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Effects of a Multimodal Exercise Program on Clinical, Functional Mobility and Cognitive Parameters of Idiopathic Parkinson's Disease Patients

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1. Introduction

This chapter has as main objective to present the effects of a multimodal exercise program on major signs/symptoms, functional mobility and cognitive parameters of people with Parkinson's disease (PD). This program is developed to improve all functional capacity components (strength, balance, aerobic resistance, coordination and flexibility) in order to increase patients' independence, autonomy and quality of life. As main result, we found maintenance of clinical status and memory after the exercise program with an increase in functional mobility. These results can be attributed to neuro-protection mechanisms enhanced by exercise and to an increase in functional capacity.

Parkinson's Disease (PD) is the second most incident neurodegenerative pathology in subjects over 60 years old (Olanow et al., 2009). PD has been described to affect approximately 0.3% of the population and 1% to 2% of those older than 60 years (de Lau & Breteler, 2006). It is a neurodegenerative pathology characterized by progressive degeneration of the dopamine-producing neurons in the substantia nigra pars compacta. The neuromotor impulses in the subcortical to cortical pathways, responsible for accurate control of muscle activation, are compromised with the decreased amount of dopamine. As a consequence, people with PD show motor (e.g. resting tremor, rigidity, postural instability, mobility and others) and non-motor (e.g. executive functions, depression, memory, humor alterations, dementia and others) (Taylor et al., 1986; Chaudhuri et al., 2006; Martinez-Martin, 2006; Olanow et al., 2009) signs/symptoms. Clinical parameters of PD patients tend to get worse progressively (Karlsen et al., 2000) even though pharmacological interventions associated with non pharmacological therapies have shown some benefits to patients (Sage & Almeida, 2009, 2010).

Motor signs/symptoms related to PD can contribute to the decline in balance control and mobility (Christofolletti et al., 2006), which subsequently can lead to a reduction in functional

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independence. As a consequence, individuals with PD experience an increase in both the difficulties in performing daily activities, such as rising from a chair or walking, that are directed related to impoverishment in balance control (Hong & Steen, 2007), and in the risk of falls (Grimbergen et al., 2004). Together with motor disturbances, cognitive deficits in PD are detectable in the early stages (Stella et al., 2007) and are evidenced primarily by impairments in executive functions, i.e., the ability to generate spontaneous action as well as to develop motor strategies in specific planning for the performance of a given task (Taylor et al., 1986; Chaudhuri et al., 2006). Although the people with PD have the ability to decode, store and consolidate new information preserved, they present difficulty in retrieving these information (Dubois & Pillon, 1997; Dujardin & Laurent, 2003; Costa et al., 2008). These tasks involve transient working memory (handling, maintenance and temporary activation of the memory) and episodic memory (conscious recollection of individual events, reported within a specific context of space and time) (Dujardin & Laurent, 2003). Executive functions are regulated by both the prefrontal areas and the frontostriatal circuitry (Dujardin et al., 2003; Owen, 2004). In the prefrontal cortex, the transmission of dopamine by the dopamine receptors (D1) plays an important role in the functioning of working memory and learning (Cropley et al., 2006; Rashid et al., 2007), while the frontostriatal circuitry is related to motor planning (Olanow et al., 2009).

