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Effects of Endurance Exercise Training on The Motor and Non-Motor Features of Parkinson's Disease: A Review

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Abstract.
Background: Despite the benefits of medications and surgical interventions for Parkinson's disease (PD), these treatments are not without complications and neuroprotective strategies are still lacking. Therefore, there is a need for effective alternative approaches to treat motor and non-motor symptoms in PD. During the last decade, several studies have investigated endurance exercise training as a potential treatment for individuals with PD.
Objective: This paper reviews the therapeutically beneficial effects of endurance exercise training on motor and non-motor symptoms in PD.
Methods: First, we performed a systematic review of the literature on the effects of endurance exercise training on motor and non-motor signs of parkinsonism, functional outcomes including gait, balance and mobility, depression and fatigue, quality of life and perceived patient improvement, cardiorespiratory function, neurophysiological measures, and motor control measures in PD. Second we performed a meta-analysis on the motor section of the UPDRS. Then, we focused on several important factors to consider when prescribing endurance exercise training in PD such as intensity, duration, frequency, specificity and type of exercise. In addition, we identified current knowledge gaps regarding endurance exercise training in PD and made suggestions for future research.
Results: A total of eight randomized controlled trials met the inclusion criteria and were reviewed. This systematic review synthesizes evidence that endurance exercise training at a sufficiently high level enhances cardiorespiratory capacity and endurance by improving VO_2 max and gait in moderately to mildly affected individuals with PD. However, there is not yet a proven effect of endurance exercise training on specific features of PD such as motor signs of parkinsonism.
Conclusion: Endurance exercise training improves physical conditioning in PD patients; however, to date, there is insufficient evidence to include endurance exercise training as a specific treatment for PD. There is a need for well-designed large-scale randomized controlled trials to confirm benefits and safety of endurance exercise training in PD and to explore potential benefits on the motor and non-motor signs of PD.

Keywords: Parkinson's disease, endurance, exercise, aerobic exercise, motor activity, gait, balance

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INTRODUCTION

Parkinson's disease (PD) is a clinical syndrome characterized by the gradual onset of motor symptoms such as bradykinesia, rigidity, tremor, gait dysfunction and postural instability, as well as non-motor symptoms such as cognitive impairment and mood disorders among others. PD is related to progressive nigrostriatal dopaminergic pathway degeneration and symptoms tend to worsen with time, leading to a general decrease in activity and an altered quality of life with increased risk of falling, immobility, and cognitive impairment [1, 2]. To date, there is no neuroprotective strategy available in PD. There is a need for new therapies that can reduce the functional and cognitive declines seen with advancing disease, and slow disease progression. Epidemiological studies have supported a link between moderate to vigorous exercise habits in midlife and the reduced risk of later developing PD [3, 4]. In a large population of American older adults, a higher level of moderate to vigorous physical activity between ages 35 to 39 or in the past 10 years was associated with a lower risk of developing PD [3]. The same authors demonstrated an association between higher moderate to vigorous physical activity and a lower risk of PD in both men and women in a meta-analysis of prospective studies [3]. There is also increasing evidence, from animal models of PD to clinical trials, supporting exercise-induced improvement for motor and non-motor function in PD [5–8]. The underlying mechanisms for these potential effects are not fully understood yet. Exercise could be beneficial for the brain through several hypothetical mechanisms. In healthy young and older adults, it has been proposed than exercise could increase angiogenesis, neuroplasticity, neurogenesis, neuroprotection, anti-inflammatory effect, improve mitochondrial function and oxidative stress, increase brain connectivity and increase level of neurotrophic factors such as brain-derived neurotrophic factor [5, 9, 10]. There is no clinical evidence that patients with PD would benefit more from exercise than healthy older adults. Exercise may have the same beneficial effects in PD as in healthy people, and a recent review suggested that exercise may have the potential to improve motor learning and behavioral performance in PD by promoting neuroplasticity and restoring basal ganglia circuitry [5].

Several modes of exercise have been investigated in PD including resistance exercise, balance and gait training, and endurance exercise. Recent reviews have suggested that resistance exercise can be effective and worthwhile in people with mild to moderate PD in order to improve strength, functional outcomes such as walking capacity and potentially non-motor symptoms of the disease [8, 11]. Interventions that target balance and gait such as Tai chi or dance training have been found to reduce balance impairments, improve functional capacity and reduce falls in patients with mild-to-moderate PD [12–14]. Several studies have investigated the effects of endurance training on the motor and non-motor features of PD [15–22]. However, results have not been consistent across studies, and it is unclear if improving endurance capacity in individuals with PD can also improve the clinical hallmarks of PD such as the motor signs of parkinsonism, functional performance, non-motor symptoms or quality of life. Thus, this review will synthesize the literature that has examined the effect of endurance (i.e. aerobic) exercise on the motor and non-motor signs of PD, as well as functional performance and quality of life of individuals with PD.

Endurance exercise training can be defined as an exercise that improves cardiorespiratory power and cardiorespiratory endurance [23, 24]. Cardiorespiratory power is measured in terms of maximal oxygen uptake or VO_2 max (the gold standard objective physiological measure of aerobic power determined during a cardiovascular endurance test). Cardiorespiratory endurance is a function of how long an individual can perform an activity using large muscle groups and is correlated with VO_2 max. Endurance training is expected to improve cardiorespiratory endurance if the person is training at 40% to 85% of VO_2 max [25]. Endurance is associated with exercise intensity, which is frequently measured with absolute heart rate (HR), relative HR expressed as a % of maximum (%HRmax), or metabolic equivalents (METs). Based on a linear relationship between VO_2 and HR, the American College of Sports Medicine recommends that training for improved cardiorespiratory endurance should be performed at a minimum of 55% to 65% HRmax, depending on the initial fitness of the individual, and can be performed up to 90% HRmax [25, 26]. A linear relationship between VO_2 and HR has also been shown in individuals with PD during treadmill walking between speeds of 1.0 to 3.5 miles per hour (Fig. 1) [27]. Although HR and VO_2 were higher in PD patients than age-matched healthy controls at all walking speeds (Fig. 1) [27], VO_2 max of PD patients has been shown to be no different from that of controls [27, 28]. In clinical trials, moderate intensity endurance activities are frequently defined as 60 to 75% HRmax and high-intensity endurance activities are frequently defined as 75 to 90% HRmax [24, 29]. In contrast,

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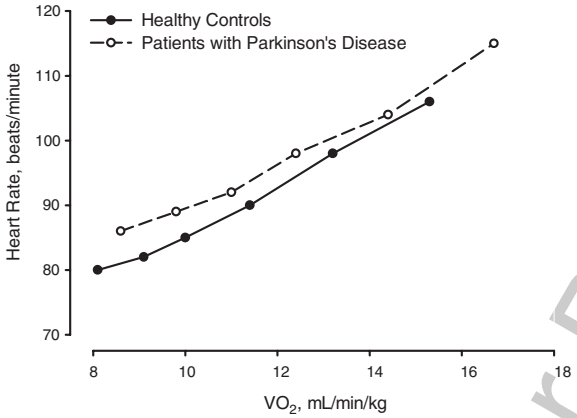


Fig. 1. Relation between VO_2 and HR during treadmill walking at speeds ranging from 1.0 to 3.5 miles per hour in patients with Parkinson's disease and in age- and sex-matched healthy controls. Adapted from: Christiansen et al. [29].

light-intensity activities have a relative intensity less than 60% HRmax and do not typically generate a measurable improvement in cardiorespiratory endurance [24, 29]. Thus, this review will focus on studies that utilized endurance exercise intensities greater than 60% HRmax.

