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Long-Term Multimodal Exercise Program Improves Motor and Non-Motor Parameters of People with Parkinson's Disease

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<http://dx.doi.org/10.5772/57104>

1. Introduction

Parkinson's disease (PD) is a neurodegenerative pathology characterized by progressive death of the dopamine-containing neurons in the *substantia nigra pars compacta*. Although motor symptoms (i.e. resting tremor, postural instability, rigidity and gait impairment) are more commonly described in the literature, people with PD can also show cognitive symptoms (i.e. deficits in executive function, depression and dementia). Furthermore, these clinical characteristics of PD negatively impact functional capacity (Barbieri et al., 2012) and tend to get worse progressively (Karlsen et al., 2000).

Physical exercise has been described to benefit both clinical symptoms (motor and cognitive symptoms) and functional capacity of people with PD. In this concern, our research group has published a couple of studies demonstrating the benefits offered by a long-term multimodal exercise program on executive functions (Tanaka et al., 2009), balance (Gobbi et al., 2009), gait parameters (Vitório et al., 2011), and mobility (Pereira et al., 2012).

The aim of current chapter is to discuss the effects of long-term multimodal exercise program on motor and cognitive symptoms, as well as on function capacity in people with PD. To reach this objective, this chapter is going to revisit the findings of our research group.

2. Intervention

Although promising, studies of exercise in PD have been limited in scope (program duration and specificity). Most have addressed the effects of short-term (over 4 to 12 weeks) specific exercise programs. The benefits of longer and nonspecific exercise intervention remain poorly understood. The cardinal clinical manifestations of PD are resting tremor, rigidity, bradykinesia, and gait dysfunction (Damier, Hirsch, Agid & Graybiel, 1999; Olanow; Stern & Sethi, 2009). However, it is known that PD is also associated with many non-motor features, including autonomic dysfunction, pain and sensory disturbances, mood disorders and sleep and cognitive impairment (Olanow; Stern & Sethi, 2009). In this way, a specific physical activity program may not be efficient in achieving many of these symptoms, and consequently to improve the quality of life of these patients. Furthermore, studies have shown that the annual rate of clinical decline in people with PD is between 3.5% (Alves, Wentzel-Larsen, Aarsland & Larsen, 2005) and 11.2% (García-Ruiz, Meseguer, Del Val & Vazquez, 2004), indicating the importance of knowing the effects of exercise are opposed to the advancement of the disease in the long term.

In this context, all the studies reviewed and included in this chapter used the same training protocol, characterized by a long duration multimodal program. Our multimodal exercise program aimed to develop the patients' functional capacities and to improve their quality of life. In contrast to specific programs, this one targeted a holistic improvement of PD patients.

The multimodal program took place over a 6-month period (72 sessions, 3 times a week and 60 minutes per session). Each session consisted of five parts (warm-up, pre-exercise stretching, exercise session, cool down and post-exercise stretching). The main exercise session lasted 40 minutes. The program was structured into six phases; each phase was composed of 12 sessions, each lasting approximately one month. At the end of each phase there was a progressive load increment. In each session, exercise intensity (remained between 60% and 80% of maximum heart rate, 220 minus the participant's age in years) was controlled by a heart rate monitor (Polar®).

The exercise program execution was supervised by at least three physical education professionals and one physiotherapist each time. The multimodal program was composed of a variety of activities that simultaneously focus on the components of functional capacity, such as muscular resistance (specific exercises for gastrocnemius, quadriceps femoralis, hamstrings, rectus abdominalis, and trunk dorsal muscles), motor coordination (rhythmic activities), and balance (recreational motor activities on different surfaces and obstacles) (Table 1).

