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Lamotte is with the Department of Neurology, University Hospital of Caen, Caen, France. Skender is with the Department of Kinesiology and Nutrition, University of Illinois at Chicago, IL. Rafferty is with the Graduate Program in Neuroscience, University of Illinois at Chicago, IL, and the Department of Physical Therapy & Human Movement Sciences, Northwestern University, Chicago, IL. David, Sadowsky, and Corcos are with the Department of Physical Therapy & Human Movement Sciences, Northwestern University, Chicago, IL. Corcos is also with the Department of Neurological Sciences, Rush University Medical Center, Chicago, IL. [AUQ1]

Effects of Progressive Resistance Exercise Training on the Motor and Nonmotor Features of Parkinson's Disease: A Review

Guillaume Lamotte, Elizabeth Skender, Miriam R. Rafferty, Fabian David, Steve Sadowsky, and Daniel M. Corcos

Objective: This paper reviews the therapeutically beneficial effects of progressive resistance exercise training (PRET) on motor and nonmotor symptoms in Parkinson's disease (PD). ***Methods:*** First, we perform a systematic review of the literature on the effects of PRET on motor signs of PD, functional outcomes, quality of life, and patient perceived improvement, strength, and cognition in PD. Second, we perform a meta-analysis on the motor section of the UPDRS. Finally, we discuss the results of our review and we identify current knowledge gaps regarding PRET in PD. ***Conclusion:*** This systematic review synthesizes evidence that PRET can improve strength and motor signs of Parkinsonism in PD and may also be beneficial for physical function in individuals with PD. Further research is needed to explore the effects of PRET on nonmotor symptoms such as depression, cognitive impairment, autonomic nervous system dysfunction, and quality of life in individuals with PD.

Keywords: Parkinson's disease, progressive resistance exercise, exercise, resistance exercise, motor activity, gait, balance

Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor symptoms such as bradykinesia, rigidity, tremor, gait dysfunction, and postural instability, as well as nonmotor symptoms such as cognitive impairment and mood disorders, among others. Symptoms of PD 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 (Morris, Huxham, McGinley, Dodd, & Iansek, 2001; Olanow, Stern, & Sethi, 2009). To date, there is no neuroprotective strategy available for PD. Consequently, there is a need for new therapies that can slow disease progression and reduce the functional and cognitive declines seen with advancement of the disease. Epidemiological studies have supported a link between moderate to vigorous exercise habits in midlife and the reduced risk of later developing PD (Chen, Zhang, Schwarzschild, Hernán, & Ascherio, 2005; Xu et al., 2010).

Recently, the American College of Sports Medicine issued new guidelines to promote exercise in older adults (Garber et al., 2011). According to these recommendations, older adults should exercise regularly and combine endurance exercise training and muscle strengthening activities (Garber et al., 2011). We recently reviewed the literature on the effect of endurance exercise training in PD (Lamotte et al., 2014). This review will synthesize the literature that has examined the effects of progressive resistance exercise training (PRET) on the motor and nonmotor signs of PD. PRET can be defined as a method of exercise that systematically and progressively increases the ability of muscle to generate force (Taylor, Dodd, & Damiano, 2005). PRET is based on three principles: (1) to perform a small number of repetitions until fatigue, (2) to allow sufficient rest between exercises for recovery, and (3) to increase the resistance as the ability to generate force increases (Taylor, Dodd, & Damiano, 2005). Several studies have shown that patients with PD have reduced muscle strength compared with controls (Allen, Canning, Sherrington, & Fung, 2009; Cano-de-la-Cuerda, Perez-de-Heredia, Miangolarra-Page, Munoz-Hellin, & Fernandez-de-Las-Penas, 2010). The fact that muscle weakness and bradykinesia may share common underlying mechanisms involving a dysfunction of the nigrostriatal pathway that alters corticospinal activation supports the use of PRET in this population (David et al., 2012). PRET has been established as a safe form of exercise, and a recent meta-analysis depicted PRET as having a moderate positive effect on strength and

improved functional performance in PD (Lima, Scianni, & Rodrigues-de-Paula, 2013).

In this paper, we first present a systematic literature review of the current clinical evidence for PRET-induced changes in PD, restricting the review to randomized controlled studies. We will focus on several outcomes: motor signs of PD, functional outcomes, quality of life, and patient perceived improvement, strength, and cognition. We will then present the findings of a meta-analysis on the effect PRET on motor signs of Parkinsonism in PD assessed by the Unified Parkinson's Disease Rating Scale (UPDRS) motor subscale in PD. Finally, we will identify and list knowledge gaps for PRET prescription in PD.

Methods

Search Strategy

The following electronic databases were searched: PubMed (1990 to September 1, 2014), Cochrane Library (1990 to September 1, 2014), Embase (1990 to September 1, 2014) and Google Scholar (1990 to September 1, 2014). Searches were performed utilizing the following terms: exercise, weight lifting, weight training, strength training, muscle strengthening, progressive resistance, Parkinson's disease, and Parkinson. 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; (2) PRET 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 PRET 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 randomized controlled study, restricting the review to class I and II studies according to the classification of level of evidence of the American Academy of Neurology (French & Gronseth, 2008); and (7) the study was available as of August 1, 2014. A study was excluded if: (1) Exercise training as defined previously was used as an assessment tool rather than as a therapeutic intervention tool; (2) PRET was provided as a part of a multimodal training program, unless the control group used identical exercise modalities except for PRET or the inclusion of other types of exercise was considered the standard of care; or (3) animals were studied.

We conducted a meta-analysis on the effect of PRET on motor signs of Parkinsonism assessed by the UPDRS-III in PD. We included studies that met the inclusion criteria for this current systematic review. We first included studies that provided the baseline and postintervention UPDRS motor scores to assess within-group differences (class IV level of evidence). Then we included studies that provided the UPDRS motor scores and compared PRET with a control group (no activity or other type of exercise training) (class II level of evidence). The meta-analysis was conducted using Review Manager (Cochrane, Oxford, UK). When the change-from-baseline standard deviation was not available, we used a correlation coefficient from another study included in the meta-analysis that provided change-from-baseline standard deviation. Because of the significant variability between studies, we chose not to perform a meta-analysis for the other outcomes.

Results

A total of six randomized controlled trials met the inclusion criteria and were reviewed (Corcos et al., 2013; Dibble et al., 2006; Hass, Collins, & Juncos, 2007; Hirsch, Toole, Maitland, & Rider, 2003; Li et al., 2012; Schilling et al., 2010). We also included secondary analyses of the Corcos et al. (2013) and the Dibble et al. (2006) studies (Dibble, Hale, Marcus, Gerber, & LaStayo, 2009; Prodoehl et al., 2014; David et al., unpublished[AUQ2]). The main characteristics and results of each study are summarized in Table 1.

