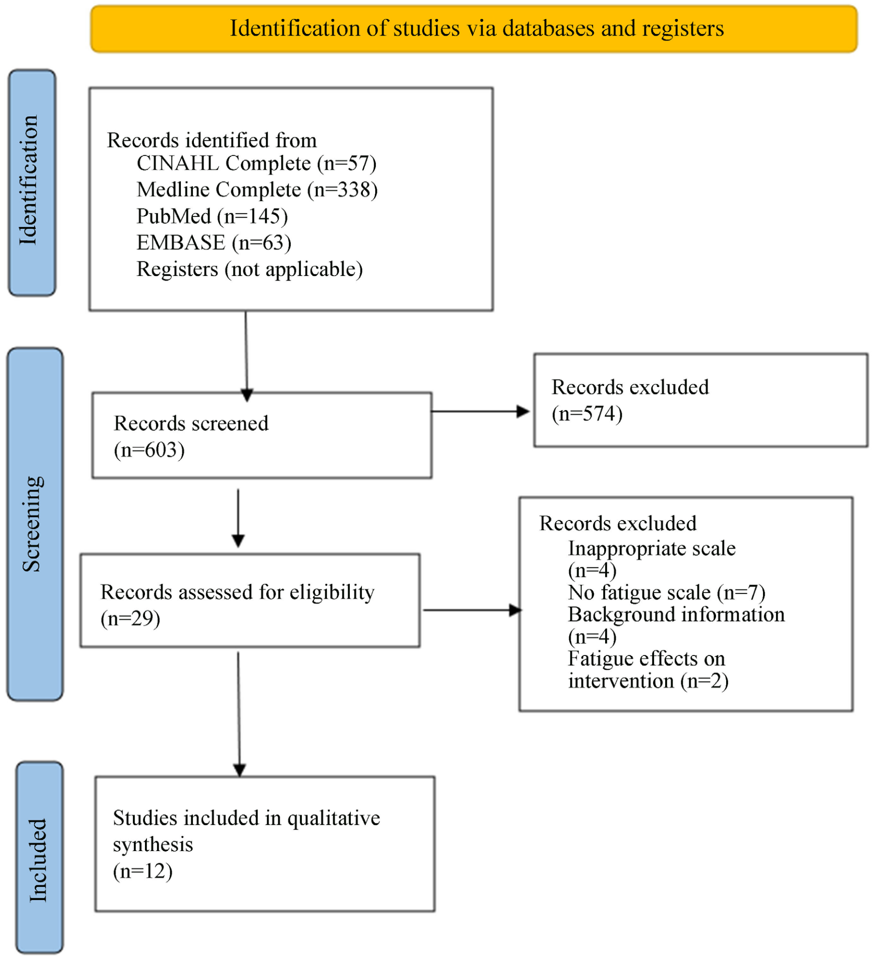

Figure 1. PRISMA flow diagram of the study selection.

This systematic review included various exercise interventions such as home-based exercise program, resistance training program, exergaming, etc. Outcome measure, fatigue, was assessed by fatigue visual analog scale (VAS), Parkinson Fatigue Scale (PFS), modified fatigue impact scale (MFIS), and others. **Table 1** lists the above and additional information about study characteristics of all included trials [11]-[22].

3.2. Quality Assessment

The PEDro scores were in the range from 4/10 to 8/10 with a mean of 6.3 (1.1), indicating a fair to strong methodological quality of the trials (**Table 1**).

3.3. Effect of Intervention

Out of the 12 included studies, eight trials reported significant improvement in fatigue in intervention group compared to control group ($p < 0.05$ to $p < 0.000$)

[11]-[14] [17] [18] [21] [22]. Those studies utilized home-based treadmill walking/home-based exercise, body weight supported treadmill training, LSVT BIG, Nordic walking, resistance training, and exergaming, and home-based exercise. In addition, borderline improvements in fatigue were found in the Tango dance group compared to control ($p = 0.058$) [19]. The other two studies, administering Nordic walking and high-intensity exercise boot camp, demonstrated significant reductions in fatigue from pre to post intervention ($p < 0.05$) [15] [16]. No significant change was observed in either between-subjects or within-subjects associated with Sardinian folk dance [20].

