PRINCIPLES AND PRACTICE OF CLINICAL RESEARCH
A Global Journal of Clinical Research

Advances of Research in Exercise Training for Parkinson's Disease: A Standard Reporting of An Exercise Protocol According to the Consensus on Exercise Reporting Template (CERT)

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Introduction

Parkinson's disease (PD) is the second most common progressive neurodegenerative disorder, and its prevalence is projected to rise from 6.2 million in 2015 to over 12 million people by the year 2040 (Dorsey and Bloem, 2018). The available medications for PD are symptomatic and act to improve the motor symptoms related to the dopamine deficit in the substantia nigra neurons. Therefore, exercise protocols have been proposed as interventions that could decrease the risk of developing PD, modify the progression of the disease, or attenuate the symptoms caused by PD.

Investigating modifiable protective/risk factors for PD, Belvisi et al. (2020) reviewed longitudinal studies. They found six prospective cohorts, five indicating the protective effect of physical activity against PD. These studies were based on 43,368 to 143,325 participants followed up for 9 to 12 years and identified between 286 and 767 PD individuals and reported a range of PD risk reduction between 50 to 30% (RR=0.50 to 0.70). One prospective study did not find the same result, and according to the authors, it was probably because of the lower number of participants and PD diagnosis rate.

Previous studies that evaluated the functional connectivity by the MRI in this population related to reduced connectivity in the supplementary motor area (Agosta et al., 2014), posterior putamen (Tessitore et al., 2019), and within the basal ganglia network (Rolinski et al. 2015; Szewczyk-Krolikowski et al. 2014). Moreover, other studies reported increased connectivity in the primary motor cortex and cerebellum and disrupted connectivity between the cerebellum and sensory-motor network (Wu et al. 2011), interpreted as a compensatory mechanism to maintain motor function. In this regard, exercise has been proposed as a modification of disease therapy. A recent systematic conducted by Li et al. (2023) included forty-nine trials, and the authors suggested that exercise promotes neuroplasticity by improving activation and network connectivity or by improving the efficiency of compensatory networks, effects indicative of attenuating PD progression. Besides that, other studies have shown that exercise increases serum brain-derived neurotrophic factor levels and decreases inflammation in PD patients (Zoladz et al., 2014; Frazzitta et al., 2014; Marusiak et al., 2015).

In this context, Amara et al. (2019) conducted a case-control study for four years to investigate the relationship between levels of physical activity and the progression of motor and non-motor symptoms in individuals in the early stage who are not yet taking prescribed PD-specific medications. The authors observed no differences in the self-reported physical activity of the cases and controls. Still, activity levels decreased significantly over the course of the study in the PD participants. They also found that higher self-reported levels of physical activity were associated with less progression of motor symptoms, postural instability/gait disorder phenotype, activ-

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Received: January 3, 2024 **Accepted:** March 5, 2024
Published: May 23, 2024
Editor: Alma Sanchez Jimenez
Reviewers: Juan Antonio Valverde-Espinoza, Thaila P. Schmidt, Augusto José Mendes, Nury Tatiana Rincon
Keywords: Parkinson's disease, exercise
DOI: http://dx.doi.org/10.21801/ppcrj.2024.101.9

ities of daily living, cognitive decline, depression, anxiety, and sleep disturbances. Therefore, strategies to increase physical activity levels in early PD could potentially modify the disease course.

The exercise also has been recommended as a supplementary approach in treating Parkinson's disease (PD), and various studies have examined its impact on diverse outcomes. The term "therapeutic exercise" in the PD context is ambiguous, covering various variables such as the type of exercise, dosage, and delivery method. These factors play a crucial role in influencing the clinical effectiveness of exercise and the overall success of the treatment. The ideal prescription for exercise in PD varies based on individual patient characteristics, including age, weight, baseline fitness, PD severity, risk of falls, and any accompanying health conditions.

Additionally, crafting a suitable exercise prescription is essential not only for maximizing improvements in motor and non-motor symptoms but also for enhancing adherence to the exercise. However, the programs described in the literature vary depending on frequency, intensity, duration, and type of exercise, which makes it difficult to determine and design the best exercise program for PD patients. Despite the exercise's known protective and modifier effects, a consensus on the optimal dosage has yet to be reached (Cui et al., 2023). Therefore, there is still a gap in translating exercise protocols to evidence-based clinical practice in PD. To help advance this limitation, we are proposing an example of a protocol to demonstrate how it could be described in future randomized clinical trials.