\insert Table 1

Intervention

One study evaluated a PRET intervention against a no-exercise standard care control group (Schilling et al., 2010), while another study compared it with an active control group consisting of activities such as stretching, balance exercise, and nonprogressive strengthening (Corcos et al., 2013). Dibble et al. (2006) compared two groups utilizing PRET, with one group substituting traditional lower body resistance exercises with a high-force eccentric ergometer. Other studies compared PRET with both Tai Chi and a stretching control group (Li et al., 2012), PRET plus balance training versus balance training alone (Hirsch et al., 2003), and PRET plus creatine monohydrate supplementation versus PRET with a placebo supplement (Hass et al., 2007). The frequency and duration of the interventions ranged from 120–180 min per week for 2–24 months.

The resistance progressed heterogeneously among all six studies. One study used weighted vests or ankle weights as the form of resistance, beginning with vests that were 1% of each subject's body weight and increasing the weight by 1–2% of body weight every fifth week until 5% of body weight was achieved (Li et al., 2012). One study began subjects at 30–40% of their one repetition maximum (1-RM) for upper body exercises and 50–60% of 1-RM for lower body exercises during the first week, which was increased by at least 5% when the subject was able to perform a set of the exercises with acceptable form and perceived ease (Corcos et al., 2013). Subjects started with one set of eight repetitions, and increased to three sets of eight repetitions within 8 weeks of the intervention (Corcos et al., 2013). After 8 weeks on the strength program, subjects switched to a strength plus speed program with emphasis on the speed with which each repetition was completed. The resistance was set at 70–80% of their 1-RM and each subject performed two sets of 12 repetitions. Every 8 weeks subjects alternated between

the strength and strength plus speed training programs. The resistance was set at where subjects left off for the respective programs and progressed as mentioned above. In one study, subjects started at three sets of five to eight repetitions, and when eight repetitions could be achieved in all three sets, the weight was increased by 5–10% (Schilling et al., 2010). Another study required subjects to perform 8–12 repetitions at 50–70% of their 1-RM and increased the resistance by 5–10% when 12–20 repetitions could be performed (Hass et al., 2007). Hirsch and colleagues' (2003) protocol called for subjects to perform one set of 12 repetitions at 60% of 4-RM for the first 2 weeks and then increased to 80% of 4-RM at the end of the second week. Each subject's 4-RM was assessed every 2 weeks and their stimulus was adjusted accordingly to sustain a load of 80% of the 4-RM (Hirsch et al., 2003). In the control group that performed traditional PRET, Dibble et al. (2006) assessed each subject's 1-RM weekly and subjects performed three sets of 12–15 repetitions at 60–70% of their 1-RM. Subjects in the high-force eccentric ergometry group began with 3–5 min at a rating of perceived exertion (RPE) of 7 on a scale of 6–20, and increased by approximately 5 min and two RPEs each week until the fifth week, where subjects were cycling between 15 and 30 min at an RPE of 13 (Dibble et al., 2006).

Subjects trained under direct supervision of certified personal trainers, strength and conditioning coaches, and health and fitness instructors in four studies (Hass et al., 2007; Hirsch et al., 2003; Li et al., 2012; Schilling et al., 2010). In one study, a personal trainer directed both weekly sessions for the first 6 months, then one weekly session after 6 months (Corcos et al., 2013). Dibble et al. (2006) did not report if subjects were supervised during training sessions or who delivered the intervention. Only one study reported that the intervention was carried out in a group setting, with 8–12 subjects per exercise instructor (Li et al., 2012).

Participants

A total of 302 subjects with PD participated in the six studies reviewed. The minimum number of subjects in a study was 15 (Hirsch et al., 2003), and the maximum was 195 divided between three exercise groups (Li et al., 2012). The Hoehn and Yahr (H&Y) scale was used to measure disease status in six studies, with one study utilizing the UPDRS motor score as well (Corcos et al., 2013). Studies included patients with PD at H&Y stages 1, 2, 3, and 4.

Outcomes

Motor Signs of Parkinson's Disease.

Four studies examined the effects of PRET on motor function in individuals with PD using the UPDRS motor score (Corcos et al., 2013; Dibble et al., 2006; Hass et al., 2007; Li et al., 2012). These four studies assessed UPDRS while on medication and one study assessed UPDRS while off medication as well (Corcos et al., 2013). Three studies found no significant changes in UPDRS motor scores on medication (Corcos et al., 2013; Dibble, Hale, Marcus, Gerber, & LaStayo, 2009; Hass et al., 2007), although one study reported that the PRET group's improvement exceeded that of the control group based on effect size (ES) (EXP ES = 0.32 vs. Control ES = 0.17) (Dibble et al., 2009). Corcos et al. (2013) found significant between-group differences in UPDRS motor scores off medication, with the PRET group displaying greater change in UPDRS at 12 (p = .02), 18 (p = .03), and 24 months (p < .001). Li et al. (2012) did not find any significant between group differences (Tai Chi vs. PRET) in UPDRS motor scores on medication, but did report a significant time effect (p < .001), with subjects decreasing scores by an average of 5.07 points. No significant differences were found in UPDRS total score in one study (Hass et al., 2007). H&Y scores significantly increased for the PRET group over the course of the intervention (pretraining 2.2 ± 0.2, posttraining 2.6 ± 0.2, p = .02), but remained unchanged for the PRET plus creatine monohydrate supplementation group (Hass et al., 2007). The between-group difference was not statistically significant (Hass et al., 2007).

The meta-analysis comparing pre- and post-PRET UPDRS scores included 4 studies (Corcos et al., 2013; Dibble et al., 2009; Hass et al., 2007; Li et al., 2012). The UPDRS motor scores in this meta-analysis were off medication in one study (Corcos et al., 2013) and on medication in the other studies (Dibble et al., 2009; Hass et al., 2007; Li et al., 2012). It provides class IV level of evidence that motor signs of Parkinsonism in PD improves with PRET (mean difference: 3.69 [2.14, 5.24]) (Figure 1). When compared with a control group, PRET significantly improved motor signs of Parkinsonism in patients with PD (mean difference: 2.97 [1.69, 4.26]) (Figure 1).

\insert Figure 1

Physical Performance: Gait, Balance, and Functional Mobility.