Phases	Coordination	Muscular Resistance	Balance
1	Movements of upper, and lower limbs	Exercises without weights	Recreational activities stimulating the vestibular system
2	Movements of trunk, upper, and lower limbs	Exercises with hoops, ropes, and batons	Recreational activities stimulating the vestibular system
3	Head movements instead of trunk	Exercises with barbells, ankle, weights, and medicine balls	Stimulation of visual and somatosensory systems
4	Head, trunk, upper, and lower limb movements	Increase in intensity or repetitions (volume increment)	Integration of visual, somatosensory, and vestibular systems
5	Four different movement sequences: two with same movements for upper and lower limbs and two alternating movements	Gym exercises: leg press, pulley, seated cable rows, peck deck, and bench press. Two series with 15 repetitions	Activities including static balance, and half-turn and complete turn (all with visual cues)
6	Four different movement sequences: two alternate movements for upper and lower limbs and two with different movements	Increase in load and volume: addition of series of 15 repetitions	Addition of tactile cues

Table 1. Phases of the multimodal exercise protocol with progressive increments in volume, intensity and complexity.

2.1. Evaluations

Participants were tested before commencing the multimodal program (pretest) and upon completion (posttest). All assessments were carried out in the morning, in the “on-medication” state, 1 hour after participants’ first morning dose of medication. The assessments included clinical, cognitive and motor standard instruments.

2.2. Clinical evaluations

Unified Parkinson's Disease Rating Scale (UPDRS; Fahn & Elton, 1987) was used to follow the longitudinal course of Parkinson's disease and assessed the impairments in psychological, functional and motor functions. This scale ranges from 0 to 176 points (I- psychological: 16 points, II-functional: 52 points, III-motor: 108 points).

Hoehn and Yahr Scale (Hoehn & Yahr, 1967; Goetz et al., 2004) was used for describing how the stages of Parkinson's disease progress. This scale ranges from 1 to 5 stages: stage 1 - Unilateral involvement only; stage 1.5 - Unilateral and axial involvement; stage 2 - Bilateral involvement without impairment of balance; stage 2.5 - Mild bilateral disease with recovery

on pull test; stage 3 - Mild to moderate bilateral disease; some postural instability; physically independent; stage 4 - Severe disability; still able to walk or stand unassisted; and stage 5 - Wheelchair bound or bedridden unless aided.

2.3. Cognitive evaluations

Mini-Mental State Examination (MMSE) (Folstein, Folstein, & Mchugh, 1975; Brucki et al., 2003), a brief 30-point questionnaire test was used to screening cognitive impairment. This test evaluates orientation, memory, arithmetic and visuo-constructive praxis. For Brazilian population the cutoff score for cognitive impairment considers the educational level (illiterate people - 19 points; from 1 to 4 years of schooling - 24 points; from 5 to 8 years of schooling - 26 points; from 9 to 11 years of schooling - 28 points and educational level ≥ 12 years - 29 points).

Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Kay, & Curtiss, 1993; Paolo, Troster, Axelrod, & Koller, 1995) specifically assessed abstraction, mental flexibility and attention respectively by the subtests "Categories Completed", "Perseverative Errors" and "Failure to Maintain Set".

Wechsler Memory Scale – Revised (WMS-R; Wechsler, 1997), a neuropsychological test designed to measure different memory functions. Subtests used in reviewed studies were logical memory, for short-term memory (logical memory I) and episodic declarative memory (logical memory I I), and Symbol Search, for attention capacity.

State-Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, & Lushene, 1979; Gorenstein & Andrade, 1996), a psychological inventory based on a 4-point Likert scale and consisted in 2 self-report questionnaires that measured two types of anxiety: state anxiety (anxiety about an event) and trait anxiety (anxiety level as a personal characteristic). Higher scores represent higher levels of anxiety.

2.4. Motor evaluations

Functional capacity was assessed by means of AAHPERD tests (flexibility, muscle strength, agility, coordination and aerobic endurance; Osness et al., 1990). Flexibility test: a standard sit-and-reach test in which participants were seated, with their heels 12-in apart and over a line that runs perpendicular to a measuring tape. They were asked to reach with both hands as far along the measuring tape as they comfortably can while keeping both knees straight. The score was their highest tape measure mark in three attempts.

