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Resistance Training with Instability for Patients with Parkinson's Disease

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ABSTRACT

Purpose: This randomized controlled trial compared the effects of resistance training (RT) and RT with instability (RTI) on the timed up and go test (TUG), on-medication Unified Parkinson's Disease Rating Scale motor subscale score (UPDRS-III), Montreal Cognitive Assessment (MoCA) score, Parkinson's Disease Questionnaire (PDQ-39) score, and muscle strength in the leg-press exercise (one repetition maximum [1RM]) of patients with Parkinson's disease (PD). **Methods:** Thirty-nine patients with moderate to severe PD were randomly assigned to a non-exercising control group (C), RT group, and RTI group. The RT and RTI groups performed progressive resistance training twice a week for 12 weeks. However, only the RTI group used high motor complexity exercises (*i.e.*, progressive resistance training with unstable devices), for example, half-squat exercise on the BOSU® device. The primary outcome was mobility (TUG). Secondary outcomes were on-medication motor signs (UPDRS-III), cognitive impairment (MoCA), quality of life (PDQ-39), and muscle strength (1RM). **Results:** There were no differences between RTI and RT groups for any of the outcomes at post-training ($P>0.05$). However, there were differences between RTI and C groups in the TUG, MoCa, and muscle strength values at post-training ($P<0.05$). Only the RTI group improved the TUG (-1.9 seconds), UPDRS-III score (-4.5 score), MoCA score (6.0 score), and PDQ-39 score (-5.2 score) from pre to post-training ($P<0.001$). Muscle strength improved for both training groups ($P<0.001$). No adverse events were reported during the trial. **Conclusions:** Both training protocols improved muscle strength, but only RTI improved the mobility, motor signs, cognitive impairment, and quality of life, likely due to the usage of high motor complexity exercises. Thus, RTI may be recommended as an innovative adjunct therapeutic intervention for patients with PD. **Key Words:** exercise training; motor complexity; mobility; motor signs; cognitive impairment; quality of life.

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor (*i.e.,* bradykinesia, rigidity, tremor, and postural instability) and non-motor (*e.g.,* cognitive impairment) signs accompanied by significant mobility impairment. It has been suggested that mobility impairment (postural instability and gait difficulty) is the main determinant of poor quality of life, disability (31), and is a predictor of reduced survival (28) in patients with PD. However, mobility impairment represents a therapeutic challenge as pharmacologic treatment (dopaminergic medication) has limited effects (45, 46). Therefore, non-pharmacological treatment strategies, such as physical exercise, which are able to mitigate mobility impairments in PD as well as improve motor signs, cognitive impairment, and quality of life, are needed.

Resistance training (RT) improves muscle strength (39) and quality of life (14, 16) in patients with PD. However, the positive effects of RT on mobility, motor signs (on-medication state), and cognitive impairment are equivocal. For instance, no study has observed minimal detectable changes (smallest amount of difference in individual scores that represents true change beyond random measurement error) on the timed up and go test (TUG) after RT (38, 40). This test has been reported as a sensitive and reliable tool to assess the mobility of patients with PD (8). Regarding on-medication motor signs, it showed no changes when measured by the Unified Parkinson's Disease Rating Scale motor subscale score (UPDRS-III) (13, 14, 16, 23). Finally, cognitive impairment is highly prevalent in non-demented patients with PD. Importantly, the decline in cognitive domains, such as attention, executive function, visuo-spatial, and memory is considered as a predictor of dementia (17, 21). There is one randomized controlled trial reporting cognitive improvements (attention and working memory) in patients with PD after RT (15). However, no study has investigated RT effects on several cognitive domains that are predictors of dementia in patients with PD. Thus, it is reasonable to speculate that the limited

effects of RT on mobility, motor signs, and cognitive impairment in PD may be related to the characteristics of this exercise mode.

There is evidence suggesting that exercises requiring a high degree of attention, memory, and motor difficult (*i.e.*, high motor complexity) produce higher cortical activation than low motor complexity exercises (10, 30). Increases in exercise-induced cortical activation are related to improvements in motor control and cognitive function in healthy individuals (10, 30). Thus, exercise interventions with high motor complexity may help alleviate deficits in mobility, motor signs, and cognitive impairment of patients with PD.

RT with instability (RTI) is a training mode in which conventional RT is performed using unstable devices (*e.g.*, balance pad, dyna discs, balance discs, BOSU®, and Swiss ball) (2, 4-7). It may be considered as a high motor complexity intervention for patients with PD (see Video, Supplemental Digital Content 1, which demonstrates the resistance training with instability, http://links.lww.com/MSS/A682) because performing RT on unstable devices (*e.g.*, half-squat exercise on BOSU® device) requires high attentional and motor control demands, and the production of muscle force necessary to overcome the load and also maintain stability (2, 4-7, 25), which are enhanced with the concomitant and progressive increase in the degree of instability and load/resistance of the training exercises.

Therefore, this randomized controlled trial compared the effects of RT and RTI on the mobility (primary outcome), motor signs, and cognitive function of patients with PD. Due to the higher motor complexity in RTI than RT, we hypothesized that RTI would produce greater improvements in mobility, motor signs, and cognitive impairment than RT. Other outcome measures included quality of life and muscle strength.