4. Discussion

This study systematically reviewed 12 trials consisting of various exercise interventions and their effects on fatigue in patients with PD. To our best knowledge, this is one of the first systematic reviews to examine the efficacy of exercise and physical therapy on PD-fatigue. The findings of this study showed that various forms of exercises can be effective in managing fatigue experienced by patients with PD compared to usual and conventional care.

In four trials showing insignificant between-group differences, three studies included active comparators rather than usual care [15] [16] [19]. In addition, the sample size was relatively small in those trials [15] [16] [19] [20]. The combined factors might explain the findings obtained from those studies.

In recent years, an aggregation of research revealed that exercise induced changes in protein concentration of the brain-derived neurotrophic factor (BDNF) [23]. BDNF plays a role in neuroplasticity and neurogenesis which improve and maintain cognitive function, memory, mood, and have positive effects on overall mental health [24] [25]. Ample evidence has indicated that physical exercise training increases BDNF blood levels in patients with PD [26] [27]. One of the studies included in this review also measured plasma BDNF and found significant increases in both intervention and control groups [16]. Exercise increases serum BDNF levels that were accompanied by reduced motor severity and improved motor symptoms in patients with PD [28]. Improved motor function is expected to increase physical activity level in this patient population. This might have contributed to reducing fatigue as research showed significant association of increase physical activity with reduced fatigue [29]. And exercise has been observed to increase dopamine D2 receptor expression, brain activation and functional connectivity and enhanced neuroplasticity in patients with PD [30] [31].

PD related fatigue may be associated with striatal and limbic serotonergic dysfunction. Pavese *et al.* [32] compared patients having fatigue with those without fatigue and found significantly reduced levels of serotonin transporter binding within the basal ganglia and limbic structures. Similar findings were also reported in animal studies that showed increased releases and synthesis of serotonin caused by increased firing rates of serotonin neurons after increasing motor activity in rats [33]. Tryptophan levels (*i.e.*, a precursor for serotonin) have been observed to rise during exercise on rats [34]. A higher amount of this precursor can lead to a subsequential rise in serotonin synthesis during and after exercise. Based on these studies, it is plausible to infer that exercise may be an effective strategy to increase levels of serotonin in the basal ganglia and limbic structures of the brain and help to relieve symptoms of fatigue experienced in patients with PD.

Besides exercise intervention, non-pharmacologic treatments of symptoms in Parkinson's disease also include non-invasive brain stimulation such as transcranial direct current stimulation (tDCS). Research has shown that tDCS can modulate functional connectivity of the cortico-striatal and thalamo-cortical circuits in the human brain and enhance neuroplasticity in patients with neurological disorders such as PD [35]-[38]. Both motor and cognitive function improved in people with PD following applications of tDCS to the motor cortex while brain stimulation was administered a stand-alone and an adjunctive therapy [36]. Kaski *et al.* [39] found that tDCS with concurrent physical training increased gait velocity and improved balance, with a stronger effect than physical training alone. Future research is warranted to explore efficacy of combining tDCS with physical therapy in management in PD-fatigue.

This systematic review is subject to a few limitations. The sample size is relatively small. The participants included only individuals in the early stages of PD, and were excluded if they exhibited motor fluctuations, dyskinesias, or cognitive decline that are common signs and symptoms associated with progression of the disease process, thereby limiting generalizability beyond the investigated patient group. Future studies using larger sample sizes and examining individuals at advanced stages of PD are needed to investigate the impact of exercise on all stages of the disease process. Another limitation was a lack of follow-up with participants post-intervention in many of the included studies. Of the studies that did include a follow up period, duration was short and could not adequately assess the retaining effects. The long-term effects of the impact of exercise on PD-fatigue requires further research.

5. Conclusion

All interventions, except for dance, showed improvement in fatigue, suggesting that exercise is effective for managing PD-fatigue. More research is needed to determine the optimal frequency, duration and intensity of exercise needed to produce substantial and long-term effects in treatment of fatigue for patients with PD.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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