In this paper, we will first conduct a systematic literature review of the current clinical evidence for endurance exercise-induced changes in PD, restricting the review to class I and II studies according to the classification of level of evidence of the American Academy of Neurology [30]. We will focus on seven types of outcomes: motor signs of parkinsonism, functional outcomes, depression and fatigue, quality of life and patient perceived improvement, physiological measures (cardiorespiratory function, neurophysiological measures, and motor control measures), as well as adverse events and patient safety. We will then conduct a meta-analysis on the effect of endurance exercise training on motor disability in PD assessed by the UPDRS motor subscale. We will discuss the results of our review, and consider factors that are important in prescribing exercise for individuals with PD. Finally, we will identify knowledge gaps for endurance exercise training prescription in PD and make suggestions for future research.

METHODS

Search strategy

The following electronic databases were searched: Pubmed (1990 to August 1st 2014), Cochrane Library (1990 to August 1st 2014), Embase (1990 to August 1st 2014) and Google Scholar (1990 to August 1st 2014). In addition, citation tracking was used to identify reference lists from included studies.

A study was included in the present review if it met the following criteria: 1. The target population was patients with idiopathic PD according to the UK Parkinson's Disease Society Brain Bank criteria [31]; 2. Endurance exercise training as previously defined was the intervention evaluated for at least one of the groups tested; 3. The effects of treatment intervention were tested as the primary outcome; 4. The effects of endurance training were compared with control or comparison groups, including other forms of physical activity or exercise; 5. The paper was available in English; 6. The study was a class I or II level of evidence according to the American Academy of Neurology classification of level of evidence [30]; and 7. The study was available as of August 1, 2014. A study was excluded if: 1. Endurance exercise training as defined previously was used as an assessment tool rather than as a therapeutic intervention tool; 2. The study had a class III or IV level of evidence according to the classification of level of evidence [30]; 3. Animals were studied.

We also conducted a meta-analysis on the effect of endurance exercise training on motor disability in PD assessed by the UPDRS motor subscale. We first included studies that provided baseline and post-intervention UPRDS motor scores to assess within group differences (class IV level of evidence). Then we included studies that compared endurance exercise training to a control group (normal activity level or other type of exercise training) (class II level of evidence). The meta-analysis was con-

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ducted using Review Manager (RevMan) (Version 5.0, Copenhagen, Denmark) [32]. When the change-from-baseline standard deviation was not available, we used a correlation coefficient from another study that provided change-from-baseline standard deviation [33]. Because of the high variability and the lack of consistency in the choice of outcomes between studies, we chose not to perform a meta-analysis for the other outcomes.

RESULTS

A total of eight randomized controlled trials met the inclusion criteria and were reviewed [15–22]. Table 1 summarizes the principal characteristics and the main results of these eight studies.

Intervention

All studies investigated endurance exercise training with a target HR >60% HRmax for at least one group, with the target exercise intensity between 60% and 85% HRmax. Three studies evaluated an endurance exercise intervention against a no-exercise control group [19, 21, 22], two studies compared three different types of intervention, one of which was a non-endurance exercise intervention [15, 16], two studies compared two different endurance exercise interventions [15, 17], and two studies compared endurance exercise training with another exercise intervention and a control group with a normal activity level [18, 20]. Across all of the studies, the interventions were clinically heterogeneous with regards to the frequency and duration of exercise being undertaken and duration of intervention: between 60 and 180 minutes per week for 6 to 64 weeks. The studies were also heterogeneous with regards to the exercise interventions: one study used body weight-supported treadmill walking [20], two studies used non-body weight-supported treadmill training [15, 19], one study used treadmill walking and cycling [21], one study used walking activities accompanied by music [22], one study used treadmill, bicycle or elliptical trainer [16], one study used a stationary tandem bicycle [17], and one study used a semi-recumbent elliptical device [18]. All studies reported supervision for the exercise intervention although one study did not report details of who delivered the intervention or the setting [21]. Patients trained under direct supervision of exercise physiologists or physicians for each exercise session in seven studies [15, 17–22]. In the eighth study, endurance exercise training was supervised by an exercise trainer for each session for 4 months, and then monthly for 16 months total [16]. All endurance interventions took place within an outpatient setting, except for one study in which it was not defined [21]. All endurance interventions used an individual approach except for one study that used groups of four participants [18]. All studies included in this review except the study by Ridgel et al. examined the exercise-induced changes on individuals with PD in the on-medicated state. Exercise progression was also heterogeneous across studies. The duration of the exercise sessions was progressively increased in one study [21] and remained constant in seven studies [15–20, 22]. A period of training adaptation with progressive exercise intensity (increased target HR) occurred in three studies [15, 17, 22], while the target HR remained constant during the duration of the intervention in five studies [16, 18–21]. In studies with constant target HR throughout the duration of the intervention, parameters such as treadmill speed and incline or cycling device resistance were progressively increased in order to maintain the target HR within the prescribed range.

Participants

A total of 338 patients were included in the eight studies reported in this review and 307 patients completed their allocated intervention protocol. The number of screened patients was reported in two studies: 811 volunteers were contacted to select 121 patients for participation in one study [16] and 945 volunteers were contacted to select 67 patients for participation in the second [15]. The minimum number of participants with PD in a study was 8 [21], and the maximum was 121 divided across three exercise groups [16]. PD status was described using Hoehn and Yahr's (HY) measure of disease severity in 6 studies, and using the Unified Parkinson's Disease Rating Scale (UPDRS) motor score in 2 studies [17, 18]. Studies included PD patients at HY stages 1, 2 and 3. For the two studies that did not use the HY scale, all patients had a on medication UPDRS motor score lower than 35 in one study [18], and the mean off medication UPDRS motor score was 48.4 ± 12.7 for the forced endurance exercise group and 49.0 ± 15.4 for the voluntary endurance exercise group in the other study [17].

Outcomes

Motor signs of parkinsonism

Six studies examined the effects of endurance exercise training on motor functions in individuals with PD across several outcomes including the UPDRS total

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Table 1
Class I and II studies that examined the effects of endurance exercise in Parkinson's disease