METHODS

Participants

All of the patients were recruited from the Brazil Parkinson Association. The diagnosis of idiopathic PD was confirmed by a movement disorders specialist in accordance with UK Parkinson's Disease Society Brain Bank diagnostic criteria (24). Eligibility criteria were: 1) Hoehn and Yahr stage between 2 and 3, 2) stable medication, 3) age between 50 and 80 years, 4) not being engaged in any exercise training (e.g. aerobic and resistance training) in the past three years, 5) not presenting with a neurological disorder other than PD, 6) not having significant arthritis, cardiovascular disease, and cognitive impairment by Mini-Mental State Examination (score <23) (20). All of the patients were informed of the inherent risks and benefits prior to signing an informed consent form. This study was approved by the University's Ethical Committee (approval number - 2011/12) and it was registered at the National Clinical Trial (www.ensaiosclinicos.gov.br; RBR-53S3RK).

Experimental Design

We conducted a prospective, single center, parallel-group, randomized controlled trial between March 2013 and September 2014. All of the patients were assessed in the clinically defined "on" state (fully medicated) within 1.5 to 2 hours of taking their morning dose of dopaminergic medication. Primary outcome measure was mobility because deficits in mobility (*i.e.*, postural instability and gait difficulty) is strongly associated with disability of patients with PD (31). Secondary outcome measures included motor signs, cognitive function, quality of life, and muscle strength. Outcome measures were conducted at baseline and following three months of intervention in the same order. On the first day, a physical therapist blind to the experimental

design, assessed the motor signs of the patients in accordance with the UPDRS-III (18), cognitive function with the Montreal Cognitive Assessment (MoCA) (34), and quality of life with the Parkinson's Disease questionnaire (PDQ-39) (36). During the second day, mobility was assessed by the TUG (37). Afterwards, patients underwent two familiarization sessions and the pre-test, separated by at least 48 hours with the leg-press exercise to determine the one repetition maximum (1RM) (9). After baseline assessments, patients were classified into quartiles regarding their mobility scores. Patients from each quartile were randomly assigned to the non-exercising control group (C), RT group, or RTI group.

Outcome measures

Mobility – Primary outcome

The patient was timed while he or she rose from an arm chair (seat height 46 cm), walked as quickly as possible at a comfortable and safe pace, to a line on the floor three meters away from the chair, turned and walked back to the chair and sat down again. Time was recorded from the instant the patient's buttocks left the chair (standing up) until the next contact with the chair (sitting down). Before the test, the patients performed two familiarization attempts separated by at least one minutes. Following, two test trials were performed, with one a minute interval between trials (37). The shortest time was used for analysis.

Motor Signs

The UPDRS-III includes 14 items scored from 0 to 4 (0 no motor signs and 4 severe motor signs). Most of these 14 items have right and left scores, resulting in a maximum possible score of 108, which indicates great motor severity (18). In cases of missing values, pro-rated

imputation was implemented following the procedures described previously (22). Lin's Concordance Correlation Coefficient was equal to 0.997 between the missing values UPDRS-III scores and the UPDRS-III scores using the pro-rated imputation strategy. The UPDRS-III score was used for analysis.

Cognitive Function

The MoCA was designed as a screening instrument for mild cognitive impairment (34). However, evidence has shown that the MoCA can be used to observe changes in cognitive function after exercise training in different populations (29, 32, 33). Thus, the MoCA was used as outcome in the present study. The assessment was conducted in a quiet room without distractions by a physical therapist trained in the administration of the MoCA questionnaire. The maximum score is 30 and a score of $\leq$25 indicates mild cognitive impairment (34, 35). A point is added to the total score for those with 12 or fewer years of education. The MoCA assesses seven cognitive domains, such as visuo-spatial and executive functions (5 points), naming (3 points), attention (6 points), language (3 points), abstraction (2 points), delayed recall (5 points), and orientation (6 points). Thus, the MoCA score, the proportion of patients with mild cognitive impairment, and MoCA cognitive domains were used for analysis.

Quality of life

The PDQ-39 has 39 items on mobility, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort. The total PDQ-39 score is a percentage derived from dividing the actual score by the total possible score of 156 and multiplying by

100. Lower scores for the PDQ-39 indicate better quality of life, while higher scores on this scale indicates poorer quality of life (36). The PDQ-39 score was used for analysis.

Muscle Strength

The 1RM test was assessed using the 90° leg-press exercise according to procedures following the guidelines of the American Society of Exercise Physiologists (9). The patient performed two familiarization sessions with the testing procedures and the pre-test to achieve 1RM stabilization separated by at least 48 hours. The patient was deemed familiarized with the 1RM tests if the inter-session variability in test results was lower than 5%. In short, the patient started with a general warm-up consisting of a 10-min warm-up on a bicycle ergometer (40 rpm). Then, a specific warm-up routine of eight repetitions at 50% of estimated 1RM followed by a set of three repetitions at 70% of estimated 1RM was performed. Warm-up sets were separated by a 2-min interval. After the completion of the second set, individuals rested for three minutes before the beginning of the test. Testing included single attempts at progressively heavier weights until the 1RM load was identified, which typically required five attempts. A three-minute interval was allowed between attempts, and strong verbal encouragement was provided during the attempts (23). The attempt with the highest 1RM value was used for analysis.