Muscular strength: requires female participants to lift a 4-lb object, and male participants to lift an 8-lb object, using a biceps curl motion, as many times as possible in 30-s.

Agility: patients started from a seated position and were asked to rise from a chair, walk to the right around a cone, and return to the seat and sit down, stand again, walk to the left around a cone, return to their seat and sit down, and then repeat the entire procedure. Two attempts were given to the participants, and the raw score represented the faster of the two.

Coordination: involved the movement of three 12-oz soda cans, using the dominant hand. The cans are placed on a table, topside-up and on a line indicated by a 30-in length of masking

tape. The cans are located at 10-in intervals. The participants were seated at the table with the line of cans well within their grasp and they were then asked to place each can top-side-down in a space adjacent to its original position. Then they returned the cans to their original top-side-up position. Each attempt consisted of performing these movements twice, and the raw score reflected the faster of two attempts.

Aerobic resistance: an 880-yd walk, at the participant's maximum speed.

Modified Timed "Up and Go" test (TUG; Schilling et al., 2009; Gobbi et al., 2009) consisted of the participant stand up from a sitting position in an armless chair with a seat height of 46.5 cm, walk a 3-m distance, pass around a cone, return, and sit back down in the chair. Each participant was instructed to perform the task as quickly as possible, but without running. At least one practice attempt was offered to the participants at the beginning of the procedure so that they could become familiar with it. Three attempts were performed for testing purposes, and the time to perform the task was measured in seconds. Time was recorded from the instant the person's buttocks left the chair until the next contact with the chair. The mean value of the three attempts was considered for statistical analysis.

Berg's Functional Balance Scale (FBS; Scalzo et al., 2009), measured the static and dynamic balance abilities by 14 simple balance related tasks, ranging from standing up from a sitting position, to standing on one foot. For each task this test ranged from 0 (unable) to 4 (independent). The better score is 56 points with the increased risk of falls below a score of 45 and a significant increase below 40 points.

Postural-Locomotor-Manual Test (PLM; Hong & Steen, 2007) was designed to assess movement patterns. The test movement is a compound movement involving a postural phase (rising up), a locomotion phase (walking), and a manual phase (pendulous arm movement and positioning of a test object on a pedestal). The PLM test consisted of a complex motion during which the patients moved an object from the floor 1.5-m forward and positioned it on a stand at their chin height, as fast as possible. The time to complete the test was record.

Kinematic gait parameters: the walking task required participants to walk, at a self speed, on an 8m long pathway. Three attempts were performed. For the kinematic data recording, two passive markers (reflective, adhesive Styrofoam) were attached to the following anatomic landmarks: lateral face of the right calcaneus and medial face of the left calcaneus. The images of the right sagittal plane of one stride at center of the pathway were recorded with a frequency of 60Hz by one digital camcorder (JVC, GR-DVL 9800), generating 2D kinematic data. Markers were digitized automatically on Digital Video for Windows (DVIDEOW) software.

3. Results

The multimodal exercise program improved several aspects related to quality of life of patients with PD. First, we showed the benefits of six months of the exercise program on clinical parameters. Exercise program improved the UPDRS-II (functional aspects) score. After exercise program patients with PD decreased the score (Table 2). The exercise program seems

be able to improve clinical parameters, agreeing with the benefits to functional capacity components, mobility and locomotion, which are aspects relate to functional activities. Therefore, the improvement in the clinical parameters is important for quality of life for this population.