Trial	Design	Intervention	Sample	Outcomes	Results	Limitations
Shulman et al. 2013 [15]	RCT	3 arms (1) High-intensity treadmill (HIT), 30 min, 70–80% HRreserve (approximately 75–85% HRmax), 3/w (2) Low intensity treadmill (LIT), 50 min, 40–50% HRreserve (approximately 55–65% HRmax), 3/w (3) Stretching and resistance exercises (SR), 3/w Duration of intervention: 12 w	67 PD, HY1-3, mild to moderate gait or balance impairment, MMSE >23 HIT: allocated 26, analyzed 23 LIT: allocated 26, analyzed 22 SR: allocated 28, analyzed 22	(a) Motor disability: UPDRS total, UPDRS-III. On-medication (b) Function: 10mWT, 6MWT – VO_2 max: HIT and LIT >SR (c) Depression and fatigue: BDI, 16-item Parkinson Fatigue Scale (d) QOL and self perceived improvement: PDQ-39, Falls Efficacy Scale, Schwab and England Activities of Daily Living Scale (e) Physiological measures: VO_2 max, 1-repetition maximum strength	Between-group differences: – VO_2 max: HIT and LIT >SR – Strength SR > HIT and LIT Within-group differences: – 6MWT: LIT (.001), SR (.019), HIT (.07) – VO_2 max: HIT (.003), LIT (.004), SR (.92) – UPDRS total: no change in any group; UPDRS-III SR (–3.5 pts. $p < 0.05$), LIT and HIT ($p > 0.05$) – No changes for any non motor outcomes, disability or home ambulatory	Design: lack of a non-exercise PD control group. Difference in duration of exercise between LIT and HIT so that it was not clear whether the difference between conditions was intensity or duration
Schenkman et al. 2012 [16]	RCT	3 arms (1) Flexibility/balance/ function (FBF), 5–7/w (2) Aerobic exercise (AE) using treadmill, bike, or elliptical trainer (65–80% HRmax for 30 min), 5–7/w (3) Home-based exercise (fitness counts = control) (C), 5–7/w Duration of intervention: 4, 10, and 16 mo	121 PD, HY1-3, MMSE>23. Allocated C 41, FBF 39 and AE 41 Completed the 16 mo follow-up: C 32, FBF 33, AE 31	(a) Motor disability: UPDRS total score, UPDRS-III. On-medication (b) Function: CS-PFP, FRT (c) Depression and fatigue: NA(d) QOL and self perceived improvement: PDQ-39 (e) Physiological measures: VO_2 max	Between-group differences: – 4mo: CS-PFP: FBF > C (.006); UPDRS-ADL: FBF > C (.029); VO_2 max: AE > C (.002) and AE > FBF (.001); no group difference in other outcomes – 10mo: VO_2 max: AE > FBF (.001); no group difference in other outcomes – 16mo: VO_2 max: AE > FBF (<.0001) et C (.0001); UPDRS-ADL: FBF > C (.041); no group difference in other outcomes Within-group differences: no significant differences for measured outcomes	Design: lack of no-exercise control group, data collected only ON medication
Ridgel et al. 2009 [17]	RCT	2 arms (1) Forced aerobic exercise (FE) with a trainer on a stationary tandem bicycle (pedaling rate 30% > preferred voluntary rate), 60–80% HRmax, 1h/sessions, 3/w, 8 w (2) Voluntary exercise (VE) group pedaled at their preferred rate, 60–80% HRmax, 1h/sessions, 3/w, 8 w Duration of intervention: 8 w, follow-up at 12 w	10 PD UPDRS-III (mean ± SD) FE=48.4 ± 12.7; VE = 49.0 ± 15.4 5FE, 5VE	(a) Motor disability: UPDRS-III. Off-medication (b) Function: bimanual dexterity task performances (c) Depression and fatigue: NA (d) QOL and self perceived improvement: NA (e) Physiological measures: VO_2 max	Between-group differences: – Cadence: FE > VE (.002) Within-group differences: – VO_2 max +17% and +11% for VE and FE-UPDRS-III +35% at 4w (.002) and similar to baseline at 8w (.09) for FE, no improvement for VE (>.17) – Bimanual dexterity task performances improved for FE (<.05) but not for VE (>.05)	Design: Small sample size, proof of concept study, no between-group statistical analysis for UPDRS and upper extremity functional outcomes; lack of no-exercise control group

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Table 1
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Trial	Design	Intervention	Sample	Outcomes	Results	Limitations
Sage et al. 2009 [18]	RCT	3 arms (1) SAFEx program: sensory attention focused exercise, 40–60 min, 3/w, 12w (2) Lower limb aerobic program (AE), 20 min, semi-recumbent elliptical device, 60–75% HRmax, 3/w, 12w (3) Controls (C): normal activity level Duration of intervention: 12 w	46 PD, UPDRS-III < 35 SAFEx 18, AE 13, C 15	(a) Motor disability: UPDRS-III. On-medication (b) Function: posture and gait (PG) score (total of UPDRS items 27–31), TUG, gait velocity, step length, and cadence (c) Depression and fatigue: NA (d) QOL and self perceived improvement: NA (e) Physiological measures: HR	Between-group differences: – UPDRS-III: SAFEx > C (<.001) – PG: SAFEx > C (<.054); – Step length: AE > SAFEx and C (<.03) Within-group differences: – SAFEx improved UPDRS-III (<.001), PG scores (<.01) and tended to improve TUG (.06) and double time support (.068) – AE improved step length (.019) and tended to improve gait velocity (.07) and TUG (.095); – Step length variability increased in C (.02)	Design: Small sample size
Kurtais et al. 2008 [19]	RCT	2 arms (1) Treadmill training (AE), 40 min/session, 3/w, 6 w, 70–80% HRmax (2) Control group (C): not further described Duration of intervention: 6 w	30 PD, without severe cognitive impairment. HY (mean ± SD) AE: HY 2.5 ± 0.7 C: HY 2.2 ± 0.8 Analyzed AE 12, C 12	(a) Motor disability: NA (b) Function: 20-m walking time, timed U-turn task, turning around a chair, climbing up and down a flight of stairs, arising from an armless chair, standing on one foot (c) Depression and fatigue: NA (d) QOL and self perceived improvement: NA (e) Physiological measures: VO_2 max, MET	Between-group differences: NA Within-group differences: – Improvement in all functional tests for AE (<.05), except standing on one foot for the left foot (.182) – AE improved in VO_2 max (.015) and MET (.008) – No changes for C (>.05) except for standing on one the right foot (.041)	Design: method of randomization not described, short follow-up time and small sample size, no analysis for between-group differences
Fisher et al. 2008 [20]	RCT	3 arms (1) High-intensity (HI): body weight supported treadmill walking (10% of the patient's body weight, and increased if necessary), up to 45 min/day, for 24 supervised sessions in 8 w, 75% HRmax (2) Low-intensity (LI): general or traditional physiotherapy, for 24 sessions in 8 w, 50% HRmax (3) No exercise (C): 6h education class over 8 w Duration of intervention: 8 w	30 PD, <3 y of evolution, HY1-2 HI 10, LI 10, C 10	(a) Motor disability: UPDRS total score, UPDRS-III. On-medication (b) Function: walking velocity, step length, stride length, step width, cadence, double-limb support time, hip, knee and ankle range of motion (c) Depression and fatigue: NA (d) QOL and self perceived improvement: NA (e) Physiological measures: VO_2 max, MET, CSP with TMS	Between-group differences: NA Within-group differences: – UPDRS total and motor: slightly improved for HI, LI, C – Gait measures improved for HI, LI and C but HI showed consistent improvement in most gait parameters – TMS: average increase in maximal CSP duration for the more and less affected hemisphere for HI but not for LI (decrease) or C (no change)	Design: small sample size, no statistical analysis for between-group differences

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Table 1
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Trial	Design	Intervention	Sample	Outcomes	Results	Limitations
Bergen et al. 2002 [21]	RCT	3 arms (1) Aerobic exercise (AE): cycling (up to 20 min and walking on the treadmill (up to 20 min), 60 to 70% HRmax, 3/w, 16 w (2) PD control group (PC): normal activity level (3) Healthy control group (HC): normal activity level Duration of intervention: 16 w	8 PD, HY2, and 6 HC AE 4, PC 4, HC 6	(a) Motor disability: NA (b) Function: MI, responses to visual and proprioceptive cues; simple flexion, simple extension, and a choice condition (flexion or extension) (c) Depression and fatigue: NA (d) QOL and self perceived improvement: NA (e) Physiological measures: VO_2 max	Between-group differences: – VO_2 max: AE > PC (.013) Within-group differences: – AE improved choice MI (.003) and simple MI (<.05) – MI times was faster for proprioceptive cues vs visual cues (.048) and for simple vs choice conditions (.003) – Simple and choice MI: pre-AE vs PC (.89), post-AE vs HC (.38)	Design: small sample size, randomization procedure not clear, effect of medication not discussed
Bridgewater et al. 1996 [22]	RCT	2 arms (1) Aerobic exercise (AE) (30 min of walking activities accompanied by music), 65–85% HRmax, 2/w for 12 w (2) Control group (C): normal activity level Duration of intervention: 12 w, follow-up at 16 w for 3 AE subjects	26 PD, HY1-3 AE 13, C 13	(a) Motor disability: WRS. On-medication (b) Function: NA (c) Depression and fatigue: LPDQ (d) QOL and self perceived improvement: HAP, NUDS (e) Physiological measures: HR, stress test duration	Between-group differences: – Stress test duration: AE > C (<.05) – WRS: AE vs C (<.05) – HAP: AE > C (<.05) – NUDS: AE > C (.023) – LPDQ: AE vs C (>.05) Within-group differences: – NUDS increased in AE (.051) an decreased in C (<.05) – LPDQ increased in AE (<.05)	Design: small sample size, randomization procedure not clear, only 3 AE subjects at 16w

AE: aerobic exercise group, BDI: Beck Depression Inventory, C: control, CSP: cortical silent period, CS-PFP: Continuous Scale—Physical Functional Performance Test, FRT: Functional Reach Test, HAP: Human Activity Profile, HIT: high intensity treadmill exercise, HR: heart rate, HY: Hoehn and Yahr scale, LIT: low intensity treadmill exercise, LPDQ: Levine-Pilowsky Depression Questionnaire, FE: forced exercise, MMSE: Mini Mental State Examination, mo: months, y: years, PG: posture and gait score (total of UPDRS items 27–31), PD: Parkinson's disease, PDQ-39: Parkinson Disease Questionnaire, RCT: randomized controlled trial, MET: metabolic equivalent task, MI: movement initiation, NA: not assessed, NUDS: Northwestern University Disability Scale, TUG: Timed Up and Go test, UPDRS: Unified Parkinson Disease Severity Rating Scale, VE: voluntary exercise, VO_2 max: maximum oxygen uptake, we: weeks, WRS: Webster Rating Scale, 6MWT: 6-minute walk test, 10mWT: 10-meter walk test.