Interventions

The C group did not perform any exercise training activities. They were provided with bingo games and education about PD through lectures and everyday activities once a week for 60 minutes by the Brazil Parkinson Association for 12 weeks. The RT and RTI groups performed only their respective training protocols. All of the patients were instructed not to engage in

additional activities throughout the intervention period. Both RT and RTI were performed twice a week for three months (24 training sessions) in a gym (Center for Psychobiology and Exercise Studies). Each training session lasted for approximately 50 min and started with a 10-minute warm-up on a cycle ergometer (20 to 40 rpm) at the same time of day (in the morning). Both RT and RTI groups performed five resistance exercises (leg-press, latissimus dorsi pull-down, ankle plantar flexion, chest-press, and half-squat). A linear periodization in which the training load progressed from high-volume low-intensity to low-volume high-intensity loads over 12 weeks was implemented in an attempt to maximize training adaptations (19). This periodization was 2-3 sets and 10-12 repetitions maximum at the first month, 3-4 sets and 8-10 repetitions maximum at the second month, and 4 sets and 6-8 repetitions maximum at the third month. An interval of two minutes was allowed between exercises and sets. For the RT group, the load/resistance of the exercises was progressively increased throughout the intervention whenever patients were able to perform two consecutive sessions with the same exercise-load. For the RTI group, there was a progressive and concomitant increase in load/resistance and degree of instability of the exercises during the three months. Unstable devices were changed throughout the experimental period from the least to the most unstable devices. All of the patients of the RTI group achieved the progression from one unstable device to another throughout the three months as presented in Table 1. The unstable device was changed to a more unstable device whenever the patients decreased body sway considerably and force production increased abruptly when performing exercises. As the emphasis of the RTI group was to progressively increase the degree of instability, if patients were not able to perform an exercise with a higher training load due to the greater instability of the new unstable device, patients maintained the load from the last session. Unstable devices (*i.e.,* balance pad, dyna discs, balance discs, BOSU®, and Swiss ball) were

placed between the bases of support of patient (i.e., the body area responsible for sustaining most of his body weight and/or on the point of force application) and each resistance exercise (Figure 1, A1 and A2 panels) or floor (Figure 1, B1 and B2 panels) (42). All of the training sessions were monitored by two investigators.

Statistical Analysis

The Shapiro-Wilk test was used to determine normality. Non-normal data were log transformed. A mixed model was performed for each outcome (TUG score, UPDRS-III score, MoCA score, MoCA domains, PDQ-39 score, and 1RM values), having groups (C, RT and RTI) and time (pre and post) as fixed factors, and patients as a random factor (43). Whenever a significant *F*-value was obtained, a post-hoc test with a Tukey´s adjustment was performed. Within-group (pre - to post - changes) and between-groups (post - changes) effect sizes (ES) were calculated using Cohen's d (12) for each outcome. ESs were classified as small (ES≤0.49), medium (ES 0.50-0.79), and large (ES≥0.80). Chi-Square was used to determine if the proportion of patients with mild cognitive impairment (score ≤25 in the MoCA assessment) decreased after interventions. The significance level was set at $P<0.05$. Results are expressed as mean ± SD. SAS 9.2®software (Institute Inc., Cary, NC, USA) was used to perform the statistical analysis.

RESULTS

Ninety-one patients volunteered for the study and signed the written consent. Thirty did not fulfill the criteria (significant arthritis and cardiovascular disease) and 15 had family problems that prevented their participation in the study. Thus, 46 patients performed baseline testing, but one had back pain, one death, and five did not want to continue in the study. Therefore, thirty-nine patients, 13 in each group, composed the final sample (Figure 2).

At baseline, there were no between-group differences in any demographic, anthropometric, and clinical characteristic and outcomes (P>0.05) (Table 2).

Both training protocols were well tolerated by the patients. No adverse effects were reported during the trial and adherence to the protocol was high for both training groups (23.6±0.5 sessions [98%] for RTG and 23.3±0.7 sessions [97%] for RTIG).

Mobility – Primary outcome

There was a significant group × time interaction for TUG ($F_{[2, 36]}$ = 34.44, P<0.0001). The RTI group significantly decreased the TUG values at post-training (mean difference [MD]= -1.9 seconds; 95% confidence interval [CI]= -2.6 to -1.2; P<0.001; ES= 0.82) while the RT group showed no significant changes (MD= -0.7 seconds; CI= -1.4 to -0.1; P=0.054; ES= 0.36). The C group increased the TUG values at post-training (MD= 1.1 seconds; CI= 0.2 to 1.7; P=0.002; ES= 0.51). The post hoc analysis revealed differences in TUG values only between the RTI and C groups at post-training (MD= -2.5 seconds; CI= -4.9 to -0.1; P=0.038; ES= 1.05) (Figure 3A).

Motor signs

There was a significant group × time interaction for the on-medication UPDRS-III scores ($F_{[2, 36]}$ = 17.82, P<0.0001). The RTI group significantly decreased the mean on-medication UPDRS-III scores at post-training (MD= -4.5 score; CI= -6.1 to -2.2; P<0.001; ES= 0.55) while the RT group (MD= -1.1 score; CI= -1.3 to 3.3; P=0.790; ES= 0.08) and the C group (MD= 1.6 score; CI= -0.5 to 4.1; P=0.230; ES= 0.18) showed no significant changes. The post hoc analysis revealed no between-group differences in UPDRS-III scores (P>0.05) (Figure 3B).

Cognitive Function

There was a significant group × time interaction for the mean MoCA scores ($F_{[2, 36]}$ = 41.00, P<0.0001). The RTI group significantly decreased the mean MoCA scores at post-training (MD= 6.0 score; CI= 4.2 to 7.7; P<0.001; ES= 1.90) while the RT group (MD= 0.4 score; CI: -2.2 to 1.2; P=0.996; ES= 0.11) and the C group (MD= -1.1 score; CI= -2.8 to 0.6; P=0.446; ES= 0.19) showed no significant changes. The post hoc analysis revealed differences in MoCA scores only between the RTI and C groups at post training (MD= -5.2 score; CI= -10.4 to 0.01; P=0.050; ES= 0.80) (Figure 3C).

The proportion of patients who scored ≤25 on the MoCA decreased from 92.3% (n = 12) to 15.4% (n = 2) only for the RTI group from pre- to post-training (P<0.001). The RT and C groups did not present any change from pre- to post-training (P>0.05).