Gait was assessed using measurements of stride length (Li et al., 2012), walking velocity (Li et al., 2012), the 6-min walk test (6MWT) (Dibble et al., 2006; Prodoehl et al., 2014; Schilling et al., 2010), and the 10-m walk test (Dibble et al., 2009). Although stride length for the Tai Chi group was superior to that of the PRET group at 24 weeks (p = .01), the PRET group had significant improvements from baseline to 24 weeks in both stride length (mean change +4.3 cm, p = .01) and walking velocity (mean change +10.0 cm/s, p = .001) (Li et al., 2012). In one study, the 6MWT distance significantly increased for the PRET group (p = .05), but there was no between-group differences (p > .05) (Schilling et al., 2010). A preplanned secondary analysis from the Corcos et al. (2013) study found that the 6MWT off medication and the walk speed on and off medication significantly improved following a PRET intervention (Prodoehl et al., 2014). However, the PRET group did not differ from the modified fitness count group on any physical function measures (Prodoehl et al., 2014). Another study reported

superior increases for the eccentric training group over time (eccentric group +21%, ES = 0.68; standard care group +5%, ES = 0.20) and between groups (p = .02) (Dibble et al., 2006). Subjects in the high-force eccentric resistance training group performed significantly better on the 10-m walk test at the end of the 12 week intervention (p = .02), and within-group effect sizes demonstrated that improvements for the eccentric resistance training group were superior to that of the active control group (eccentric group +12%, ES = 0.38; active control –2%, ES = 0.12) (Dibble et al., 2009).

Four studies assessed balance, using maximal excursion and directional control (Li et al., 2012); the Functional Reach Test (Li et al., 2012; Prodoehl et al., 2014); the Sensory Organization Test protocol with an EquiTest system (Hirsch et al., 2003); the Activities-Specific Balance Confidence Scale (ABC), sway on floor, sway on foam, maximum balance range in standing (Schilling et al., 2010); and the Berg Balance Scale (BBS) (Prodoehl et al., 2014). Although the Tai Chi group scored significantly better than the PRET group in both maximal excursion (p = .01) and directional control (p = .002), the PRET group did significantly improve scores for maximum excursion (mean change +4.02 percentage points, p = .02) (Li et al., 2012). The PRET group significantly increased functional reach scores at the end of the intervention in two studies (Li et al., 2012; Prodoehl et al., 2014). However, in one study the Tai Chi group outperformed the PRET group (p = .01) (Li et al., 2012), while there was no significant difference between the PRET group and the modified fitness count group in the other study (Prodoehl et al., 2014). Balance assessed with the BBS improved following 24 months of PRET training in one study, however this change was not significantly different from the one observed for the modified fitness count group (Prodoehl et al., 2014). One study did not report a significant time effect for either group on the average EquiTest balance score, but summary balance scores for the combined high intensity resistance training plus balance group were significantly higher than the balance training only group (p = .006) (Hirsch et al., 2003). In the same study, latency to fall and percentage of trials resulting in falls significantly improved for both groups (p < .05), although this difference was not significant 4 weeks postintervention (Hirsch et al., 2003). There were no significant group or time interactions found with the ABC scale (Schilling et al., 2010).

Five studies assessed general functional mobility using a variety of different measures (Corcos et al., 2013; Dibble et al., 2006; Dibble et al., 2009; Hass et al., 2007; Li et al., 2012; Schilling et al., 2010). The average off-medication mPPT score increased from baseline for both modified fitness counts and PRET groups at 6 months and at 24 months with no significant difference between groups (Corcos et al., 2013). In a secondary analysis, Prodoehl et al. (2014) reported similar results for the sit-to-stand test and the timed-up-and-go test (TUG). Two other studies used the TUG test and found no significant group or time interactions (Li et al., 2012; Schilling et al., 2010), but one study reported that TUG scores were significantly better for the high-force eccentric training group when compared with the active control (Dibble et al., 2009). One study assessed functional mobility using stair ascent and descent (Dibble et al., 2006). The high-force eccentric resistance training group increased mobility assessed by stair ascent time by 11% (ES = 0.41) and descent time by 18% (ES = 0.53), versus the active control group who increased mobility assessed by ascent time by 1% (ES = 0.03) and descent time by 0% (ES = 0.01) (Dibble et al., 2006). The difference in stair descent time was significantly different between groups (p = .007), and stair ascent time between groups approached significance (p = .06) (Dibble et al., 2006). In one study, the PRET plus creatine supplementation group significantly decreased the time it took to perform three consecutive chair rises (p < .05), but no significant time effect was noted for the PRET group with a placebo supplement. The difference between groups was not significant (Hass et al., 2007).

Quality of Life and Patient Perceived Improvement.

Two studies investigated the effects of PRET on quality of life using the PDQ-39 (Corcos et al., 2013; Dibble et al., 2009). Six months after beginning the intervention, the PRET group's scores were significantly better than the modified fitness counts group's scores (p = .02), but at 24 months there was no difference between groups in one study (Corcos et al., 2013). Dibble et al. (2009) reported that the high-force eccentric resistance training group's quality of life was significantly better than the active control group at 3 months (p = .04), and that there was a significant time effect reported for the PDQ-39 single index score, and ADL and bodily discomfort subsections (p < .006). Within-group effect sizes suggested that the high-force eccentric training group improved their quality of life to a greater extent than the active control group (Exp ES = 0.45, Control ES = 0.08) (Dibble et al., 2009). Using the UPDRS-ADL subtest, which is a self-report questionnaire, one study revealed no significant time or group interactions (Hass et al., 2007).

Improved Physiological Measures: Strength, Torque, Muscle Volume, and Body Composition.

Knee extensor strength was evaluated in four studies using maximal voluntary isometric force (Dibble et al., 2006; Hass et al., 2007; Hirsch et al., 2003; Schilling et al., 2010), and all four found that knee extensor strength was significantly greater than preintervention values following a PRET intervention. Two studies found that the knee extensor strength of the PRET group was significantly better than that of the standard care (Schilling et al., 2010) and balance training (Hirsch et al., 2003) control groups, and that significance remained during follow-up assessments 4 weeks postintervention (Hirsch et al., 2003). Two studies measured knee extensor torque (Dibble et al., 2006; Li et al., 2012), one study measured knee flexor torque (Li et al., 2012), and another study measured elbow flexion torque (Corcos et al., 2013). Li et al. (2012) found

that peak knee extensor and knee flexor torque values significantly increased over time in the PRET group. However, peak torque changes were not significantly different between the PRET group and the Tai Chi group. Dibble et al. (2006) reported increases in average torque in both the more affected and less affected leg, with differences between groups not revealing significance.