DEMOGRAPHIC CHARACTERISTICS			
Age (years)	67.77 ± 7.28		
Body height (cm)	161.00 ± 8.74		
Body mass (kg)	70.70 ± 15.87		
CLINICAL PARAMETERS			
Dependent Variables	Pre exercise	Post exercise	p values
H&Y (stage)	1.47 ± 0.72	1.53 ± 0.72	0.15
UPDRS - Functional (score)	11.07 ± 6.36	9.73 ± 6.04	0.02
UPDRS - Motor (score)	20.13 ± 12.26	21.00 ± 14.53	0.72
UPDRS – Total (score)	34.87 ± 18.89	34.07 ± 20.71	0.45
MMSE (score)	26.20 ± 3.47	25.90 ± 4.35	0.77

H&Y: Hoehn & Yahr Stage; UPDRS: Unified Parkinson’s Disease Rating Scale; MMSE: Mini-Mental State Examination.

Table 2. Means and standard deviations for the demographic characteristics and clinical dependent variables at before (pre) and after (post) the multimodal exercise program.

Second, the exercise program affected motor aspects. The multimodal exercise program was efficient to improve the functional parameters, such as functional capacity (some components), mobility and locomotion. For functional capacity components, the coordination and muscle strength (Table 3) improved after the multimodal exercise program, which indicates a control of the motor symptoms effects. Moreover, the exercise program maintained the other components, which was an important finding since PD and ageing decreases progressively the functional capacity. For functional mobility, patients with PD were faster in TUG and PLM (Table 3) after the enrolment in the multimodal exercise program. The exercise seems to act on bradykinesia symptom revealing that patients PD were able to perform functional tasks faster. In addition, our results for locomotion corroborated with functional mobility. Patients with PD increased gait velocity after exercise program (Table 3). Still, the multimodal exercise program improved stride length (Table 3), indicating a positive change for hypometria symptom. Therefore, the exercise program seems to be an important aspect for PD patients, improving the quality of life and decreasing the dependency.

FUNCTIONAL CAPACITY			
Dependent Variables	Pre exercise	Post exercise	p values
balance (score)	52.86 ± 4.15	53.57 ± 2.71	0.19
flexibility (cm)	47.56 ± 12.10	50.14 ± 10.53	0.17
coordination (s)	18.50 ± 7.58	15.89 ± 6.84	0.01
agility (s)	28.82 ± 12.37	30.74 ± 11.54	0.64
strength (rep)	19.79 ± 6.57	23.50 ± 5.33	0.01
aerobic resistance (min)	10.08 ± 2.45	10.13 ± 2.90	0.83
TUG (s)	10.10 ± 4.32	8.46 ± 2.16	0.01
PLM (s)	4.03 ± 1.42	3.58 ± 0.76	0.01
GAIT PARAMETERS			
Dependent Variables	Pre exercise	Post exercise	p values
Stride Length (cm)	95.1 ± 14.8	102.4 ± 15.5	0.01
Stride duration (s)	1.06 ± 0.17	0.97 ± 0.11	0.06
Stride velocity (cm/s)	92.7 ± 21.1	105.7 ± 15.5	0.01
Cadence (strides/s)	0.97 ± 0.13	1.04 ± 0.12	0.07
Swing phase (%)	36.5 ± 4.1	37.2 ± 2.3	0.93
Single support (%)	37.5 ± 3.7	38.3 ± 2.3	0.83
Double support (%)	26.0 ± 7.3	24.5 ± 4.0	0.86

TUG: Timed Up and Go Test; PLM: Posture-Locomotor-Manual Test.

Table 3. Means and standard deviations for each functional capacity component and gait dependent variables at before (pre) and after (post) the multimodal exercise program.

Third, even though it was not the purpose of the multimodal exercise program, the individuals with PD improved the non-motor symptoms (Table 4). Patients with PD improved short-term memory (logical memory I), episodic declarative memory (logic memory II), abstraction capacities (categories completed) and mental flexibility (perseverative errors) after the enrolment in the multimodal exercise program. Again, these findings indicated an improvement of quality of life for patients with PD. So, the multimodal exercise program seems to improve cognitive function.