For the MoCA domains, there were significant group × time interactions for the visuo-executive ($F_{[2, 36]}$ = 8.78, P=0.0008), attention ($F_{[2, 36]}$ = 12.63, P=0.0001), abstraction ($F_{[2, 36]}$ = 9.65, P=0.0004), delayed recall ($F_{[2, 36]}$ = 8.20, P=0.0012), and orientation, ($F_{[2, 36]}$ = 3.46, P=0.0421). The RTI group significantly increased the visuo-executive (P=0.001; ES= 1.49),

attention (P<0.001; ES= 1.95), abstraction (P<0.001; ES= 1.21), delayed recall (P=0.007; ES= 0.49), and orientation (P=0.031; ES= 1.54) at post-training. The post hoc analysis revealed differences in the visuo-executive (P=0.018; ES= 1.55) and orientation (P=0.035; ES= 1.37) only between the RTI and C groups at post training (Table 3).

Quality of life

There was a significant group × time interaction for the mean PDQ-39 score ($F_{[2, 36]}$ = 19.98, P<0.0001). The RTI group significantly decreased the mean PDQ-39 score at post-training (MD= -5.2 score; CI= -7.2 to -3.1; P<0.001; ES= 0.50) while the RT group (MD= -1.2 score; CI= -3.2 to 0.8; P=0.521; ES= 0.12) and the C group (MD= 0.7 score; CI= -2.7 to 1.3; P=0.883; ES= 0.05) showed no significant change. The post hoc analysis revealed no between-group differences in PDQ-39 score (P>0.05) (Figure 3D).

Muscle strength

There was a significant group × time interaction for the leg-press 1RM values ($F_{[2, 36]}$ = 21.18, P<0.0001). The RT and RTI groups increased leg-press 1RM values similarly at post-training (MD= 21.7 kg; CI= 7.9 to 35.4; P<0.001; ES= 0.93, and MD= 34.7 kg; CI= 21.0 to 48.5; P<0.001; ES= 1.22, respectively) while the C group showed no significant change (MD= -6.4 kg; CI= -7.3 to 20.2; P<0.720; ES= 0.25). The post hoc analysis revealed differences in the leg-press 1RM values only between the RTI and C groups at post training (MD= 42.3 kg; CI= 8.5 to 76.1; P=0.007; ES= 1.61) (Figure 3E).

DISCUSSION

This randomized controlled trial showed that only RTI improved mobility, motor signs, cognitive impairment, and quality of life of patients with PD from pre to post-training (Figure 3 and Table 3). However, RTI and RT both increased maximum strength (Figure 3).

We hypothesized that RTI would produce greater improvements in mobility, motor signs, and cognitive impairment than RT. Although we did not observe differences between RTI and RT, only RTI was effective in improving these outcomes, which produced significant differences from C group at post-training for mobility, cognitive function, and muscle strength. Mobility impairment is strongly associated with disability (31) and it is a predictor of reduced survival (28) in patients with PD. Mobility represents a therapeutic challenge as the pharmacologic treatment has limited effects on it (45, 46). Thus, our results are clinically relevant for these patients as lower TUG values (change score of -1.9 seconds) after RTI were greater than the minimal detectable change of 1.6 seconds suggested for patients with PD at moderate stages of the disease (27). Such changes have not been observed after RT (38, 40) or after a modified fitness counts exercise program consisting of low-intensity stretching, constant load strengthening, breathing, and balance exercises (38). Taken together, it is conceivable that the improvements not only in muscle strength but also in motor signs and cognitive impairment observed after RTI are necessary to enhance mobility. A recent review suggests that for optimal mobility in patients with PD, studies should design exercise programs able to improve multiple aspects of the postural control system impaired in these patients, such as, muscle strength, motor coordination, sensory organization, and cognition (44). As RTI encompass most of the cited aspects, it is reasonable to suggest that this intervention is beneficial for improving mobility of the patients with PD.

A recent systematic review suggested that RT can improve motor signs of patients with PD (26). However, these findings should be interpreted with caution as on-medication motor signs showed no changes when measured by the full UPDRS part III after either three months (16, 23) or 24 months of RT (14). We found no significant changes in on-medication UPDRS-III scores after three months of RT (Figure 3B). Taken together, these findings suggest that increases in muscle strength itself do not cause significant changes in on-medication motor signs. Thus, interventions that require increased motor complexity and that also increase muscle strength may be more effective to improve on-medication motor signs since only the RTI group decreased on-medication UPDRS-III score by -4.5 points, which exceeds the moderate range of clinically important changes in motor signs (41). Improving UPDRS-III score after such a short intervention is critical as motor severity progresses on average 3.3 points per year (1).

Regarding cognitive function, the overall MoCA score increased ~6.0 points after RTI (Figure 3C), as a result there was an 84% reduction in the proportion of patients with mild cognitive impairment. To the best of our knowledge, this is the first study that observed improvements in not only the overall MoCA but also several cognitive domains, such as visuo-executive, attention, abstraction, delayed recall, and orientation in patients with PD after RTI (Table 3). These findings are vital for non-demented patients with PD because executive function, attention, memory, and visuo-spatial abilities worsen with PD progression and are predictors of the development of dementia (21). Although MoCA has been considered as a screening test for dementia and mild cognitive impairment, it was used as outcome in this study because evidence has shown that the MoCA can be used to observe changes in cognitive function after exercise training in different populations (29, 32, 33). Moreover, the PD task force recommends the use of MoCA as an outcome measure if evidence demonstrates its ability to

detect treatment effects (11). Our findings in this study demonstrated that MoCA has indeed the ability to detect the effects of exercise interventions on the cognitive function of patients with PD. We did not observe changes in any cognitive domain after RT (Table 3). However, one previous study demonstrated that longer RT intervention (*i.e.*, ≥12 months of intervention) may improve some cognitive domains in patients with PD, such as attention and working memory (15). Taken together, these findings support the notion that either longer RT interventions or training methods with high motor complexity (*i.e.*, RTI) in short time intervention are required to achieve significant improvements in cognitive function as observed in this study.