The PRET plus creatine monohydrate supplementation group increased chest press and biceps curl 1-RM values over the course of the intervention ($p < .05$), whereas the PRET group without supplementation saw significant changes only in chest press 1-RM values ($p < .05$). There was a significant between-group difference for both of these strength values, favoring the PRET plus creatine supplementation group ($p < .05$) (Hass et al., 2007). Elbow flexion torque values were significantly larger in the PRET group when compared with the modified fitness counts group both on and off medication at 12, 18, and 24 months (Corcos et al., 2013).

Muscle volume in both the more affected (+6%) and less affected (+6%) leg increased over time and was significantly more affected by high-force eccentric training than the active control using traditional PRET (more affected $p = .014$, less affected $p = .03$) (Dibble et al., 2006). Muscular endurance was measured in one study, which reported that PRET significantly increased both chest press endurance and leg extensor endurance (Hass et al., 2007). Body composition assessments showed no significant differences between groups in body mass, body fat percentage, fat mass, or fat free mass, and no significant changes over time for body mass, body fat percentage, or fat mass (Hass et al., 2007). Fat free mass increased for both groups (PRET plus creatine $p = .02$, PRET $p = .01$) (Hass et al., 2007).

Cognition.

Two studies measured the effects of PRET on cognition (David et al., unpublished; Hass et al., 2007). As a secondary analysis from the Corcos et al. (2013) study, David et al. (unpublished) used three measures of cognition: Digit Span Forward and Backward, Stroop Color-Word, and Brief Test of Attention. There were no significant between-group differences found for any of these measures (David et al., unpublished). However, a main effect of time was observed for all three cognitive measures. To elaborate, at the study end-point of 24 months, averaging across the mFC and PRE groups, significant improvements relative to baseline were observed on the Digit Span Forward and Backward test, the Stroop Color-Word Interference Score, and the Brief Test of Attention (David et al., unpublished). Hass et al. (2007) administered the UPDRS mental subtest to subjects but found no significant differences between groups or over time for neither the intervention nor control group.

Discussion

Lessons from Randomized Controlled Trials That Examined Progressive Resistance Exercise Training in Parkinson's Disease

Motor Signs of Parkinson's Disease.

The UPDRS is the gold standard assessment tool for characterizing disease severity in persons with PD (Movement Disorder Society Task Force on Rating Scales for Parkinson's, 2003). This current review provides class II and class IV level of evidence that PRET improves motor signs of Parkinsonism in PD. However, this result should be interpreted cautiously. The UPDRS motor scores in the meta-analysis were off medication in one study (Corcos et al., 2013) and on medication in the other studies (Dibble et al., 2009; Hass et al., 2007; Li et al., 2012). Only one study assessed motor signs of PD independently while on and off medication. They found significant between-group differences at 12, 18, and 24 months when assessed off medication, but found no differences between groups when assessed on medication (Corcos et al., 2013). This study supports a positive effect of PRET on disease severity in PD and demonstrates the influence of medication on motor symptom assessments in mild to moderate PD. All other studies assessed motor signs while subjects were in a medicated state, which could have masked the results (Dibble et al., 2009; Hass et al., 2007; Li et al., 2012). The meta-analysis performed in this review found a significant improvement of UPDRS-III following PRET. The mean difference was 3.69 (2.14. 5.24), which is lower than a change of five points, which was found to be the most appropriate cutoff score for clinical significance for H&Y stages I to III (Schrag, Sampaio, Counsell, & Poewe, 2006). However, one should take into consideration the progression of motor impairment in PD with a mean annual change of 3.3 points (on medication) in a population-based cohort of treated patients with PD (Alves, Wentzel-Larsen, Aarsland, & Larsen, 2005). Thus, a mean improvement of 8.70 (2.05. 15.35) points on the UPDRS motor subscale off medication at 24 months observed in one study represents a clinically significant improvement (Corcos et al., 2013).

With regard to other types of exercise training, Tai Chi is another intervention that has been associated with significant improvement in the UPDRS-III in a recent meta-analysis with a mean difference of –4.34 points, 95% confidence interval (–6.67, –2.01) (Ni, Liu, Lu, Shi, & Guo, 2014). We recently reviewed the effect of endurance exercise training in PD and concluded that there is not yet a proven effect of endurance exercise training on specific features of PD such as motor signs of PD (Lamotte et al., 2014). One recent review concluded that aerobic exercise showed immediate beneficial effects in improving motor function assessed by the UPDRS-III in PD (Shu et al., 2014). However, the authors included several studies that did not fit our definition of endurance exercise and some of these studies did not monitor heart rate or VO_{2max}. The main effect on the UPDRS-III in the meta-analysis by Shu

et al. (2014) was driven by studies on dance therapy and Tai Chi (Hackney & Earhart, 2008, 2009; Li et al., 2012). Other factors besides the potential aerobic component of these programs may explain the positive effect on motor symptoms. Indeed, practicing standing balance activities, motor skill learning in the presence of external cues provided by a partner, music in dance therapy, or the psychological benefits of Tai Chi such as reducing stress and anxiety and increasing self-esteem could play a role in motor improvement in PD (Duncan & Earhart, 2012; Ni et al., 2014; Wang et al., 2010).

There is a need for a well-designed controlled clinical trial that is powered to detect differences in the motor signs of PD that includes both on and off medication testing to truly assess motor signs of PD changes without any confounding effect of medication. There is also a need for a controlled clinical trial that would compare the effect of PRET on motor signs of Parkinsonism in PD with other types of interventions such as endurance exercise training.

Physical Performance: Gait, Balance, and Functional Mobility.

Parkinsonian gait is described as festinating with decreased stride length, moderately decreased cadence, overall decreased velocity of movement, and associated disturbances in range of motion (Morris et al., 2001). With regard to the studies included in this current review, there is evidence that a supervised and structured PRET protocol may improve functional performances in individuals with PD. Gait, balance, and functional mobility clearly improved following a PRET intervention in two studies included in this review (Li et al., 2012; Prodoehl et al., 2014). This is in accordance to a past study comparing the effects of PRET on gait in patients with PD versus healthy controls that found that a PRET intervention significantly increased stride length and gait velocity in patients with PD after 8 weeks of training (Scandalis, Bosak, Berliner, Helman, & Wells, 2001). Prodoehl et al. (2014) showed a time effect but not a group-by-time interaction for gait parameters, balance, and functional mobility. One of the reasons for the absence of between-group difference could be the mild to moderate PD participants who were not impaired enough to see significant change. A second reason could be a ceiling effect on the many of the assessments used in the Corcos et al. (2013) study that are designed to classify patients on mobility and balance in the community and not to detect change following an intervention. However, in another study that included PD subjects with gait impairment who had reported a fall within the last year, the addition of PRET to a balance training program was not found to improve both fast and comfortable walking speed in comparison with a balance training group (Allen et al., 2010). Li et al. (2012) found that Tai Chi may be more beneficial than PRET to improve balance in PD. The results of this review tend to favor a positive influence of PRET on gait for mild to moderate PD. However, patients with PD with some postural instability and gait disturbances may not have the same benefit of muscle strengthening, and PRET may not be the best type of exercise to improve physical function in PD in comparison with other types of exercise such as Tai Chi. More research is needed to explore the positive effect of PRET on gait in PD.