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score [15, 16, 20], the UPDRS motor score [15, 18, 20], and the Webster Rating Scale (WRS) [22]. Each of the tools was specific for PD. In one study, UPDRS motor score was completed while patients were off anti-parkinsonian medication [17]. PD patients were tested on medication in the other studies [15, 16, 18–22]. Five studies did not find any significant changes in UPDRS total or motor score or in WRS with endurance exercise training [15, 16, 18, 20, 22]. Ridgel et al. found a statistically significant 35% (–12 points) improvement of the off medication UPDRS motor score in the forced endurance exercise group after 8 weeks of training ($p = 0.002$) (patients exercised with a trainer on a stationary tandem bicycle and pedaled at a rate 30% greater than their preferred voluntary rate) [17]. However, they argued that this improvement was due to the forced nature of exercise rather than to its aerobic component. Indeed, with the same intensity of 60 to 80% HRmax, the comparison exercise group, who pedaled at their preferred voluntary rate, did not show a significant improvement in the off medication UPDRS motor score ($p > 0.17$). Improvement in off medication UPDRS motor score in the forced exercise group was not statistically significant 4 weeks after training ended ($p = 0.09$) [17]. The meta-analysis comparing pre- and post-endurance exercise training UPDRS motor scores included 5 studies [15–18, 20]. This meta-analysis found no statistically significant improvement in motor disability following endurance exercise training (mean difference 1.85 [−0.20. 3.90]) (Fig. 2). When compared to a control group, there was no evidence that endurance exercise training improved motor disability in PD (mean difference: 0.85 [−1.11. 2.80]) (Fig. 2).

Physical performance: Gait, balance, and functional mobility

Four studies assessed gait velocity: one study involved training on a semi-recumbent elliptical device [18] and three studies of treadmill training [15, 19, 20]. Within group comparisons in all four studies supported trends or significant improvement in comfortable gait velocity (mean change 0.02–0.13 m/s, $p = 0.012$–0.16). Two of these studies also supported significant improvements in fast walking velocity following moderate to high intensity treadmill training (mean change 0.07 – 0.10 m/s, $p = 0.025$–0.049) [15, 20]. Two studies documented improvement in comfortable step length following endurance exercise training (mean change 4 – 4.65 cm, $p = 0.019$) [18, 20]. Secondary gait variables such as cadence, double support time, base of support, and step length variability did not significantly change following endurance exercise training on the semi-recumbent elliptical [18]. Cadence also did not appear to change following treadmill training [20]. In contrast, double support time and lower limb range of motion during gait tended to improve following treadmill training [20]. Shulman et al. compared higher-intensity treadmill exercise (30 min, 70%–80% HRreserve ≈ 75%–85% HRmax) with lower-intensity treadmill exercise (50 min, 40%–50% HRreserve ≈ 55%–65% HRmax) and with stretching and resistance exercises in PD [15, 34]. Walking distance, assessed using the 6-minute walk test (6MWT), improved following longer duration, lower-intensity treadmill training ($p = 0.001$). However, 6MWT did not improve following the shorter duration, higher-intensity exercise ($p = 0.07$) [15].

Balance was assessed in two studies [16, 19]. Single limb stance improved significantly (7.3 sec, $p = 0.05$) on the right foot, but not the left, in response to treadmill training [19]. The functional reach test (FRT) improved approximately 1.0 cm (0.4 in) following 4 months of endurance exercise training when participants had the option of training on a treadmill, bike, or elliptical trainer [16]. This was not significantly different from a flexibility and balance trained group or a home based group.

General functional mobility was assessed using a variety of measures in 3 studies [16, 18, 19]. Improvements in functional mobility were not detected with the Timed Up and Go test (TUG) [18] or the Continuous Scale-Physical Functional Performance test (CS-PFP) [16]. In contrast, Kurtais et al. (2008) measured significant improvements ($p < 0.01$) in functional mobility with a variety of timed measures including U-turns, turning around a chair, stair climbing, and arising from a chair [19].

Depression and fatigue

Two studies investigated depression. Shulman et al. investigated depression with the Beck Depression Inventory (BDI) [15], whereas Bridgewater et al. used the Levine-Pilowsky Depression Questionnaire (LPDQ) [22]. Through post-hoc analysis, a comparison of baseline and final assessment showed a significant improvement in the LPDQ in the endurance exercise group ($p < 0.05$) [22]. However, there was no significant group-by-time session interaction across LPDQ assessments compared to PD patients in the normal activity level group [22]. Shulman et al. did not find any significant change for depression [15]. Only one study assessed fatigue using the 16-item Parkinson Fatigue Scale, and endurance exercise training did not decrease patient reported fatigue in PD [15].

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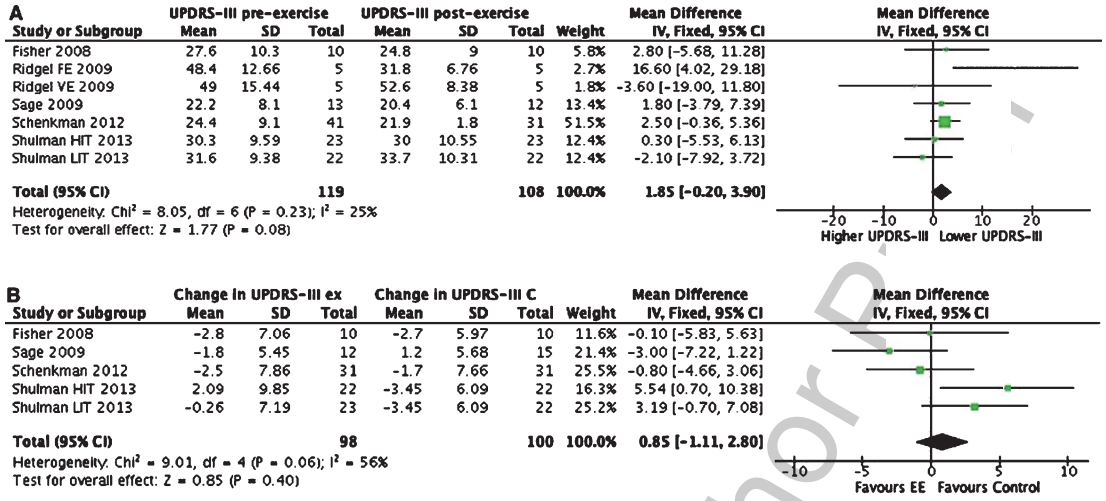


Fig. 2. Meta-analysis on the effect of endurance exercise training on motor disability in PD assessed by the UPDRS motor subscale. A. Meta-analysis comparing baseline and post-intervention UPRDS motor scores (within group difference). B. Meta-analysis comparing endurance exercise training with a control group. The control group did not exercise in two studies (Fisher et al. [20], Sage et al. [18]), the control group exercised using the National Parkinson Foundation Fitness Counts program in one study (Schenkman et al. [16]), and a combined resistance and stretching program in another study (Shulman et al. [15]). Squares indicate the individual mean difference in each study. The size of each square is proportional to the percent weight of that individual study in the meta-analysis, and the horizontal line represents the 95% confidence interval (CI). Pooled mean differences and 95% CIs are indicated by the solid diamond. C: control group, Ex: endurance exercise training group, FE: forced exercise, HIT: higher intensity training, LIT: lower intensity training, VE: voluntary exercise.