Material and Methods

The proposed interventional exercise protocol was prepared based on clinical practice guidelines from the American Physical Therapy Association (Osborne et al., 2021) and other randomized clinical trials and in accordance with the Consensus on Exercise Reporting Template (CERT) which comprises 16 items divided into 7 domains: what (materials); who (provider); how (delivery); where (location); when, how much (dosage); tailoring (what, how); and how well (compliance/planned and actual) (Slade et al., 2016). Furthermore, the CERT recommended that the authors report the adverse events, assess the adherence to the exercise intervention, and describe the extent to which the intervention was delivered as planned. If an item of the Consensus is not applicable, the reasons should be stated.

Results

What: Materials

The required materials will be 1 step, 8 cones, 2 standard chairs, a 10-meter walking space, a wall, and a standard treadmill. As part of the protocol, all participants will wear a safety belt, which one of the therapists will hold during the exercises to prevent falls.

What: Procedures

This protocol is aimed at patients with PD in the first to fourth Hoehn and Yahr stages during the "on" medication phase. It consists of the following components: warm-up, balance exercises, gait exercises, and relaxation. The exercise protocol was divided into A (for individuals in stages 1 to 3) and B (for individuals in stage 4), as presented in Table 1. It will not have any home program or non-exercise component. Moreover, the participants will be requested not to make any significant lifestyle or exercise practice changes during the study.

Who: Provided

The proposed exercise training was designed to be delivered by two physical therapists. They had ten years of clinical experience with neurological disorders. Balance and gait training may be more effective when administered under close supervision of a physical therapist.

How: Method of delivery

The exercises will be performed in person, individually, and supervised by physical therapists.

Where: Location

The proposed exercise protocol focuses on gait and postural stability training in the context of an outpatient clinic.

When and how much: Timing and dosage

Each session will take 20 minutes and will be provided 5 times per week (100 minutes) over the two weeks (a total of 10 sessions). The number of repetitions, sets, and duration of the exercises are presented in Table 1.

Tailoring: What and how

The balance and gait exercises will be progressed

Component	Parameters (FITT)	Exercises	Instructions	Materials	Progression
Warm up					
	F: 5 days/week **I**: ROM limit or tolerable discomfort **T**: static stretching **T**: 1 min / 4 x 15 s	Whole body stretch forward	Sit in a comfortable position. Please reach both arms to the ceiling as far as you can safely and comfortably go. Keep this position for 10 seconds then bend forward reaching both arms towards the floor as far as you can safely and comfortably go. Keep this position for 5 seconds.	Standard chair	None
	F: 5 days/week **I**: as high as possible **T**: pumping **T**: 1 min / 2 x 10	Toe raise	Stand with your feet shoulder width apart, your knee straight in an upright posture in front of the wall and rise in your toes as high as you can safely and comfortably go. Hold this position for 3 seconds then you can slowly return your heels to the floor.	Wall	None
	F: 5 days/week **I**: self- selected velocity, big movements **T**: walking **T**: 1 min / 4 x 15 s approximately	Warm-up walk	Walk forward down the hallway with exaggerated arm swing and big steps at a safely accelerated pace.	10-meter walking space	None
Balance					
Group A	**F**: 5 days/week **I**: change direction as quick as possible **T**: balance training **T**: 4 min / 1 min each direction approximately	Walking with changing in directions	Walk as safely as possible and at a speed that is quick to you. Practice taking large steps in different directions responding quickly to a verbal cue to change direction. First, the patient will be required to go forward or backward. Then, they will go to the right or left.	10-meter walking space	The therapist will change the verbal cue in a shorter interval of time.
	F: 5 days/week **I**: comfortable and safe speed **T**: balance training **T**: 5 min/ 2 sets x 10 reps (each side - left/right)	Step and reaching	Climb on step as safely as possible and at a speed that is comfortable to you, and alternate reaching your arm across midline to tap therapist shoulder; e.g. climb with right foot, right arm reaches to tap therapist right shoulder. Return to the floor.	Step	The participant will be required to switch arms and legs after each repetition.