One possibility for the treatment of PD is the pharmacological therapy, i.e., the administration of synthetic dopamine (levodopa). Studies in patients with early stage of the disease have shown antagonistic effects during the *on phase* of the medication. Positive effects have been observed in locomotor (Pieruccini-Faria et al., 2006) and cognitive (Cools, 2006; Pascual-Sedano et al., 2008) parameters. However, over the years as the disease progresses, the effect of drug decreases and higher doses are needed for treatment. As a result, patients start to present motor fluctuations and dyskinesias (involuntary movements), which are side effects associated with long-term drug treatment (Obeso et al., 2000). Associated with drug therapy, non-pharmacologic therapies related to PD, such as physical exercises and nutrition, helped to attenuate the disease's severity or reduce its progression (Hirayama et al., 2008; Morris et al., 2009). The regular practice of physical exercise is effective to provide improvements in quality of life of this group of patients (White et al., 2006; Hirayama et al., 2008). Forced aerobic exercise affected both the scores in motor sub-section of the UPDRS and the performance in manual skills (Ridgel et al., 2009) while the sensory focused exercise program improved functional mobility and the motor symptoms (Sage & Almeida, 2010) in people with PD. The physical exercise can act as a protector factor generating brain changes due to a greater cerebral oxygenation, such as neuroplasticity, brain repairing and an increase of the dopaminergic cells (Smith & Zigmond, 2003; Fox et al., 2006). Besides, when the exercise is introduced in the early stages of the disease, the disease progression can slow down (Fox et al., 2006).

Physical exercise is an important factor that can improve functional capacity in the elderly (Cyarto et al., 2008). Crizzle and Newhouse (2006), reviewing the literature, concluded that, through exercise, patients with PD improve their physical performance and the performance of activities of daily living. Recently, some evidences have been showed positive changes after the exercise program not only in balance and mobility (Gobbi et al., 2009; Hackney & Earhart, 2010) but also for the motor (Sage & Almeida, 2009; Sage & Almeida, 2010) and non-motor signs/symptoms (Tanaka et al., 2009) in PD patients. Therefore, systematic participation in physical exercise programs can help individuals with PD to maintain their motor repertoires and their cognitive ability to perform daily living activities.

Any type of physical exercise is better than no exercise to improve the level of functional capacity (Brach et al., 2004). However, little is known about the effect of exercise on cognitive function in patients with PD. For healthy elderly, without PD, studies have shown positive results of exercise on cognitive functions, especially on memory (Chiari et al., 2010). Aerobic exercises are the more effective ones to improve memory parameters of older people when compared to cognitive exercises and the ones that combine aerobic and cognitive exercises (Fabre et al., 2002). The positive results found for the elderly population may suggest that people with PD also benefit from physical exercise practice. Physical exercise programs for people with PD that focus on improvements in functional capacity and mobility vary according to the type of proposed activity, whether it will be practiced individually or in a group, the program's duration, the frequency and duration of the weekly sessions, and the means of evaluation. Such programs include intensive sports training (Reuter et al., 1999), treadmill training with body weight support (Miyai et al., 2000), resistance training (Scandalis et al., 2001; Dibble et al., 2009), aerobic exercise (Bergen et al., 2002), alternative forms of exercise (Hackney & Earhart, 2009), home-based exercise intervention (Nocera et al., 2009), and the practice of movement strategies (Morris et al., 2009).

The results of our group, using a multimodal exercise program based on the improvement of the functional capacity components (strength, balance, aerobic resistance, coordination and flexibility) revealed a positive effect on the executive functions (Tanaka et al., 2009) and on the functional mobility and balance (Gobbi et al., 2009). Tanaka et al. (2009) analyzed the effects of an aerobic exercise program on executive functions in older people with PD. We found significant improvements in executive functions in people with PD after six months of participation in aerobic exercise program. Such benefits were expected to play an important role on independence, autonomy and quality of life of such population. Gobbi et al. (2009) investigated the effects of two intervention programs, a multi-mode exercise program and an adaptive program, on the mobility and functional balance in people with PD. We found that both the intensive and adaptive exercise programs improved balance and mobility in patients with PD.

Within this context, the purpose of this chapter is to demonstrate the effectiveness of a long-term multimodal exercise program in improving clinical parameters, functional mobility and cognitive function in people with PD. We analyzed the benefits of the long-term exercise interventions in motor and non motor signs/symptoms in a more holistic point of view, since this type of physical exercise intervention for people with PD have not been reported.

2. Methods

This study adhered to the guidelines of the Declaration of Helsinki, and was approved by the local Ethics Committee. All patients signed informed consent forms before involvement in the study.