Quality of life and patient perceived improvement

Two studies assessed quality of life using the Parkinson's Disease Questionnaire (PDQ-39) [15, 16]. In these two studies there was no statistically significant improvement in quality of life following 3 and 16 months of endurance exercise training [15, 16]. Activities of daily living (ADL) were assessed by questionnaire, using the Northwestern University Disability Scale (NUDS) in one study [22], the UPDRS ADL subsection in two studies [16, 20], and the Schwab and England ADL scale in one study [15]. Patient-perceived improvement was also reported using the Falls Efficacy Scale (FES) and the Human Activity Profile (HAP) [15, 22]. One study reported a statistically significant improvement of the HAP and the NUDS in favor of the endurance exercise intervention compared to the control group [22]. Self perceived rating of independence based on ADL (Schwab and England ADL scale), self perceived confidence to prevent falls (FES), and ADL did not improve with endurance exercise training in other studies [15, 16, 20].

Improved physiological measures

a. *Cardiorespiratory function:* Five studies investigated VO_2 max changes with endurance intervention [15–17, 19, 21] and one study investigated stress test duration changes [22]. All of these studies reported statistically significant improvement of cardiorespiratory capacity with endurance training (between-group and within-group comparisons).

b. *Neurophysiological measures:* One study examined the effect of endurance exercise training on corticomotor excitability measured through transcranial magnetic stimulation (TMS) [20]. In the high intensity group, increases in cortical silent period duration were seen for the five patients tested with TMS in both hemispheres [20]. The high-intensity group (target HR of 75% HRmax) demonstrated an average 32-ms increase in the maximal cortical silent period duration for the more affected hemisphere compared with an average 17 ms decrease in cortical silent period duration for the low-intensity group (target HR of 50% HR max). There was no change in cortical silent period duration in the no exercise control group [20].

c. *Motor control measures:* Two studies assessed upper limb motor control [17, 21]. Of these, one found an improvement in movement initiation time for elbow flexion and extension under both simple and choice reaction time conditions with endurance exercise training [21]. In the other

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study, an upper limb bimanual dexterity task improved in the forced high pace exercise group but not in the voluntarily paced exercise group indicating that the forced nature of exercise, and not the endurance component, was responsible for the improvement [17].

Attrition, adverse events and safety

Endurance exercise training was well tolerated. Not unexpectedly, the attrition rate was higher in the programs that lasted a longer period of time. The highest attrition rate was reported in a 16 month randomized controlled trial in which 75.6% of the PD patients allocated to the endurance exercise group completed the study [16]. All patients completed the exercise protocol in 3 studies [17, 20, 21]. Attendance rate (total sessions attended/absolute number of sessions) was high for the endurance exercise group with 95% in the study of Bridgewater et al. [22], and 86.8% in the study of Sage et al. [18]. Adverse events were not mentioned in 5 studies [17–19, 21, 22]. One study reported no exercise-related adverse events [20], and two other studies reported only a few non-serious adverse events including soreness, pain, and orthostatic hypotension [15, 16].

DISCUSSION

Lessons from randomized controlled trials that examined endurance exercise training in PD

Motor signs of parkinsonism

The UPDRS is the gold standard assessment tool for characterizing impairments in persons with PD [35]. Considering the studies reviewed here, there is no evidence to support an improvement in the motor signs of parkinsonism in PD with endurance exercise training. The heterogeneity between the control groups in the studies included in the meta-analysis could have influenced the result. Indeed, a combined resistance and stretching program was used as the control group in one study [15]. This group had significantly lower UPDRS motor scores post-intervention compared to baseline, which was not the case for the two other groups following an endurance exercise training program [15]. Thus, as discussed by the authors, this could suggest that UPDRS items are more responsive to muscle strengthening than endurance exercise training. One recent study found a significant improvement in the on medication UPDRS motor score with endurance exercise training [36]. In this study, all the completers were pooled ($n = 49$) for data analysis according to an a priori analysis plan. Therefore, this interventional study provides only Class IV level of evidence that a moderate to vigorous endurance exercise program (mean HR = 79.7% HRmax) improves motor function in mild to moderate PD [36]. This result is encouraging, but the lack of a control group for the main analysis prevents the authors from proving efficacy of the walking program on motor symptoms in PD patients. More randomized controlled clinical trials are needed to assess if endurance exercise has a positive effect on motor disability in PD.

This lack of effect of endurance exercise training on motor disability is in contrast to Tai Chi, another intervention program that has been associated with significant improvement in the UPDRS-III in a recent meta-analysis [37]. One recent study with class II level of evidence found that progressive resistance exercise significantly improved off medication UPDRS motor score at 24 months compared with a stretching, balance, and strengthening exercise program (mean difference −7.3 points, $p < 0.001$) [38]. However, other studies did not find any significant improvement in the on medication UPDRS-III using progressive resistance exercise [39, 40].

In this review on endurance exercise training, the small sample size in some studies and the fact that evaluations were conducted in the on medicated state without withdrawal from anti-parkinsonian medication may have influenced the results of the studies. There is a need for a well-designed controlled clinical trial that is powered to detect differences in the motor signs of parkinsonism that includes both on and off medication testing to truly assess motor signs of PD changes without any confounding effect of medication.

Physical performance: Gait, balance, and functional mobility

The results of these studies suggest that endurance exercise training can be beneficial for a variety of physical performance measures, including gait. A recent meta-analysis concluded that treadmill training can improve gait speed and stride length [41], but the effect of training intensity, duration, and modality is unknown. Two of the eight studies included in their meta-analysis were included in our review [19, 20], but the other six treadmill training studies in their meta-analysis [41] did not define the aerobic intensity achieved during training. The three studies in our review that reported improved gait parameters in response to endurance exercise training used long duration training sessions on a treadmill (40–50 minutes) at low to moderate [15] or high intensity levels [19, 20].

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In contrast, two studies with shorter duration training sessions (20–30 minutes) on a recumbent elliptical and treadmill did not show improvements in gait parameters [15, 18].

Reduced balance is associated with falls, poor mobility, disability and reduced quality of life in PD and balance is poorly responsive to levodopa [42, 43]. A recent meta-analysis concluded that exercise and motor training can improve the performance of balance-related activities in people with PD and recommended that highly challenging balance exercises be part of a rehabilitation program for patients with PD [44]. Our review indicates that endurance exercise training alone is not sufficient to improve balance measures [18, 19]. This finding may be due to a lack of training specificity for balance in many endurance exercise interventions or the lack of sensitive balance testing. Endurance studies in this meta-analysis and in our review did not explore balance with the Berg Balance Scale (BBS), the Mini-BESTest, or the functional gait assessment (FGA), which have high reliability and validity for assessing balance in individuals with PD [45–47].

Results of improved functional mobility were positive in one study of high intensity treadmill training with long duration (40 min) training sessions [19]. The measures included by Kurtais and colleague were less common timed mobility tests, including timed U-turn, turning around a chair, time to ascend/descend one flight of stairs, and time to arise from an armless chair [19]. Functional mobility assessed by the TUG and the CS-PFP did not improve in two other studies with shorter duration training sessions (20 min on a semi-recumbent elliptical in one study and 30 min using varied exercise equipment in the other study) [16, 18]. The variability in these findings could be due to differences in exercise session duration, exercise modality, or outcome measure used.