Reduced balance is associated with falls, poor mobility, disability, and reduced quality of life in PD, and balance is poorly responsive to levodopa (Boonstra, van der Kooij, Munneke, & Bloem, 2008; Franchignoni, Martignoni, Ferriero, & Pasetti, 2005). 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 (Allen, Sherrington, Paul, & Canning, 2011). Our review indicates that PRET may improve balance in individuals with PD. However, this review suggests that elements of balance training should be present in the exercise program to produce the most beneficial effects. One study specifically included balance training as a part of the intervention (Hirsch et al., 2003), and one study used exercises that require some degree of balance to perform, such as lunges, squats, and forward/lateral step ups (Li et al., 2012). Each of these studies did report beneficial effects on balance outcomes. In two other studies, results on balance outcomes were contradictory when subjects performed resistance exercises such as leg presses, seated leg curls, and calf presses, which do not require the same degree of balance (Prodoehl et al., 2014; Schilling et al., 2010). Therefore, there is no clear evidence that PRET alone can improve balance in PD, although incorporating some balance training in an exercise program may produce a task-specific training for balance.

This review suggests that PRET is capable of improving some functional mobility outcomes, although whether this improvement translates to clinical significance is not as definite. Nearly all studies either showed improvements over time or significant group differences for measures of functional mobility, with the exception of no differences found for the mPPT (Corcos et al., 2013) and the TUG test in two out of four studies (Li et al., 2012; Schilling et al., 2010). In the study by Corcos et al. (2013), the control group was not sedentary and engaged in nonprogressive resistance and balance exercises, which may explain why no postintervention between-group differences were found for physical function outcomes. The fact that the studies in this current review have included mild to moderate PD with preserved functional mobility at baseline may also have influenced the results. In the two studies where TUG improved, it improved by 1.44 s at 12 weeks in one study (Dibble et al., 2009), and the median change from baseline was 0.99 s at 24 months in the other study (Prodoehl et al., 2014). Minimal detectable change values are useful in determining whether change during or after intervention is clinically significant. It has been reported that the minimal detectable change for the TUG test for patients with PD is 4.85 s (Dal Bello-Haas, Klassen, Sheppard, & Metcalfe,

2011). Therefore, although scores were significantly superior to that of the control group in one study, the improvement was likely not clinically significant (Dibble et al., 2009). Interestingly, PRET was found to be as effective as balance training in improving latency to fall and percentage of trials resulting in falls in one study (Hirsch et al., 2003). In another study not included in the current review because of a multimodal intervention, self-reporting falls did not improve following PRET combined with some balance training (Allen et al., 2010). It was unclear if PRET was insufficient to reduce self perceived risk of falls in a subset of patients with PD with gait impairment or whether the Falls Efficacy Scale was insensitive to the exercise changes. PRET has been shown to improve strength and functional performance in older adults, which potentially could lead to a reduced risk of falls (Liu & Latham, 2009). Therefore, more research is needed to assess the specific effect of PRET on functional mobility in PD and to determine if PRET can reduce or prevent falls or fear of falling in individuals with PD.

Quality of Life and Patient Perceived Improvement.

Quality of life (QOL) is impacted by several factors in PD including reduced motor function, gait disturbances, and depression (Global Parkinson's Disease Survey Steering, 2002). The PDQ-39 is a reliable and validated self-administered questionnaire to assess quality of life in PD subjects (Jenkinson, Fitzpatrick, Peto, Greenhall, & Hyman, 1997). Using this questionnaire, one study failed to show any improvement in QOL at the end of a 24-month PRET intervention (Corcos et al., 2013), while another study found a significant improvement of QOL following PRET (Dibble et al., 2009). However, Dibble et al. (2009) specified that after correction to the a priori level of significance, the result was not statistically significant. In one study, QOL scores favored PRET at 6 months, but not thereafter, even as off medication UPDRS-III scores improved (Corcos et al., 2013). It is unclear if the PRET program was insufficient to improve QOL at 12, 18, and 24 months, if it was limited to only a transient improvement, or whether the PDQ-39 was insensitive to the exercise changes after 6 months for mild to moderate disease severity PD subjects. Exercise intervention studies provide social engagement and interaction in individuals with PD. However, one could imagine a potential burden for patients with PD associated with an exercise program repeated several times a week with the same type of exercise for 24 weeks, and this could have influenced self-reported well-being. We conclude that further research is needed to explore the effect of PRET on QOL 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 subjects and the effect of exercise on counterbalancing these factors is not clear (Chrischilles, Rubenstein, Voelker, Wallace, & Rodnitzky, 2002; Global Parkinson's Disease Survey Steering, 2002; Whetten-Goldstein, Sloan, Kulas, Cutson, & Schenkman, 1997).

Physiological Measures.

Muscle weakness contributes to bradykinesia, which is thought to result from the inability of basal ganglia output to support the cortical processes involved in preparing and executing movement (Berardelli, Rothwell, Thompson, & Hallett, 2001; David et al., 2012). In this review, results were largely consistent and convincing that PRET increases muscle strength, torque, volume, and endurance. When considering bradykinesia, tremor, rigidity, and weakness, reduced muscle strength has been found to be the biggest contributor to reduced muscle power in medicated individuals with PD (Paul, Canning, Sherrington, & Fung, 2012). Moreover, muscle power was correlated with walking velocity and reduced fall risk in individuals with PD in one study not included in this review (Allen et al., 2010), illustrating the potential benefit of strength training on ambulation in individuals with PD.

Cognition.