2.1 Participants

Fifteen idiopathic PD patients were enrolled in the study. All had a diagnosis of idiopathic PD, with no other major neurological problems. Inclusion criteria were: disease in Stages I-III of the Hoehn and Yahr Rating Scale (H&Y; Hoehn & Yahr, 1967), independent walker, and no cognitive impairment, as judged by Brucki et al.'s (2003) suggestions for utilization

of the Mini-Exam of Mental Status (MEMS; Folstein et al., 1975) in Brazil. Demographic data of PD patients are outlined in Table 1.

Subject	Gender	Age (years)	Body height (cm)	Body mass (kg)	H&Y (stage)	Years since diagnosis
A	female	66	162.2	85.5	1	3
B	female	60	163	56.7	2	2
C	female	67	153	47.5	1	3
D	female	59	154.4	67	1	2
E	female	60	142.8	57.5	1	2
F	female	82	153	71.7	3	4
G	female	65	151.8	39.5	1.5	4
H	female	60	162	70.4	1	3
I	male	75	176.5	62.5	1.5	4
J	male	64	161.8	85.1	3	19
L	male	69	174	69.7	1	3
M	male	59	165.5	88.7	1	2
N	male	78	165.5	88.7	2	1
O	male	65	163.3	77.9	1	1
P	male	73	165.5	91.6	1	4
Mean		67	161.0	70.7	1.5	3.8
SD		7.28	8.74	15.87	0.7	4.33

Table 1. Demographic characteristics of the participants.

2.2 Intervention

The aim of the multimodal exercise program was to develop the patients' functional capacity, cognitive functions, posture, and locomotion through a program that is primarily aerobic. It was composed of a variety of activities that simultaneously focus on the components of functional capacity, such as muscular resistance (specific exercises for large muscle groups), motor coordination (rhythmic activities), and balance (recreational motor activities). These components were selected because they seem to be those most affected by PD. The multimodal program took place over a six-month period (72 sessions, 3 times a week, and 60 minutes per session). Each session consisted of five components (warm-up, pre-exercise stretching, the main exercise session, cool-down and post-exercise stretching). All sessions were conducted in the morning, in the "on medication" state, between 1 and 1½ h after participants' first morning dose of medication. The program was designed in six phases and each phase was composed of 12 sessions and lasting approximately one month. At the end of each phase there was a progressive increase of load (Chart 1). Heart rate during the sessions remained between 60% and 80% of maximum heart rate (220 minus the participant's age in years), which characterizes training with aerobic predominance. The exercise program was supervised by at least three physical education professionals at any

one time. Each participant was required to attend at least 70% of the sessions in order to be included in the data analysis. This protocol has been previously described by Tanaka et al. (2009).

Phases	Capacities		
	<i>Coordination</i>	<i>Muscular Resistance</i>	<i>Balance</i>
<i>Phase 1</i>	Upper and lower limbs movements.	Exercises without weights.	Recreational activities that stimulated the vestibular system.
<i>Phase 2</i>	Trunk movements were added to upper and lower limbs movements.	Light-weight equipment (hoops, ropes and batons).	Recreational activities that stimulated the visual and vestibular systems.
<i>Phase 3</i>	Trunk movements were substituted by head movements.	Heavier equipments (barbells, ankle weights, medicine balls).	Recreational activities that stimulated the visual and somatossensorial systems.
<i>Phase 4</i>	Head, trunk and upper and lower limb movements.	Load was again increased with heavier equipment for resistance training (increase of intensity) or increased repetitions (increased volume).	Recreational activities integrated the vestibular, visual and somatossensorial systems.
<i>Phase 5</i>	Four different movement sequences, two of which were the same for upper and lower limbs and two other sequences that alternated movements for upper and lower limbs in place and in movement.	Exercises were done with weights: leg press, pulley, seated cable rows, pecdeck, and bench press, in two series of 15 repetitions.	Recreational activities included static balance, dynamic balance, half-turn and complete turn (all with visual cues).
<i>Phase 6</i>	Four sequences of different movements, two sequences of alternating movement for upper and lower limbs and two sequences of different movement for upper and lower limbs, with or without trunk movement and equipment (balloons, balls, hoops and rope).	Series of 15 repetitions were added.	Recreational activities were composed of activities with tactile cues.