Depression and fatigue

Depression is a common neuropsychiatric feature of PD and a meta-analysis found a prevalence of 31% among patients with PD [48]. The relationship between exercise and depression has been studied in healthy individuals, and a systematic review of 11 randomized controlled trials that investigated endurance, resistance and balance training concluded that exercise in general is an effective treatment for depression [49]. Given the studies reviewed here, there is no clear evidence that endurance exercise training can improve depression in PD. However, patients with PD who enrolled in these studies were mild to moderate PD patients and may have had less depression at baseline and, therefore, exercise may have been less likely to improve this specific outcome. Indeed, in the study by Shulman et al., baseline mean BDI scores in each group were lower than 11, which indicates that patients were not depressed and had ups and downs that could be considered normal [15, 50]. In a recent randomized clinical trial with a delayed start design, Park et al. suggested that exercise could improve depression in PD patients [51]. In this study, the exercise program was based on two, 12-week fitness cycles that mixed endurance and resistance training [51], thus making it impossible to delineate which specific intervention accounted for improvement. Another interventional study provided class IV level of evidence that brisk walking was associated with improvement in depression assessed by the Geriatric Depression Scale ($p = 0.041$) and the UPDRS part I ($p = 0.025$) in PD patients [36]. In studies that investigated exercise in PD, depression has been included as an exploratory outcome and not as a primary outcome. Additional clinical trials that include depression as a primary outcome variable are needed to explore the potential benefit of exercise on depression in PD patients.

Fatigue is a common symptom in PD and in a community-based study, 44.2% of PD patients self-reported experiencing fatigue [52]. In the general population, fatigue has been shown to be inversely correlated with physical activity and physically active people have about a 40% reduced risk of experiencing feelings of low-energy and fatigue compared with sedentary comparison groups [53]. The current review provides no evidence that endurance exercise training is associated with improvement of self-reported fatigue in PD. However, endurance exercise training was associated with improved feeling of energy and lower fatigue in two other studies not included in this review [54, 55]. Exercise is well tolerated in individuals with PD [15, 56], and a paradoxical effect with increased exercise-induced fatigue seems unlikely. Given the heterogeneity in clinical presentation and severity of the disease, further clinical trials are needed to understand the relationship between exercise and fatigue in PD.

Quality of life and patient perceived improvement

Quality of life is impacted by several factors in PD including impairment of motor function, gait disturbances and depression [57]. The PDQ-39 assesses different domains such as mobility, activity of daily life, emotional well-being, stigma, social support, cognition, communication and bodily discomfort. This self-administered questionnaire is a reliable and

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validated scale to assess quality of life in PD [58]. The mean baseline PDQ-39 summary index was relatively low in the endurance exercise group in two studies we included, indicating that patients enrolled had a good quality of life at baseline and, therefore, the endurance exercise intervention would have been less likely to improve this outcome [15, 16]. Further research is needed to explore the effect of endurance exercise training on quality of life in PD. Furthermore, other factors such as pain and fatigue, cognitive deterioration, sleep problems, detrimental social functioning and economic impact of the disease contribute to the negative impact of quality of life in PD and the effect of exercise on counter balancing these factors is not clear [57, 59, 60].

With regards to patient self-perceived improvement, endurance exercise training seems to have a positive effect in PD. The HAP is a self-report measure of physical activity levels. It is a 94-item questionnaire that investigates activities from very easy (getting in and out of chairs or bed) to very strenuous (running or jogging 3 miles (5 km) in 30 min or less) [61]. Because this questionnaire focuses on physical activity, it is not surprising that endurance exercise training improved the HAP score in one study [22]. Given the current review, it is unclear if endurance exercise training can improve ADL. One possible explanation is that PD patients included in these studies had mild to moderate disease severity (HY 1-3) and were independent in most activities and, therefore, the endurance exercise intervention may be less likely to improve this outcome. In one study, at baseline, all patients had a mean score on the Schwab and England ADL scale higher than 80%, which indicates that they were independent in most ADL [15]. The same study failed to show a significant reduction in the risk of falls assessed by the FES [15]. It was unclear if endurance exercise training was insufficient to reduce perceived risk of falls in PD or whether the FES was insensitive to the exercise changes for mild to moderate disease severity patients with a low risk of falls. In addition, no endurance exercise training study in PD has looked at actual falls prevention. Endurance exercise training has been shown to reduce number of falls in the healthy general older population [62, 63]. For these reasons, further research is required to determine if endurance exercise training in individuals with PD reduce or prevent falls or fear of falling.

Improved physiological measures

a. *Cardiorespiratory function:* The benefits of endurance exercise training for cardiovascular function are well established for several diseases including heart disease, diabetes and obesity [64–66]. The precise incidence of cardiovascular events in individuals with PD is unknown. A recent review suggested that patients with PD might have an increased risk of developing comorbid cerebrovascular complications [67]. Our review suggests that regular endurance exercise training increased VO_2 max, which is the gold standard objective physiological measure of cardiorespiratory fitness, in PD patients. By increasing cardiovascular fitness, endurance exercise training clearly benefits cardiovascular function in the PD population and may have an even greater benefit for people with PD with comorbid complications. Walking economy, defined as the steady-state aerobic demand for a given submaximal speed of walking, has been found to be impaired in patients with PD compared to aged healthy adults [27]. Endurance exercise training could improve walking economy and decrease fatigue during daily activity, which may make the accomplishments of day-to-day tasks easier for individuals with PD.

b. *Neurophysiological measures:* TMS is one non-invasive measure that can provide indirect insight into human neurophysiology [68]. Compared to healthy controls, people with PD have been found to have shortened cortical silent period durations, which can be restored with dopaminergic medication [69]. Fisher et al. demonstrated that eight-weeks of high-intensity endurance exercise also lengthened cortical silent period duration in people with PD [20]. They attribute the exercise-induced changes in cortical silent period to increased dopaminergic activity in the basal ganglia affecting GABA-B receptor mediated intracortical inhibition or BDNF mediated increases in the number of GABAergic interneurons [20]. Another recent study, using PET imaging with the radioligand [18F] fallypride, found that endurance exercise training increased the dopamine D2 receptor binding potential in patients with early-stage PD [70]. This study supports an endurance exercise-induced increase in dopaminergic D2 receptor expression in the basal ganglia of patients with early-stage PD, and according to the authors this could reflect a beneficial compensatory mechanism to boost dopaminergic signaling within the indirect striatopallidal pathway [70]. The increase in D2 receptors appeared specific to PD patients [70]. Unfortunately, neither TMS nor D2 receptor bind-

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ing potential can provide precise information about subcortical dopamine. TMS does not penetrate beyond cortical structures and increased D2 receptor binding potential could be due to increased number of D2 receptors, or reduced dopamine. Additional research with more participants and combinations of neurophysiological measures are needed to confirm and extend these findings.

c. *Motor control measures:* Both studies that assessed upper limb motor control demonstrated improvement in tasks that were distinct from the endurance exercise training interventions, which focused on lower limb movements [17, 21]. Improvement in elbow movement initiation time for simple and choice reaction tests [21] and bimanual coordination [17] may represent global improvement in neuromuscular function as a result of endurance exercise training.