Thus, the improvements in mobility, motor signs, and cognitive impairment were perceived as extremely positive by the patients of the RTI group. Only this group presented robust changes in quality of life (decreased PDQ-39 score by -5.2 points) (Figure 3D). Other studies have demonstrated decreases in PDQ-39 score of -5.1 and -6.5 points after six months of RT (14) and three months of high intensity eccentric resistance training (16), respectively. Thus, these findings support the notion that long-term RT (*i.e.*, six months), and short-term training with either high motor complexity (*i.e.*, RTI) or high intensity (*i.e.*, eccentric resistance training) are necessary to improve PDQ-39 score.

It is important to highlight that both training protocols increased maximum strength. The RT group exercised using larger loads than the RTI group (data not shown). Despite this fact, the RT and the RTI groups presented similar increases in lower limb muscle strength (Figure 3E). This finding is aligned with electromyography data showing similar muscle activation when performing chest-press exercises on a Swiss ball, and on a flat bench (3). In this sense, RTI may play a great role in joint stability due to high muscle activation with the use of lower loads. Thus, as the training protocols produced similar improvements in maximum strength, but only RTI

used high motor complexity exercises, one may suggest that the improvements observed after RTI in mobility, motor signs, cognitive impairment, and quality of life were due to the usage of high motor complexity exercises.

The present study has some limitations that should be considered when interpreting our findings. First, the lack of significant differences between RTI and RT groups, despite the robust changes in TUG values after RTI, may have occurred due to low statistical power. An exploratory sample size estimate suggests that a sample of in excess of 27 patients would be needed to obtain a significant interaction effect for the TUG. Even though the present study had an appropriate sample size, it is likely that the small improvements in TUG observed in the RT group prevented from finding significant differences between RTI and RT group, after the experimental period. However, it should be emphasized that we did observe a significant interaction effect, as RTI improved TUG values from pre- to post-training and produced significantly lower TUG values than C group, at the post-training assessment. Second, it was not feasible to blind the patients to the training program, as they trained in the same facility. However, the patients were blinded to the expected outcomes and the reasons for carrying out the interventions. Third, off-medication assessment has been shown to be important in the literature, because of fluctuations in medication status throughout the day. In the current study, the off-medication assessment was not performed as it presented serious challenges for the patients, caregivers, and the Brazil Parkinson Association's staff.

In conclusion, only RTI was effective in improving mobility, motor signs, cognitive impairment, and quality of life in patients with PD, while both training regimes were equally effective in improving muscle strength. Thus, exercise interventions aiming at improving mobility of patients with PD, should investigate not only interventions that prioritize increase in

muscle strength, but mainly in exercise interventions while imposing high demands to the central nervous system (*i.e.*, high motor complexity) in patients with PD. Therefore, this randomized controlled trial describes an innovative intervention able to counteract some PD-related effects.

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CONFLICT OF INTERESTS

The authors declare no conflict of interests. The results of the present study do not constitute endorsement by the American College of Sports Medicine.

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Legends

Figure 1. Initial (A1) and final (A2) phase of motion in the leg-press exercise performed with dyna discs under the feet and one dyna disc under the seat. Initial (B1) and final (B2) phase of motion in the half-squat exercise performed with dyna discs under the feet and one Swiss ball on back.

Figure 2. The trial profile with schematic representation of participant recruitment and allocation. C= control; RT= resistance training; RTI= resistance training with instability.

Figure 3. Mean ± SD for the timed up and go (TUG – A panel), Unified Parkinson's Disease Rating Scale part III motor sub-scale (UPDRS-III – B panel), Montreal Cognitive Assessment (MoCA – C panel), Parkinson's Disease Questionnaire (PDQ-39 – D panel), and leg-press one repetition maximum (1RM – E panel) outcomes at pre and post-training for the control group (C), resistance training group (RT) and resistance training with instability group (RTI). *Different from pre-training values ($P \leq 0.05$). #Different from post-training values of the C ($P \leq 0.05$).

List of Supplemental Digital Content *"Roschel_SDC1.AVI"*

Supplemental Digital Content 1. Video that demonstrates the Resistance Training with Instability (RTI).