Table 1: *Description of the proposal exercise training.*

Group B	**F**: 5 days/week **I**: comfortable and safe speed **T**: balance training **T**: 3 min / tandem 30 s each side (left/right) and walking for 2 min	Tandem standing and walking	Tandem standing: Place one foot in front of the other so that the heel of the forward foot touches the toes of the rear foot. As long as you feel safe, try to stand in this position for 30 secs. Tandem walking: Walk as safely as possible and at a speed that is comfortable to you along the line as if you were on a tightrope.	Wall and 10-meter walking space	Tandem standing will be performed with eyes closed and the walking heel-to-toe (the heel of one foot touching the toes of the other foot).
	F: 5 days/week **I**: comfortable and safe speed **T**: balance training **T**: 5 min/ 2 sets x 10 reps (each side - left/right)	Step	Climb on and out on step with one leg each time as safely as possible and at a speed that is comfortable to you.	Step	The participant will be required to switch legs after each repetition. The therapist can hold the patient's hands in front of them, if necessary.
Gait					
Group A	**F**: 5 days/week **I**: comfortable and safe speed **T**: gait training **T**: Approximately 2 min/ repeat the circuit 2 times	Multidirectional stepping and transitions	From sitting, stand up and walk down the course circuit, turn around between the cones and sit down in the chair at the end of the circuit. Then, repeat the course, return to the first chair and sit down. Please walk as safely as possible and at a speed that is comfortable to you. Sit-to-stand 3 times on each chair.	2 standard chairs and 8 cones	The therapist will increase the number of repetitions for sit-to-stand to 5 times.
	F: 5 days/week **I**: self- selected velocity **T**: gait training **T**: 6 min	Treadmill training	Step up onto the treadmill facing the computer display without holding the handrails. The therapist will start the treadmill at a slow time, and you will start walking carefully towards a fast but safe pace with big steps. The velocity will be self-selected as the focus is on quality and length of steps.	Treadmill	The participant will cross obstacles (cones) during gait training on the treadmill. One of the therapists will stand behind the patient holding the safety belt.
Group B	Approximately 2 min/ repeat the circuit 2 times.	Functional walk	Walk as safely as possible and at a speed that is comfortable to you and follow the therapist's commands to turn your head and scan your gaze (up, down, left, right).	10-meter walking space	The therapist will change the verbal cue in a shorter interval of time.
	F: 5 days/week **I**: 1 min low speed and 5 min of self-selected velocity **T**: gait training **T**: 6 min	Treadmill training	Step up onto the treadmill facing the computer display and hold the handrails. The therapist will start the treadmill at a slow time, and you will start walking carefully towards a comfortable, rhythmic and safe pace with big steps.	Treadmill	The participant will cross small obstacles (cones) during the 3 final minutes on the treadmill. One of the therapists will stand behind the patient holding the safety belt.
Relaxation					
	F: 5 days/week **I**: - **T**: breathing **T**: 1 min	Breathing exercises	Sitting, place your hands comfortably on the arm rests. Take inhalation comfortably through nose and exhalation through mouth with closed eyes. Repeat this breathing cycle 10 times.	Standard chair	None

F: frequency; I: intensity; T: type; T: time; ROM: range of motion; Min: minutes; S: seconds; Reps: repetitions.

Table 1: *(Continued) Description of the proposal exercise training.*

at the beginning of the second week, according to Hoehn and Yahr stages (protocols A and B), as it considers the postural stability and the ability to walk and stand without assistance. The difficulty of the exercises will be increased by delivering the verbal cue in a shorter interval of time, raising the repetition number, adding obstacles during the gait training on the treadmill, alternating legs and arms, closing eyes, and walking heel-to-toe. The detailed progression for each exercise is described in Table 1.

Discussion

Despite the available evidence about the benefits of exercise training in the prevention and progression of PD, exercise programs are often poorly reported in the studies. Therefore, the main objective of this communication is to present how an exercise protocol could be described in future clinical trials, taking as an example a physical therapy protocol focused on gait and balance, which is performed combined with transcranial direct current stimulation in individuals with PD at Spaulding Neuromodulation Center in an ongoing clinical trial. Just to our knowledge, this protocol lasts two weeks (5 times/week) because of the combination with tDCS (not reported here). However, it is important to highlight that exercise practice should be regular in this population, as PD is a progressive and neurodegenerative disease.

Poor reporting of interventions interferes with the quality assessment, knowledge translation, and effective implementation into clinical practice. Consequently, it may be unclear how exercise should be delivered (Hansford et al., 2022). For instance, if any exercise was shown to improve a functional outcome in individuals with PD, it is important to know the intervention parameters that led to this improvement. Therefore, evidence synthesis is also impaired by poor reporting. Previous systematic reviews lacked comparative studies of exercise parameters, then exercise comparators and interventions cannot be pooled in meta-analysis because the treatment parameters are unclear.

In this way, even the available guidelines that strongly recommend the exercise for PD are unable to detail which and how parameters should be prescribed (Osborne et al., 2021).

The considerable variability in exercise dosage for PD could stem from influences within health systems, such as funding models and available resources, or from provider preferences, including variations in facility-based, regional, or national practices. Additionally, disparities within the evidence base may arise from differences in study design, participant demographics, access to facilities, and the level of supervision provided. The absence of a consensus on the optimal exercise dosage may partly be attributed to insufficient reporting of interventions in PD research studies. Frequently, rehabilitation studies on exercise interventions lack the necessary level of detail to determine the exercise dosage and its impact on health outcomes (Burgess et al., 2021). The reproducibility of effective interventions relies on accurate and comprehensive descriptions of the intervention content and delivery (Cotterill et al., 2018). Moreover, the absence of a complete published description impedes other researchers from building upon the findings, leaving clinicians uncertain about how to effectively implement such interventions (Hoffmann et al., 2014).