COGNITIVE FUNCTIONS			
Dependent Variables	Pre exercise	Post exercise	p values
STAI - Trait	50.40 ± 8.01	48.70 ± 5.39	0.58
STAI - State	49.20 ± 6.95	48.50 ± 6.67	0.27
HAD	5.40 ± 2.59	5.40 ± 3.13	0.35
Logic memory I (score)	15.50 ± 3.60	19.50 ± 5.00	0.04
Logic memory II (score)	8.6 ± 5.95	13.8 ± 6.38	0.01
Symbol Search	22.50 ± 7.73	24.20 ± 9.12	0.60
Categories Completed (WCST)	2.80 ± 1.68	4.10 ± 1.37	0.04
Perserverative Errors (WCST)	4.00 ± 3.49	0.30 ± 0.94	0.04
Failure to Maintain Set (WCST)	6.00 ± 2.40	5.20 ± 2.34	0.64

WCST: Wisconsin Card Sorting Test; STAI: State-Trait Anxiety Inventory; HAD: Hospital Anxiety and Depression Scale.

Table 4. Means and standard deviations for the cognitive functions at before (pre) and after (post) the multimodal exercise program.

In summary, a multimodal exercise program of six months seems to improve motor and non-motor symptoms of PD. Aspects related to functional activity, mobility and cognition showed benefits with exercise program, which is a relevant finding for functionality and quality of life of PD patients.

4. Final considerations

The aim of this chapter was to discuss the effects of long-term multimodal exercise program on motor and cognitive symptoms, as well as on functional capacity in people with PD. To reach this aim, we reviewed the published data of our group and as main results we found improvements in four different domains: clinical aspects, gait parameters, functional capacity and cognitive status. All these improvements certainly increased patients' independency, mobility, functional aspects and quality of life. For functional aspects, this is clear according to the improvement of UPDRS II score. Since the UPRDS II is a self-related scale, this is also important to the patients' quality of life: patients self-perceived their own functional aspects as better after the enrolment in our program. This certainly increases patients' quality of life. However, the benefits did not only rely on PD clinical aspects, but also on peripheral gains (as strength) and improvements in brain functions, as memory and executive function. We show during this section that there is not a main cause as responsible for our results. In another way,

we demonstrate that enrolling into our exercise program allowed the patients to improve different aspects of their life.

Considering functional capacity, PD patients showed improvements on muscular strength, motor coordination, dynamic balance and functional mobility (Orcioli-Silva et al., 2013, submitted for publication). Muscular strength is a function of length and velocity (Winter, 1990), where its gain can lead to an improvement of both stride velocity and length. Motor coordination is a motor act that requires the control of body segments in an integrated way, with the aim to create a successful movement pattern. In this way, both improvements of strength and coordination could drive patients to increase their gait velocity and stride length. This is reinforced by the results of some studies which demonstrated that gait is highly influenced by coordination in PD patients (Plotnik, Giladi & Hausdorff, 2008). Due to the improvement of these both motor capacities, a more stable level was acquired, thus reflecting on functional mobility, measured through TUG and PLM tests.

Lower limbs muscular strength decrease, a reduction of stride length and velocity, and poor levels of balance and functionality can lead to higher risk of falling in PD patients (Cole et al., 2010; Kerr et al., 2010; Latt et al., 2009; Vitória, Lirani-Silva & Pelicioni, 2013). In this way, even without assessing the number of falls during our exercise program, we can suggest that the enrolment on our multimodal exercise program leads to a reduction of patients' risk of falls. Also, since patients increased their self-judgment about their functionality (increase in UPDRS II scores), this could also result in a falling risk reduction. This is based on the study of Vellas et al. (1997), which indicates that fear of falling (and therefore a reduction of own judgment about functional capacity) is directly related to the number of falling episodes.