Figure 1

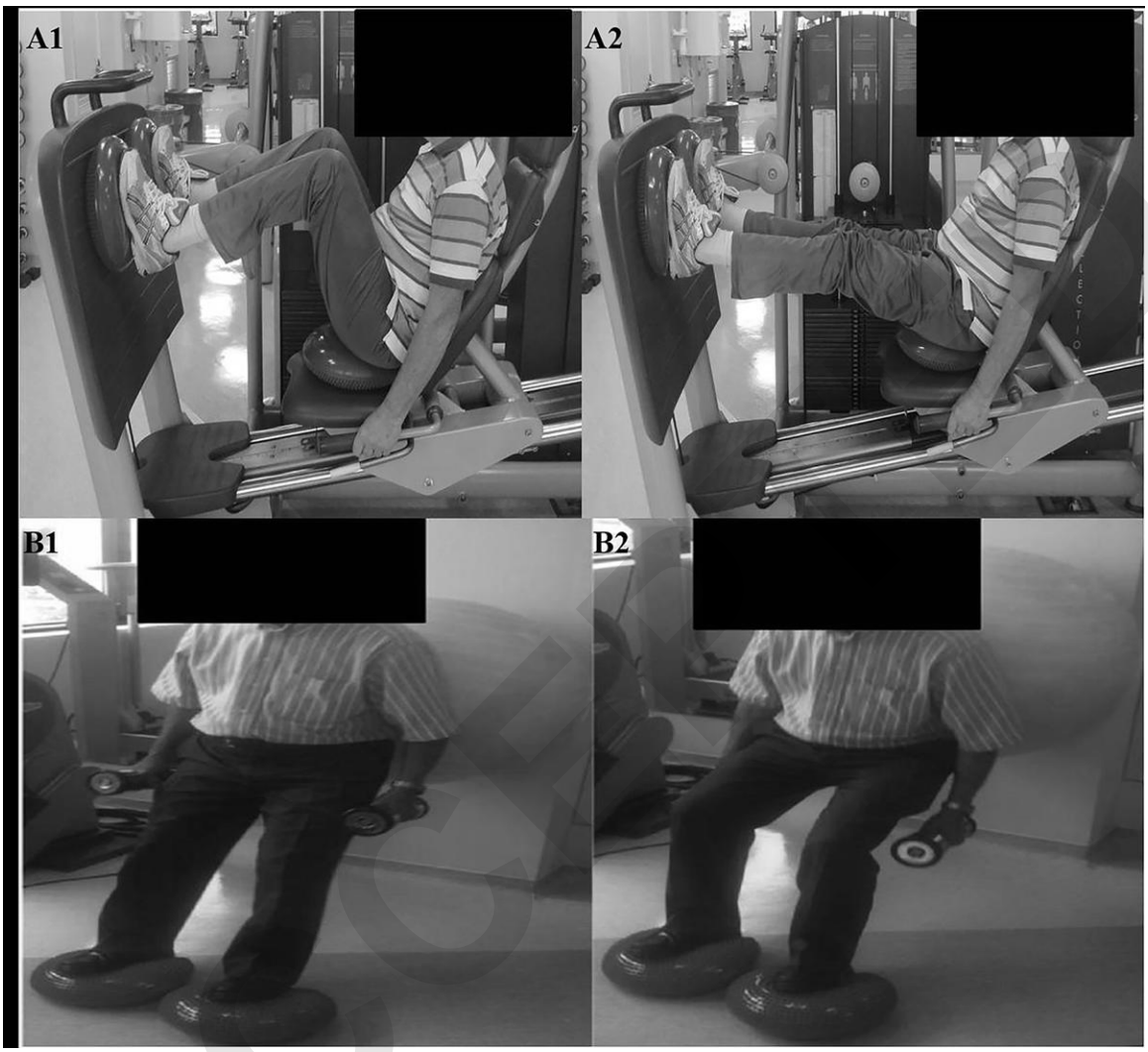

Figure 2

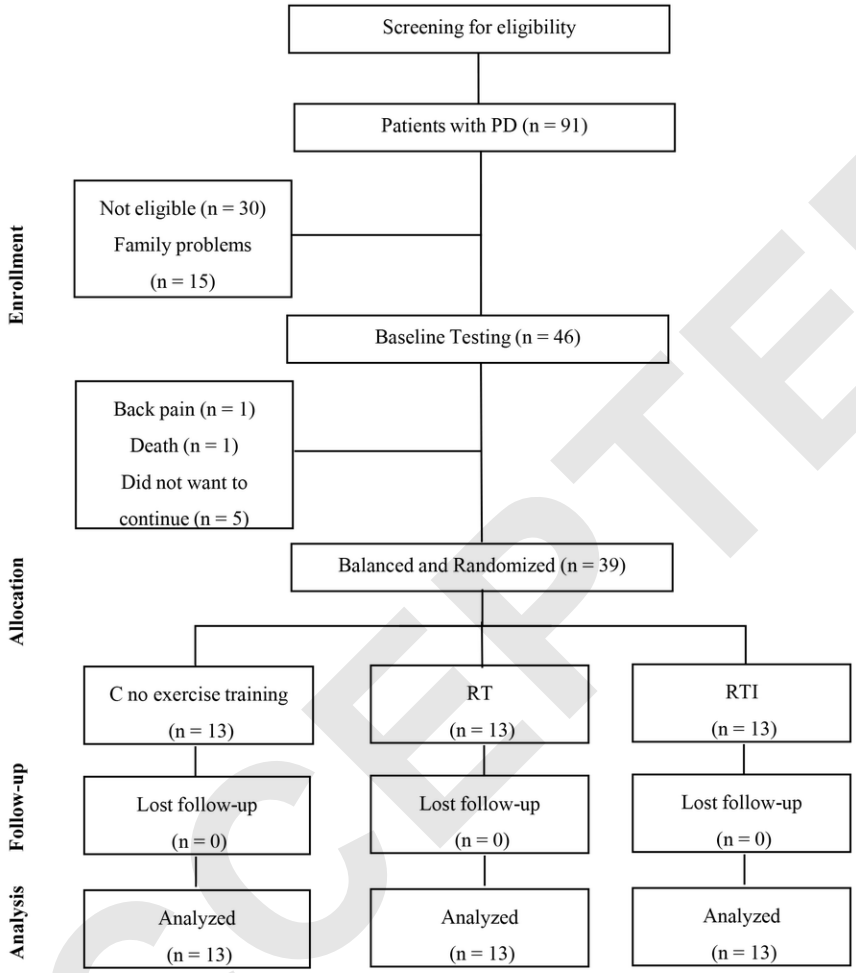

Figure 3

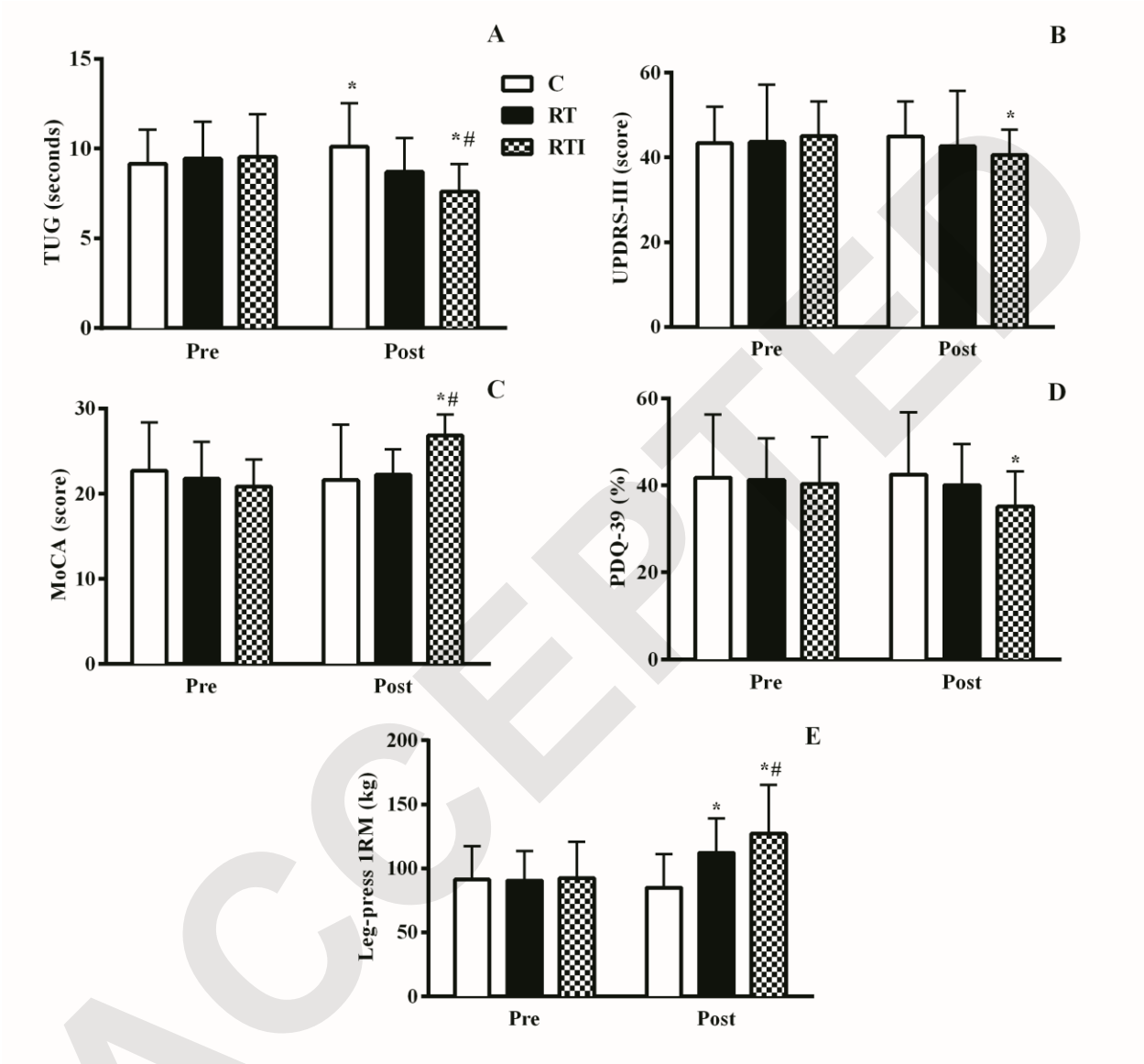

Table 1. Location and progression of the unstable devices throughout the experimental protocol (three months) on each resistance exercise.

	Leg-press	*Latissimus dorsi pull-down*	*Ankle plantar flexion*	*Chest-press*	*Half-squat*
Week 1 and 2	balance pad – feet*	balance pad - feet*	balance pad - feet*	balance pad - feet*	balance pad - feet* and Swiss ball - back
Week 3 and 4	dyna discs - feet* and one dyna disc - seat*	dyna discs - feet* and one dyna disc - seat*	dyna discs - feet* and one dyna disc - seat*	dyna discs - feet* and one dyna disc - seat*	dyna discs - feet* and Swiss ball - back
Week 5 and 6	one balance disc -feet* and one balance disc - seat*	one balance disc -feet* and one balance disc - seat*	one balance disc - feet* and one balance disc - seat*	one balance disc - feet* and one balance disc - seat*	one balance disc - feet* and Swiss ball - back
Week 7 and 8	one balance disc - feet* and one balance disc - seat*	one balance disc - feet* and one balance disc - seat*	one balance disc - feet* and one balance disc - seat*	one balance disc - feet* and one balance disc - seat*	one balance disc - feet* and Swiss ball - back
Week 9 and 10	BOSU® - feet* and one balance disc - seat*	BOSU® - feet* and one balance disc - seat*	one balance disc - feet* and one balance disc - seat*	BOSU® - feet* and one balance disc - seat*	BOSU® - feet* and Swiss ball - back
Week 11 and 12	BOSU® - feet* and one balance disc - seat*	BOSU® - feet* and one balance disc - seat*	one balance disc - feet* and one balance disc - seat*	BOSU® - feet* and one balance disc - seat*	BOSU® - feet* and Swiss ball - back

* Indicates the location of the unstable devices for each resistance exercise.

Table 2. Characteristics of the patients with Parkinson's disease (n = 39) at baseline, by group. Mean ± SD.