Finally, the use of the outcomes measures performing an exercise protocol is important to measure its effectiveness. Therefore, here are some instruments recommended in the European (Domingos et al., 2021) and American (Osborne et al., 2021) guidelines to assess the gait and balance in individuals with PD: Functional Gait Assessment, Timed Up and Go, Activities-Specific Balance Confidence Scale, Mini-BESTest and Berg Balance Test.

Conclusion

The knowledge about the effects of exercise on the prevention, progression, and treatment of PD has advanced; however, one of the main challenges is understanding what type and dose of exercise is better for optimizing different outcomes in this population. Therefore, high-quality reporting of the protocols is needed to improve their translation from research to clinical practice. Additionally, journals can encourage the authors to improve the reporting quality of exercise protocols, requiring the inclusion of a checklist as part of the submission process in a way that is similar to this protocol description.

Funding

FF is supported by NIH grants (1R01AT009491–01A1 and 1R01HD082302–01A1).

Conflicts of Interest

The authors declare no conflict of interest.

References

- Dorsey, ER (2018, Jan 1). The Parkinson pandemic- a call to action. JAMA Neurol, p.75(1): 9–10.
- Belvisi, D (2020, Feb 1). Modifiable risk and protective factors in disease development, progression and clinical subtypes of Parkinson's

disease: What do prospective studies suggest? Neurobiol Dis, p. 134:104671.
- Agosta F (2014, Nov 1). Cortico-striatal-thalamic network functional connectivity in hemiparkinsonism. Neurobiol. Aging, p.35(11):2592–2602.
- Tessitore A (2019). Functional connectivity signatures of Parkinson's disease. J. Park. Dis, p.9(4): 637–652.
- Rolinski, M (2015, Apr 9). Aberrant functional connectivity within the basal ganglia of patients with Parkinson's disease. Neuroimage Clin, p.8:126–132.
- Szewczyk-Krolikowski K (2014, Jul 5). Functional connectivity in the basal ganglia network differentiates PD patients from controls. Neurology 83: 208–214.
- Wu T (2011, Sep 1). Functional connectivity of cortical motor areas in the resting state in Parkinson's disease. Hum. Brain Mapp. 32(9):1443–1457.
- Li, JA (2023, May 1). Does exercise attenuate disease progression in people with Parkinson's disease? A systematic review with meta-analyses. Neurorehabil Neural Repair, p.37(5):328-352.
- Zoladz, JA (2014, Jun 1). Moderate-intensity interval training increases serum brain-derived neurotrophic factor levels and decreases inflammation in Parkinson's disease patients. J Physiol Pharmacol, p.65(3):441-448.
- Frazzitta G (2014, Feb 1). Intensive rehabilitation increases BDNF serum levels in Parkinsonian patients: a randomized study. Neurorehabil Neural Repair, p.28(2):163-8.
- Marusiak J (2015, Apr 1). Interval training-induced alleviation of rigidity and hypertonia in patients with Parkinson's disease is accompanied by increased basal serum brain-derived neurotrophic factor. J Rehabil Med, p.47(4):372-5.
- Amara, AW (2019, Apr 1). Self-reported physical activity levels and clinical progression in early Parkinson's disease. Parkinsonism Relat. Disord, 61(18):118–125.
- Cui, W (2023, Aug 2). The effects of exercise dose on patients with Parkinson's disease: a systematic review and meta-analysis of randomized controlled trials. J Neurol, 270(11):5327-5343.
- Osborne, JA (2021, Dec 28). Physical therapist management of Parkinson disease: A clinical practice guideline from the American Physical Therapy Association. Phys Ther, p.102(8):pzac098.
- Slade, SC (2016, Oct 5). Consensus on Exercise Reporting Template (CERT): Explanation and Elaboration Statement. Br J Sports Med, 50:1428–1437.
- Hansford, HJ (2022, Jun 1). If exercise is medicine, why don't we know the dose? An overview of systematic reviews assessing reporting quality of exercise interventions in health and disease. Br J Sports Med, 56(12):692–700.
- Burgees, LC (2021, Jun 7). The quality of intervention reporting in trials of therapeutic exercise for hip osteoarthritis: a secondary analysis of a systematic review. Trials, 22(1):388.
- Cotterill, S (2018, Jan 18). Getting messier with TIDieR: embracing context and complexity in intervention reporting. BMC Med Res Methodol, 18(1):12.
- Hoffmann, TC (2014, Mar 7). Better reporting of interventions: Template for Intervention Description and Replication (TIDieR) checklist and guide. BMJ, 348:g1687.
- Domingos JM (2021, Jan 1). The European Physiotherapy Guideline for Parkinson's Disease: translation for non-English speaking countries. J Neurol, p.268(1):214-218.