Factors to consider in prescribing endurance exercise training in PD

Intensity and duration of exercise training session

The optimal intensity of exercise for individuals with PD is not known, and cannot yet be inferred from the animal literature. Intensity is not reported in terms of HR demand in animal models of PD, nor can it be discerned how HR demands in the animal model relate to humans. In healthy individuals, Kohrt et al. showed that VO_2 max increased in individuals aged 60–71 with an endurance exercise program in which the intensity averaged $80 \pm 5\%$ HRmax, and that this adaptation was independent of sex, age, and initial level of fitness [71]. The executive summary of the Physical Activity Guidelines Advisory Committee Report indicated that there is strong evidence that vigorous-intensity exercise is associated with greater improvements for some health outcomes compared to those observed with moderate-intensity exercise [29]. High-intensity training has been demonstrated to be feasible in individuals with PD and there is some evidence that high-intensity endurance exercise training is beneficial for PD patients with a dose-response effect of exercise in this population. Fisher et al. compared high-intensity activity (75% HRmax with a range from 50% to 75%) with low-intensity activity (50% HRmax or less) on several measures including the UPDRS and altered cortical excitability in patients with PD. They found that the cortical silent period was lengthened in the high-intensity group suggesting exercise-induced neuroplasticity with high-intensity endurance exercise training [20]. Shulman et al. found a significant improvement on the 6MWT for the lower intensity treadmill group and the stretching and resistance group but not for the high-intensity treadmill group. They concluded that the lower intensity treadmill exercise was the single most effective training exercise for improving gait and fitness [15]. However, there was a difference in duration of exercise sessions between the lower intensity treadmill and high-intensity treadmill group so that it is not clear whether it was intensity or duration of exercise that accounted for the differences. As such, the best dose of endurance exercise training is still an open question. An ongoing RCT study has been designed to address this specific question in never-medicated patients and may establish if there are differences in potential symptom modifying responses to moderate (60–65% HRmax) and high (80–85% HRmax) intensity exercise in PD [72].

This current review shows that endurance exercise is feasible and safe in people with mild to moderate PD with very few adverse events related to the exercise intervention. Attrition rate of more than 20% can affect the validity and overall outcome of a study and typically downgrades an otherwise level 1 study to a level 2 study [30]. The drop-out rate in the studies included in the current review did not exceed 20%, except in a 16 month randomized controlled trial, in which a 25.5% drop-out rate was observed for the endurance exercise group at the end of the program [15, 16]. Several factors may explain the attrition in exercise studies, such as the necessity to commute to an exercise center, the inferior perception of the exercise program as a non-traditional treatment by the patient and/or his family, and the time commitment required to adhere to the exercise program given the fact that people with mild to moderate PD still have an active work and family life.

Specificity, duration and mode of exercise program

Treadmill training is the most used endurance exercise training modality. Three of the eight endurance training programs solely trained on the treadmill [15, 19, 20], one included treadmill training for some participants [16], and one included treadmill training as a part of a larger endurance training program [21]. In 2010, Mehrholz et al. conducted a meta-analysis of exercise interventions in patients with PD and concluded that: "Patients with Parkinson's disease who receive treadmill training are more likely to improve their impaired gait hypokinesia. However, the results must be interpreted with caution because there were variations between the trials in patient characteristics,

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the duration and amount of training, and types of treatment. Additionally, it is not known how long these improvements may last" [41]. Our review is consistent with this meta-analysis and supports the positive effects of endurance treadmill training on physical performance in PD.

Using an animal model of PD, Gerecke et al. have suggested that duration of a program intervention is crucial to protect dopaminergic neurons against death caused by acute MPTP-intoxication [73]. In humans, the necessary duration of an endurance exercise program intervention to improve functional outcomes in PD is unknown and most of the studies have investigated exercise-induced changes with only short-term duration and follow-up (Table 1).

The best mode of physical activity for PD patients is also a question that needs further exploration. In addition to endurance exercise, resistance exercise and balance training programs have also been evaluated for individuals with PD [8, 44]. One single study included in this review suggests that UPDRS items could be more responsive to muscle strengthening than moderate intensity endurance training [15] (Fig. 2). However, there is no clear evidence than one mode of exercise intervention is superior to another, and the mechanisms underlying exercise-induced changes for each program are not fully understood. Moreover, PD is a variable and progressive disease and it is possible that only some patients can benefit from a specific exercise regimen according to disease severity, clinical presentation, or even lifestyle or genetics. The most effective exercise intervention for patients with PD has yet to be elucidated and there is a real need for well-designed controlled clinical trials that would compare and/or combine different modes of exercise.

Knowledge gaps

Endurance exercise training, neurophysiology and neuroprotection

Studies using animal models of PD have shown that endurance exercise training promotes neuroplasticity through several mechanisms such as preservation of dopamine neurons in the striatum and the substantia nigra, increased expression of dopamine D2 receptors and downregulation of the dopamine transporter protein, or increased dendritic spines and arborization in both D1-receptor medium spiny neurons of the direct pathway and D2-receptor medium spiny neurons of the indirect pathway [5, 74–77]. Exercise-induced neuroplasticity is not restricted to the dopaminergic system. Exercise has also been shown to modulate glutamatergic neurotransmission [78, 79]. These specific examples of neuroplasticity are difficult to study in humans. Non-invasive human neurophysiology techniques, such as TMS, PET imaging, electroencephalography, and functional magnetic resonance imaging each present with limitations, such as inter-individual variability, lack of spatial and/or temporal resolution, cost, lack of knowledge regarding specific mechanisms, and lack of specificity for neuronal populations. For example the neurons that are stimulated or imaged could be excitatory, inhibitory, or state dependent. Future research is needed to confirm the repeatability of the findings in this review, and should employ combinations of human neurophysiology techniques to provide additional information about neuroplasticity.

Animal studies have also suggested a possible neuroprotective effect of exercise in experimentally induced parkinsonism [73, 80]. Similar to the general neuroplasticity research, these findings have yet to be translated in humans. The time course of exercise-induced changes in the human brain and how it varies as a function of age, and disease duration is not known. To date, no study has suggested a disease modifying effect of endurance exercise training in PD. A recent study using a delayed start design found that the Beck Depression Index score decreased more in the early-start group than in the delayed-start group, which could suggest a disease modifying effect of exercise for symptoms like depression in individuals with PD. However, there was no significant difference between the two groups regarding other outcomes including gait and balance, UPDRS or the PDQ-39 [51], and because of the mixed nature of the exercise program, the specific role of endurance exercise training cannot be inferred from the results.

Role of stage of disease progression

Most of the studies that have investigated the effects of endurance exercise training in PD have included a limited number of participants with mild to moderate disease severity and were highly supervised with a short duration. Another gap in our knowledge is whether exercise would be still beneficial to patients in the later stages of PD or with cognitive impairment. One should keep in mind the potential limitations of doing exercise therapy in these sub-populations. With the progression of the disease, PD patients develop several motor and non-motor complications, such as motor fluctuations, dyskinesia, unpredictable response to medications, increased fall risk, dysautonomia, dementia, hallucinations, depression, and

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psychosis [81]. Therefore, patients at late stage of PD with severe motor disability or motor complications associated with levodopa therapy may not be able to follow an endurance exercise protocol. Safety is another important issue. In later stages of PD, postural instability is a common complaint and has been associated with falls and fear of future falls in PD [82]. Thus, endurance exercise on a treadmill or over-ground could be associated with severe side effects such as falls and increased morbidity, and endurance exercise training using cycling devices or supervised treadmill training with safety harnesses may be safer in patients advanced PD and postural instability. Cognitive impairment, which is common in advanced PD, could also be seen as an exclusion criterion for endurance exercise. However, endurance exercise has been shown to be safe and feasible in patients with dementia [83], and endurance exercise may have a positive effect on cognition in PD (i.e. discussion on cognition). Studies with longer duration with an appropriate follow-up and an evaluation of pharmacologic therapy would be essential to confirm the probable neuroplastic action of endurance exercise training and to explore if exercise-induced changes in PD are maintained over time. Such studies will be challenging and expensive unless biomarkers of disease progression are validated and used as secondary outcome measures. Future studies need to consider the stage of disease progression, as the goal of the intervention may be different at different stages of the disease.