Characteristics	C	RT	RTI
Demographic			
Men/women (number)	9/4	10/3	10/3
Age (years)	64.2±8.3	64.1±9.1	64.2±10.6
Educational level (years)	8.7±2.1	8.5±2.5	8.1±3.1
Anthropometrical			
Body mass (kg)	69.2±11.4	70.8±10.1	71.3±8.2
Height (cm)	1.69±0.1	1.68±0.2	1.69±0.2
Body mass index (kg/m^2)	24.3±3.8	25.5±5.2	25.0±3.0
Clinical			
Mini-Mental State Examination (score)	28.5±1.8	28.5±1.9	28.8±1.7
Years since diagnosis (years)	10.7±6.1	9.6±3.9	10.5±4.1
Hoehn and Yahr staging scale (a.u)	2.5±0.4	2.5±0.5	2.5±0.4
L-Dopa equivalent units ($mg•day^{-1}$)	796.7±151.3	835.8±287.0	875.9±223.4
Primary outcome			
TUG (seconds)	9.2±1.9	9.4±2.1	9.5±2.4
Secondary outcomes			
UPDRS-III (score)	43.4±8.6	43.7±13.4	45.1±8.2
MoCA (score)	22.7±5.7	21.8±4.3	20.8±3.2
PDQ-39 score (%)	41.8±14.5	41.3±9.5	40.4±10.8
Leg-press 1RM (kg)	91.3±26.1	90.3±23.3	92.4±28.5

C= control group; RT= resistance training group; RTI= resistance training with instability group; UPDRS-III= Unified Parkinson's Disease Rating Scale part III motor sub-scale; MoCA= Montreal Cognitive Assessment; PDQ-39= Parkinson's Disease Questionnaire; 1RM = one repetition maximum.

Table 3. Montreal Cognitive Assessment cognitive domains in the pre- and post-training assessments for each group of patients with Parkinson's disease.

		Change from pre to post-training		Difference at post-training: RTI vs C		Difference at post-training: RTI vs RT	
Groups	MoCA domains	Mean difference (95% CI)	*P*	Mean difference (95% CI)	*P*	Mean difference (95% CI)	*P*
	Visuo-executive (score)						
C pre	3.6±1.3						
C post	3.5±1.3	-0.1 (-0.4 to 0.5)	0.996				
RT pre	3.8±1.3						
RT post	4.0±1.3	0.2 (-0.6 to 0.3)	0.931				
RTI pre	4.2±0.8						
RTI post	5.0±0.0	0.8 (0.3 to 1.3)	0.001	1.4 (0.1 to 2.7)	0.018	1.0 (-2.2 to 0.2)	0.206
	Naming (score)						
C pre	2.8±0.4						
C post	2.8±0.4	0 (-0.2 to 0.2)	1.000				
RT pre	2.8±0.3						
RT post	3.0±0.0	0.2 (-0.1 to 0.3)	0.821				
RTI pre	2.9±0.3						
RTI post	3.0±0.0	0.1 (-0.1 to 0.3)	0.821	0.2 (-0.5 to 0.2)	0.693	0 (-0.3 to 0.3)	1.000
	Attention (score)						
C pre	4.4±1.5						
C post	4.2±1.8	-0.2 (-0.8 to 1.2)	0.985				
RT pre	3.7±1.4						
RT post	3.5±1.4	0.2 (-1.1 to 0.9)	0.999				
RTI pre	3.2±1.0						
RTI post	5.5±1.0	2.3 (1.0 to 3.1)	<0.001	-1.1 (-2.7 to 0.4)	0.301	-1.5 (-3.1 to 0.1)	0.076
	Language (score)						

C pre	2.9±0.3						
C post	2.9±0.3	0 (-0.2 to 0.2)	1.000				
RT pre	2.8±0.4						
RT post	3.0±0.0	0.2 (-0.1 to 0.4)	0.331				
RTI pre	2.9±0.3						
RTI post	3.0±0.0	0.1 (-0.1 to 0.3)	0.905	0.1 (-0.2 to 0.4)	0.967	0.1 (-0.3 to 0.3)	1.000
	Abstraction (score)						
C pre	1.8±0.4						
C post	1.5±0.8	0.3 (-0.3 to 0.7)	0.787				
RT pre	1.7±0.6						
RT post	1.8±0.6	0.1 (-0.6 to 0.4)	0.998				
RTI pre	1.2±1.0						
RTI post	2.0±0.0	0.8 (0.3 to 1.3)	<0.001	0.5 (-0.3 to 1.2)	0.470	0.2 (-0.9 to 0.5)	0.942
	Delayed recall (score)						
C pre	2.4±1.9						
C post	1.9±2.1	0.5 (-0.4 to 1.3)	0.589				
RT pre	1.9±1.3						
RT post	1.8±1.2	0.1 (-0.7 to 1.0)	0.994				
RTI pre	1.3±1.4						
RTI post	2.2±2.0	0.9 (0.2 to 1.9)	0.007	0.5 (-2.4 to 1.5)	0.978	0.6 (-2.5 to 1.3)	0.928
	Orientation (score)						
C pre	4.6±1.5						
C post	4.5±1.5	0.1 (-0.8 to 1.0)	0.999				
RT pre	4.8±1.2						
RT post	4.8±1.2	0.0 (-1.0 to 0.9)	0.995				
RTI pre	5.0±0.9						
RTI post	6.0±0.0	1.0 (0.5 to 1.9)	0.031	1.5 (0.1 to 2.8)	0.035	1.2 (-2.5 to 0.2)	0.153

C= Control Group; RT= Resistance Training Group; RTI= Resistance Training with Instability Group; MoCA= Montreal Cognitive Assessment; CI= Confidence Interval.