Cognition is affected early in PD and progresses with disease severity. Impaired executive function is prevalent and is related to alterations in frontostriatal connectivity (Godefroy et al., 2010; Lewis, Dove, Robbins, Barker, & Owen, 2003). There is also a strong link between cognitive impairment and reduced function in PD. Indeed, cognitive impairment has been identified as an independent risk factor for falls (Latt, Lord, Morris, & Fung, 2009), and a recent study found that impairments in executive function were associated with inferior performance on measures of gait and balance in PD (Xu et al., 2014). Exercise in general has been shown to improve executive function and prevent cognitive decline in healthy individuals (Larson et al., 2006; van Gelder et al., 2004). One clinical trial provides class II level of evidence that 24 months of PRET is effective in improving attention and working memory in nondemented patients with mild-to-moderate PD when evaluated off medication, but this effect was not different than an exercising control group (David et al., unpublished). This study found a significant improvement on the Stroop test, which reflects response interference control. This is particularly important because impaired performance on the Stroop has been shown to be associated with greater risk of developing dementia in individuals with PD (Janvin, Aarsland, & Larsen, 2005). One interesting point discussed by David et al. (unpublished) is the potential role of increased social and cognitive engagement in individuals with PD participating in an exercise intervention study. Therefore PRET may improve cognitive functions, particularly executive function, in nondemented mild to moderate PD. Further study is needed to confirm this association, address the effect of exercise on other domains of cognition, and to understand central mechanisms that may be responsible for these improvements.

Knowledge Gaps

Exercise, Neurophysiology, and Neuroprotection.

The fact that exercise may promote neuroplasticity has been shown in studies using animal models of PD. Exercise could induce neural changes 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 (Cho et al., 2013; Fisher et al., 2004; Petzinger et al., 2013; Toy et al., 2014; Vučković et al., 2010). Moreover, exercise-induced neuroplasticity is not restricted to the dopaminergic system, and modulation of the glutamatergic neurotransmission has been shown secondary to exercise training (Kintz et al., 2013; VanLeeuwen et al., 2010). These specific examples of neuroplasticity are difficult to study in humans. Noninvasive human neurophysiological techniques, such as TMS, PET imaging, electroencephalography, and functional magnetic resonance imaging have limitations, such as interindividual variability, lack of spatial or temporal resolution, cost, lack of knowledge regarding specific mechanisms, and lack of specificity for neuronal populations. Future research should employ combinations of human neurophysiological techniques to provide additional information about exercise-induced neural changes. Using animal models of Parkinsonism with treadmill exercises, several studies have suggested a potential neuroprotective effect of exercise (Lau, Patki, Das-Panja, Le, & Ahmad, 2011; VanLeeuwen et al., 2010), but these findings are 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 medication, as well as disease duration, is not known. To date, no study has suggested a disease modifying effect of exercise training in PD.

Role of Stage of Disease Progression.

Most of the studies that have investigated the effects of exercise in PD have included a limited number of participants with mild to moderate disease severity and were highly supervised with a short duration. The extent to which exercise would still be beneficial to patients in the later stages of PD is unknown, although there is no reason to think that it would not be beneficial. With the progression of PD, individuals develop several motor and nonmotor complications such as motor fluctuations, dyskinesia, unpredictable response to medications, increased fall risk, dysautonomia, dementia, hallucinations, depression, and psychosis (Varanese, Birnbaum, Rossi, & Di Rocco, 2011). Therefore, patients with late stage PD who suffer from severe motor disability or motor complications associated with levodopa therapy may not be able to follow a PRET protocol. Safety is another important issue. However, besides transient muscle soreness, which is not unexpected after the first few sessions of PRET, there were no severe adverse effects related to PRET reported in the studies included in this current review. This is consistent with a review of the literature that concluded that there was little evidence to support recommendations that PRET may be inappropriate in older individuals with cardiopulmonary, musculoskeletal, or neuromuscular disorders (Taylor et al., 2005). Cognitive impairment, which is common in advanced PD, could also be seen as an exclusion criterion for exercise because the patient could have difficulties following the protocol. However, supervised exercise has been shown to be safe and feasible in patients with cognitive impairment (Forbes, Thiessen, Blake, Forbes, & Forbes, 2013), and we discussed the potential positive effects of PRET on cognition in PD. Studies with longer duration and an appropriate follow-up, including evaluation of pharmacologic therapy, would be essential to confirm the benefit of PRET and to explore if exercise-induced changes in PD are maintained over time. 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.

Exercise and Nonmotor Symptoms in Parkinson's Disease.

In addition to the commonly recognized motor symptoms, there has been a greater interest in nonmotor disturbances in PD. These nonmotor symptoms include cognitive impairment, depression, autonomic and sleep disturbances, pain, and fatigue (Garcia-Ruiz, Chaudhuri, & Martinez-Martin, 2014). These nondopaminergic symptoms are important to consider as they occur in almost all patients with PD, they affect almost all aspects of daily life, and they have been shown to have a greater effect on health-related quality of life than classic motor symptoms (Maetzler, 2014). In this review, nonmotor symptoms have been investigated as secondary outcomes and additional clinical trials that include nonmotor symptoms as primary outcome variables are needed to explore the potential benefit of exercise in patients with PD.

Exercise Duration and Best Mode of Physical Activity for Patients With Parkinson's Disease.

Gerecke, Jiao, Pani, Pagala, and Smeyene (2010) have suggested that duration of an intervention program is crucial to protect dopaminergic neurons against death caused by acute MPTP-intoxication in an animal model of PD. In humans, the necessary duration of an exercise program intervention to improve functional outcomes in PD is unknown and most of the studies have investigated exercise-induced changes with short-term duration and follow-up (Table 1). The best mode of physical activity for patients with PD is also a question that needs further exploration. This current review provides evidence that PRET improves motor signs of Parkinsonism in PD. However, this review reveals that PRET may have a limited effect on functional performance in PD. Other types of exercise such as Tai Chi or endurance exercise training may be more beneficial than PRET to improve

functional performances in PD (Lamotte et al., 2014; Ni et al., 2014). To date, the mechanisms underlying exercise-induced changes for each program are not fully understood. 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. There is a real need for well-designed controlled clinical trials that would compare or combine different modes of exercise.

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. 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 PRET can improve strength and motor signs of Parkinsonism in PD. PRET may also be beneficial for functional outcomes such as gait and balance but more research is needed to explore the specific effect of PRET on physical function in PD. Very few studies have investigated the effect of PRET on cognition in PD. However, preliminary results suggest a potential benefit on executive function in individuals with PD. Further research is needed to explore the effects of PRET on both motor symptoms and nonmotor symptoms such as depression, cognition, sleep disturbances, autonomic nervous system dysfunction, and quality of life in individuals with PD. We conclude that a highly supervised PRET program could be beneficial for mild to moderate PD. There is a need for well-designed large-scale randomized controlled trials to confirm benefits and safety of PRET for this population and to explore potential benefits on the motor and nonmotor signs of PD. Further research on exercise in PD should address specific questions about the optimal exercise mode, intensity, and duration.

Author Contributions

GL and ES contributed equally to the review of the literature, data analysis, writing and preparation of the manuscript, and the review and critique of the manuscript. MR, FD, SS and DC: data analysis, writing contribution, review and critique of the manuscript.