Beyond the benefits in patients' quality of life, we cannot forget to mention another important aspect of our motor results. The improvement of both strength and coordination after a 6-month multimodal exercise program shows us that peripheral benefits observed in healthy elderly, from exercise enrolment, can be transferred, at least in part, to PD patients. Also, the improvement on coordination leaves an open window to discuss the maintenance of learning capacity in PD patients.

Finally, about the motor benefits of our multimodal exercise program, we need to discuss the maintenance of UPDRS III score. Someone can argue that our program did not reduce motor impairments and therefore, is not so attractive. However, since a decrease of 3.2% in HY stage score per year is expected (Alves et al., 2005), the maintenance of UPDRS III score is an important result. We must remember that our program has a long lasting period and the maintenance of motor impairments after 6 months has important effects on patients' quality of life.

However, the most exciting results are those related to cognitive aspects. The improvement in executive functions (responsible to successfully plan, select and execute motor plans) could also be responsible for higher performance of gait. This is based on the study of Yogev et al. (2005), which relates the gait performance to cognitive status in PD patients. Furthermore, a higher cognitive performance can also lead to a better self-perception of functional state, increasing the UPDRS II score.

These are exciting results since they demonstrate that exercise cannot benefit only healthy adult brain, but also mental function of PD patients. Some studies had demonstrated that the practice of moderate and intense physical exercise can result in compensatory changes on the dopaminergic neurotransmission (Petzinger et al., 2007). In addition, some studies had shown that exercise could also be responsible to neural adaptations as the increase of blood flow (Hirsch & Farley, 2009) and to an increase of metabolic and neurochemical function in the brain (Petzinger et al., 2010). Other results point to an increase of neuroprotection and even to an increase of neural growth factors (Zigmond et al., 2009) in the brain after exercise programs. These results were seen mainly on animal models and at this time, we cannot assure that our exercise program promoted these adaptations. However, even without assessing these morphological and physiological aspects of physical exercise (and this is not the objective of our group), the improvement in memory and executive function point to some adaptations in brain levels. The PD brain also shows a high capacity to redesign itself in response to physical activity, providing a plausible argument related to the neuroplasticity mechanism in PD patients after physical exercises (Hirsch & Farley, 2009).

It is believed that these adaptations are due to our program design and to the exercises intensity level. High intensity exercises have shown more positive effects in PD patients when compared to low intensity exercises (Burini et al., 2006; Fisher et al., 2008). Also, physical activity programs lasting longer than 10 weeks, with a frequency more than 3 days a week and with 45-60 minutes of duration per session can lead to higher benefits to PD patients (Barbieri et al., 2013). Also, it is indicated that activities with intensity between moderate to high (Barbieri et al., 2013). Our multimodal exercise program fully respected all these statements as well as it had a continuous progression during each phase, whereas the intensity of physical exercises was kept between moderate to high. It is believed that this exercise design is better for PD patients than others since it results in compensatory changes in the dopaminergic neurotransmission (Petzinger et al., 2007; Petzinger et al., 2010).

It is also important to consider that patients enrolled in our multimodal exercise program were in between the mild to moderate stages of disease. Since these patients have a better physical condition than those on severe stages, possibly these last could not be able to execute the exercises properly. Also, patients in mild to moderate disease stages are still able to learn new motor skills (Canning, Ada & Woodhouse, 2008).

In resume, the results of our group clearly show that a 6-months multimodal exercise program was feasible and improved patients' physical and cognitive status (Gobbi et al., 2011). After 6 months, patients enrolled in our exercise program maintained their motor impairments and, moreover, improved their independency and functionality. We can state that our exercise program increased patient's mobility, with the reduction of two main symptoms: bradykinesia and hypometria. At this time is not possible to state if the positive results found after our program are mainly due to a reduction in the physiological aging process, to neural adaptations or to a combination of both. However, these improvements are not only result of motor aspects but they are also related to improvement on cognitive domain. Finally, after reviewing our results we can properly affirm that our 6-months multimodal exercise program increased patients' independency, which certainly, improved their quality of life.

Author details

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