Effect of endurance exercise training on cognition and sleep in PD

Cognition is affected early in PD and progresses with disease severity [50]. Impaired executive function is frequent in PD and is related to alterations in frontostriatal connectivity [84, 85]. Exercise in general has been shown to improve executive function and prevent cognitive decline in healthy individuals [86–88]. A meta-analysis that included different types of interventions including endurance exercise training found a possible exercise-induced improvement for executive functioning in elderly persons with cognitive impairment [89]. Four studies that were below a class II level of evidence investigated endurance exercise-induced cognitive changes in individuals with PD were not included in this review. These studies used multiple intervention methods with a combination of endurance and resistance exercise in two of the studies [90, 91]. The effect of endurance exercise training alone on cognitive function in PD has been investigated only in case series or case report format [92, 93], which creates an important selection bias. There were also differences in the cognitive tests used and definition of cognitive impairment between the studies. Moreover, most of these studies have included patients with no cognitive impairment [90, 91, 93] and only one study included 2 PD patients with cognitive impairment [92]. However, the results are promising and exercise was associated with improvement in cognitive functions such as working memory, verbal fluency and dual task performances [90, 93]. Therefore, endurance exercise training might improve cognitive functions, and especially executive functions in individuals with PD. Further study is needed to confirm this association and to understand central mechanisms that may be responsible for these improvements.

Sleep disorders have a high prevalence in PD, and can be due to various causes including bladder dysfunction, periodic limb movements of sleep, depression and anxiety, dreams and nightmares induced by dopaminergic medications, or rapid eye movement sleep behavior disorder [94]. A randomized controlled trial found that in the general population, sedentary elderly individuals with sleep dysfunction showed improvement in quality of sleep (sleep duration, sleep-onset latency) after moderate-intensity endurance exercise training [95]. No study included in this review assessed sleep disturbances in PD. One non-controlled study not included in this review reported some indication of sleep improvement in PD patients who participated in 36 supervised group sessions of endurance exercise training and muscular strengthening, although the results did not reach the level of significance ($p = 0.06$) [96]. Another recent study that did not meet the inclusion criteria for this review did not find any sleep improvement (assessed by the Pittsburgh Sleep Quality Index) with exercise in PD patients involving in a 16 weeks high intensity exercise training challenging strength, power, endurance, balance, and functional mobility [54]. More studies are needed to explore the effect of endurance exercise training on the various sleep dysfunctions in this population.

Endurance exercise training and autonomic dysfunction in PD

There is evidence of autonomic nervous dysfunction in PD. Impairment of the cardiac autonomic nervous system is a characteristic feature of PD [97] and an early noradrenergic post-ganglionic cardiac denervation in PD is supported by postmortem findings as well as imaging with heart 123I-metaiodobenzylguanidine scintigraphy studies [98, 99]. The impairment of cardiac function might be present early in the disease during the premotor phase of PD. A recent study

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showed that individuals with premotor PD exhibit chronotrophic insufficiency, or an inability of the HR to increase appropriately as intensity increases, during exercise stress testing [100]. Endurance exercise training can lead to autonomic cardiovascular adaptations with reduced sympathetic autonomic drive and increased vagal autonomic drive [101, 102]. These changes lead to an improvement of the heart rate variability in patients after myocardial infarction [103, 104]. In addition, endurance exercise training has been associated with increased cardiac β-adrenergic responsiveness [105, 106]. Orthostatic hypotension is a common symptom in PD and a reduced baroreflex response plays a role in its pathophysiology [107]. Endurance exercise training has been associated with improvement of the baroreflex function in healthy seniors [108]. Although the benefits of endurance exercise training on autonomic cardiovascular adaptations have been well demonstrated in various populations, no study has examined this relation in PD.

Constipation is another frequent manifestation of autonomic nervous system dysfunction in PD. Kaye et al. used questionnaires to assess the impact of constipation in 156 patients with PD compared to 148 controls, and the authors found that constipation was nearly three times more prevalent in PD patients (59% versus 21%) [109]. Constipation has been attributed to drug therapy, poor diet, and inadequate fluid intake, but it may be due to the disease process itself [110]. In a recent meta-analysis, a history of constipation was one of the strongest risk factors associated with later PD diagnosis [111], and Lewy body pathology is found within the enteric nervous system of PD patients [112]. In healthy individuals, physical activity is associated with a decreased risk of constipation through several possible mechanisms including increased colonic mobility and biomechanical stimulation of the gut or the colon during exercise [113]. There is no evidence of a positive effect of endurance exercise training on constipation in PD patients, but we think that patients with PD would experience a similar benefit. Similarly, endurance exercise may improve urinary and sexual dysfunctions, which are common symptoms of autonomic dysfunction in PD [114]. More studies are needed to explore the effect of endurance exercise training on autonomic dysfunctions in PD patients.

Genetic influences

Over the past decade, the identification of risk loci, genes and mutations in PD has provided new insights into disease etiology [115]. There is evidence from animal models and human research that the neurogenic response to exercise is influenced by genetic background [23]. Several genes that have been associated with the clinical presentation in PD may have an impact on exercise-induced changes. Brain-derived neurotrophic factor (BDNF) is a major regulator of synaptic plasticity, neuronal survival and differentiation and may contribute significantly to PD pathogenesis and dementia development in the course of the disease [116]. Catechol-O-Methyltransferase (COMT) is a ubiquitous enzyme that mediates biodegradation of catecholamines including dopamine and L-dopa. Although studies have shown contradictory results, COMT polymorphism has been found to interact with dopaminergic medication and could influence cognition in PD [117]. Apolipoprotein (APOE) e4 allele has been linked to clinical presentation and progression in Alzheimer's disease [118]. However, recent studies support a link between APOE e4 allele status and disease symptoms, especially cognitive impairment in PD patients [119]. COMT and BDNF polymorphisms have been shown to influence the effects of endurance exercise training in healthy individuals and APOE polymorphism has been shown to influence the interaction between cognitive decline and physical activity [120–123]. However, the influence of such genetic and epigenetic factors on exercise-induced changes in PD has still to be fully explored and future studies need to take in consideration genetic issues to understand the complex interaction between genetics and exercise in individuals with PD.

Limitations

There were several limitations to this review. We limited our search strategy and subsequent review to evidence ranked as level I or II in articles that were published in English-language, peer-reviewed publications. We included randomized controlled studies that investigated endurance exercise training as a therapeutic intervention tool and endurance exercise training was defined by an intervention performed with a target HR >60% HRmax. Therefore, studies with positive results but lower intensity of exercise or lower level of evidence were not analyzed. As noted previously, participants included were moderately to mildly affected by PD and, therefore, the results of the study are not fully generalizable to the PD population at large.

Conclusion and implications and directions for future research

This systematic review synthesizes evidence that endurance exercise training at a sufficiently high level

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can have positive effects on different outcomes that are not specific to PD. Endurance exercise training enhances cardiorespiratory capacity and endurance by improving VO_2 max and gait in moderately to mildly affected individuals with PD. However, there is not yet a proven effect of endurance exercise training on specific features of PD such as motor signs of parkinsonism. Further research is needed to explore the effects of endurance exercise training on motor signs of parkinsonism and non-motor symptoms such as fatigue, depression, cognition, sleep disturbances, autonomic nervous system dysfunction, and quality of life in individuals with PD. We conclude that endurance exercise training improves physical conditioning in PD patients; however, to date, there is insufficient evidence to include endurance exercise training as a specific treatment for PD. There is a need for well-designed large-scale randomized controlled trials to confirm benefits and safety of endurance exercise training in PD and to explore potential benefits on the motor and non-motor signs of PD. Further research on exercise in PD should address specific questions about the optimal exercise mode, intensity and duration to target specific improvements in the motor and non-motor features of PD.

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The authors have no conflict of interest to report.

AUTHOR CONTRIBUTIONS

GL: review of the literature, data analysis, writing and preparation of the manuscript, review and critique of the manuscript. MR, JP, WK, CC, TS, and DC: data analysis, writing contribution, review and critique of the manuscript.

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