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Figure 1 — Meta-analyses on the effect of PRET on motor signs of Parkinsonism in PD assessed by the UPDRS motor subscale in PD. A: Meta-analysis comparing baseline and postintervention UPRDS motor scores (within-group difference). B: Meta-analysis comparing PRET with a control group. The control group consisted of stretching exercise (Li et al., 2012), stretching and balance training (Corcos et al., 2013), and standard physiotherapy (Dibble et al., 2009). Note: Corcos et al. (2013), off medication; Dibble et al. (2009), Hass et al. (2007), and Li et al. (2012), on medication. 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.

Table 1 Randomized Controlled Studies That Examined the Effects of Progressive Resistance Exercise in Parkinson's Disease

Trial	Design	Intervention	Sample	Outcomes	Results	Limitations
Corcos et al. (2013) *David et al. (unpublished) Prodoehl et al. (2014)	RCT	2 arms (1) PRE—11 strengthening exercises, 2/w (2) mFC (C)—stretches, balance exercises, breathing, and nonprogressive strengthening, 2/w Progression: Started at 30–40% of 1-RM for upper body exercises and 50–60% of 1-RM for lower body exercises during the first week. Resistance was increased by at least 5% if perception of the exercise was somewhat easy. One set of 8 reps, increased to 3 sets of 8 reps. After 8 w: 70–80% 1-RM and 2 sets of 12 reps. Duration of intervention: 24 mo Assessments: 6, 12, 18, 24 mo	48 PD at 6 months, 38 PD at 24 months, age 50–67, on stable dopaminergic therapy, able to walk for 6 min	(a) Motor disability: UPDRS-III off medication, UPDRS-III on medication (b) Function: mPPT, 6MWT, BBS, sit to stand, FRT, TUG, BBS, walk speed (c) QOL and self perceived improvement: PDQ-39 (d) Physiological measures: Elbow F movement speed, elbow F torque *(e) Cognition: Digit Span Forward and Backward, Stroop Color-Word, Brief Test of Attention	Between-group differences: –UPDRS-III off medication: Exp < C (< .001) –Elbow F movement speed (off): Exp > C 12 mo (.009) –Elbow F torque (off): Exp > C (< .001) –Elbow F torque (on): Exp > C 24 mo (0.04) –No *SD* between Exp and C at any timepoint for UPDRS-III on medication, mPPT (on or off), elbow F movement speed on medication, PDQ-39 at 24 mo, or any cognitive outcomes Within-group differences: –UPDRS-III (off) improved with PRE (< .05) –Digit Span Forward and Backward at 24 mo: Exp +2 (0.02), C +3 (< 0.01) –Stroop Color-Word: Exp at 24 mo: +2 (0.053), C = no *SD* –Brief Test of Attention: No *SD* for either group at 12 or 24 mo	Design: Not double-blind, no "no-exercise" control group
Li et al. (2012)	RCT	3 arms (1) Tai Chi (TC)–8-form routine of 6 Tai Chi movements, 1 hr, 2/w (2) Resistance training (PRE)—weighted vests & ankle weights, 8–10 exercises (including forward/side steps, squats, forward/side lunges, heel and toe raises), 1h, 2/w (3) Stretching (C)—seated/standing, upper body & lower extremities, joint extension/flexion & trunk rotation, 1h, 2/w	195 PD, HR 1–4, age 40–85, at least one score ≥ 2 for at least one limb for tremor, rigidity, postural stability, or bradykinesia items on the UPDRS-III	(a) Motor disability: UPDRS-III (b) Function: Maximal excursion (%), directional control (%), stride length, gait velocity, FRT, TUG (c) QOL and self perceived improvement: N/A (d) Physiological measures: Knee E and F peak torque (e) Cognition: N/A	Between-group differences: –TC > PRE for maximal excursion (.01), directional control (.002), stride length (.01), and FRT (.01) –TC vs. PRE: No *SD* in UPDRS-III, gait velocity, peak torque knee E, peak torque knee F, or TUG Within-group differences for PRE and C: –UPDRS-III: PRE –5.07 (< .001), C –1.40 (.05), TC –6.42 (< .05) –Maximum excursion: TC +9.56 (< .001), PRE +4.02 (.02) –Directional control: TC +8.02 (<	Design: No "no-exercise" group

		Progression: Vests started at 1% of body weight, increased by 1–2% of body weight every fifth week until 5% of body weight was achieved. Ankle weights started at 1 lb/limb, increased to 3 lb. 1–3 sets of 10–15 reps. Duration of intervention: 24 w Assessments: 3, 6, 9 mo			.001), PRE –2.43 (.35) –Stride length: TC +10.3 (< .001), PRE +4.3 (.01) –Gait velocity: TC +10.4 (< .001), PRE +10.0 (.001) C –4.50 (.01) –Peak torque knee E: TC +13.9 (.001), PRE +14.6 (< .001) –Peak torque knee F: TC +5.1 (.01), PRE +8.9 (.001) –FRT: TC +5.0 (< .001), PRE +2.2 (.007)	
Schilling et al. (2010)	RCT	2 arms (1) Leg press, seated leg curl, & calf press, maximum effort to volitional fatigue (Exp), 2/w (2) Standard care (C) Progression: 3 sets of 5–8 reps. When 8 reps completed for all 3 sets: weight increased 5–10%. Duration of intervention: 8 w	15 PD, HR state of 1–2.5 while on medication	(a) Motor disability: N/A (b) Function: 6MWT, TUG, ABC (%) (c) QOL and self perceived improvement: N/A (d) Physiological measures: Knee E 1-RM (e) Cognition: N/A	Between-group differences: –Knee E 1-RM: Exp > C (.001) –No *SD* for 6-min walk, TUG, or ABC Within-group differences: –6-min walk improved with PRE (.005) –TUG: No significant time effect for Exp (.069) –ABC (%): No significant time effect (.664) –Knee E 1-RM: improved with PRE (.001)	Design: Short duration (8 w)
Dibble et al. (2009) Dibble et al. (2006)	RCT	2 arms (1) High-force eccentric resistance training (eccentric ergometer) + active control exercises (Exp). 3/w, 45–60 min (2) Active control (C)—light calisthenics & stretching, treadmill walking, cycle ergometer, & lifting weights (machines & free weights) with upper extremities & 3 lower limb exercises. 3/w, 45–60 min Progression: 1-RM for each exercise assessed—exercise prescription for each week included 3 sets of 12–15 reps at 60–70% of 1-RM weight. Eccentric ergometer started at 3–5 min and RPE of 7, increased in	19 PD, HR 1–3, age 40–85	(a) Motor disability: UPDRS-III (b) Function: 10-m walk test, TUG, 6MWT, stair ascent, stair descent (c) QOL and self perceived improvement: PDQ-39 (d) Physiological measures: Muscle volume in quadriceps, knee E torque, unilateral quadriceps MVC (e) Cognition: N/A	Between-group differences: –Exp > C for 10-m walk test (.02), TUG (.03), 6-min walk (.013), stair ascent (.06), stair descent (.007), PDQ-39 (.04) –Muscle volume: More affected leg: Exp > C (.014), less affected leg: Exp > C (.03) –Average torque, quad MVC: no *SD* (> .05) Within-group differences (effect size): –UPDRS-III: Exp ES = 0.32, C ES = 0.17 –10-m walk test: Exp +12% ES = 0.68, C –2% ES = 0.12 –TUG: Exp +17% ES = 0.59, C –2% ES = 0.07 –6-min walk: Exp +23% ES =	Design: No "no-exercise" control group, the active control group did traditional PRET

		amount of time spent on ergometer by approximately 5 min and +2 RPE each week until subjects were cycling 15–30 min at an RPE of 13. Duration of intervention: 12 w			0.68, C +5% ES = 0.20 –Stair ascent: Exp +11% ES = 0.41, C +1% ES = 0.03 –Stair descent: Exp +18% ES = 0.53, C 0% ES = 0.01 –PDQ-39: Main effect for time (p <.006) Exp ES = 0.45, C ES = 0.08 –Muscle volume: More affected leg: Exp +6% ES = 0.27, C –0.3% ES = 0.04; less affected leg: Exp +6% ES = 0.26, C +1% ES = 0.14 –Knee E torque: More affected leg: Exp +29% ES = 0.77, C +7% ES = 0.25; less affected leg: Exp +19% ES = 0.73, C +2% ES = 0.06 –Quad MCV: main effect for time (p = .01)	
Hass et al. (2007)	RCT	2 arms (1) Creatine monohydrate + resistance training (Exp) (leg extension, leg flexion, chest press, lat pull down, overhead press, triceps extension, biceps curl, back extension, calf raises), 2/w (2) Placebo (lactose monohydrate) + resistance training (C), 2/w Progression: 1 set of 12 reps. Started at 50–70% 1-RM, increased by 5–10% when 12–20 reps could be completed. Duration of intervention: 12 w	20 PD, HR stage 3 or lower	(a) Motor disability: UPDRS total, UPDRS-III, HR (b) Function: UPDRS-II, chair rise (c) QOL and self perceived improvement: N/A (d) Physiological measures: Body mass, body fat %, fat mass, fat free mass, chest press strength and endurance, leg E strength and endurance, biceps curl 1-RM (e) Cognition: UPDRS-I	Between-group differences: –Chest press 1-RM: Exp > C (< .05) –Biceps curl 1-RM: Exp > C (< .05) –No *SD* for chair rise, leg E 1-RM, leg E endurance, or chest press endurance –No between-group data provided for UPDRS, HR, body mass, body fat %, fat mass, or fat free mass Within-group differences: –Exp Pre > Post for chair rise (< .05) –Exp Pre < Post for biceps curl 1-RM (< .05) –Exp and C Pre < Post for body mass (.06), fat free mass (.02), chest press 1-RM (< .05), chest press endurance (< .05), leg E 1-RM (< .05), leg E endurance (< .05) –C Pre < Post for HR (.02) –No *SD* for either group for UPDRS total, mental, ADL, or motor, body fat %, or fat mass	Design: No direct measure of systemic creatine levels or supplementation compliance, no "no-exercise" control group

Hirsch et al. (2003)	RCT	2 arms (1) High intensity resistance training (knee E and F, ankle plantar-flexion) + balance training (Exp), 30 min balance, 15 min resistance, 3/w (2) Balance training (C) under altered visual & somatosensory conditions, 3/w Progression: 1 set of 12 reps. Started at 60% of 4-RM, increased to 80% 4-RM at end of second week and reassessed every 2 w and adjusted accordingly Duration of intervention: 10 w Assessment: Up to 14 w	15 PD HY (mean ± *SD*) Exp: 1.8 ± 0.3 C: 1.9 ± 0.6	(a) Motor disability: N/A (b) Function: Balance (EquiTest-SOT), latency to fall, % trials resulting in falls (c) QOL and self perceived improvement: N/A (d) Physiological measures: Knee E strength, knee F strength, ankle PF strength (e) Cognition: N/A	Between-group differences: –Mean EquiTest score: Exp > C (.006) –Muscle strength: Exp > C at 10 w & 14 w for average strength of the 3 muscles (.001) Within-group differences: –EquiTest: No *SD* for either group –Latency to fall: Pre < Post for both groups (.025). No significant decline at 14 w –% trials resulting in falls: Pre > Post for both groups (.018) –Average strength: Post > Pre & follow-up strength –Main effect for muscle group: Quadriceps > hamstring and gastrocnemius –Combined group: +52% from Pre to Post (< .05), lost 10% at 14 w vs. 10 w (< .05) –C: +9% from Pre to Post (< .05) Time by muscle group interaction (p = .001): –Knee E: Post = follow-up > Pre –Knee F: Post = follow-up > Pre –Ankle PF: Post > follow-up and Pre	Design: Lack of "no-exercise" control group, lack of a resistance training alone group

Note. RCT = randomized controlled trial; PRE = progressive resistance exercise; w = week; mFC = ?; [AUQ3]C = control group; 1-RM = one repetition maximum; rep = repetition; mo = month; PD = Parkinson's Disease; UPDRS = Unified Parkinson's Disease Rating Scale; mPPT = modified physical performance test; 6MWT = 6-min walk test; BBS = Berg Balance Scale; FRT = functional reach test; TUG = timed up-and-go test; QOL = quality of life; PDQ-39 = Parkinson's disease questionnaire; F = flexors; Exp = experimental group; TC = Tai Chi; HR = ?[AUQ4]; E = extensors; ABC = Activities-Specific Balance Confidence Scale; RPE = rating of perceived exertion; MVC = maximal voluntary contraction; PRET = progressive resistance exercise training; ES = effect size; ADL = activities of daily living; HY = Hoehn & Yahr scale; SOT = sensory organization test; PF = plantar flexors.

*[AUQ5]

Author Queries

[AUQ1] Please ensure author bios are accurate and that author names are all spelled correctly.

[AUQ2] Even though this source is unpublished, it still needs to be added to the reference list; please add.

[AUQ3] Please define.

[AUQ4] Please define.

[AUQ5] What does the asterisk in the table denote?