Chart 1. Designed phases of the 6-month intervention protocol with progressive increments on load and complexity for people with Parkinson’s disease (adapted from Tanaka et al., 2009).

2.3 Evaluation protocol for the dependent variables

Participants were tested before commencing the multimodal program (pre-test), and upon completion (post-test). All assessments were carried out in the morning, in the “on medication” state, at least 1 h after participants’ first morning dose of medication. The participants were evaluated by the same trained assessor (blinded as to the study purpose) under the same conditions in both moments (pre- and post-tests).

2.3.1 Clinical evaluation

A neuropsychiatrist performed a clinical assessment by means on the Unified Parkinson's Disease Rating Scale (UPDRS; Fahn & Elton, 1987), MEMS, and H&Y. Higher scores on the UPDRS and H&Y represent higher commitment levels of the disease. Conversely, higher scores on the MEMS indicate a more preserved cognitive function. For data analysis, scores on the UPDRS sub-sections I (Mentation, Behavior, and Mood), II (Activities of Daily Living), and III (Motor) were considered separately.

2.3.2 Functional mobility evaluation

Basic functional mobility was assessed by means of the Timed Up and Go Test (TUG; Podsiadlo & Richardson, 1991) and the Postural Locomotion Manual test (PLM; Steg et al., 1989).

- i. TUG: The task consisted of the participant to stand up from a sitting position in an armless chair with a seat height of 46.5 cm, walk a distance of 3 m, circumvent a cone, return, and sit back down in the chair. Participants were instructed to perform the test as quickly as possible, but without running. At least one practice trial was offered to the participants at the beginning of the procedure so that they could become familiar with it. Three trials 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 (standing up) until the next contact with the chair (sitting down). The mean value of the three attempts was considered for statistical analysis.
- ii. PLM: This test measures postural control, locomotion and a goal directed reaching arm movement and the efficacy with which these movements compose a smooth dynamic action of the whole-person. To perform the PLM test, the participants were asked to move a small squared object (500 g), from a clearly marked starting place on the floor, to a stand located at eyes level, 1.82 m away in front of the starting place. Subjects had to deal with postural changes during the different phases of the test (to bend the upper body to pick up the object, walk forward and place the object on the stand). Time to perform the task was recorded from the "go" sign to the first contact of the object with the stand. The mean value of the three attempts was considered for statistical analysis.
- iii. Since each subject performed three attempts of each task, we also compared these attempts (Attempt 1 vs Attempt 2 vs Attempt 3) before and after the training program.

2.3.3 Cognitive evaluation

The following tests were applied for cognitive function assessment:

- i. Executive Functions, by the Wisconsin Card Sorting Test - WCST (Heaton et al., 1993; Paolo et al., 1995). This test specifically assesses abstraction, mental flexibility and attention. It consists of 4 stimulus cards and 128 response cards that must be combined with the stimulus cards by following the hints "right" or "wrong" provided by the evaluator. From this hint, without pre-established rule, the participant must find the right combination (according to color, shape or number). Every 6 consecutive hits, the evaluator changes the mix and the participant must change his or her strategy. The test continues until the participant completes 6 categories of combinations or the 128 attempts. The WCST was chosen due to: a) its good construct validity for people with PD; b) it assesses three executive functions at the same time (abstraction, mental flexibility, attention) and; c) it does not require high level of schooling and this also

makes it appropriate for the population involved in our study. Within the executive functions, mental flexibility was the variable of interest for this study. It was assessed based on the number of perseverative errors made by patients.

- ii. The subtest Logical Memory I and II, Wechsler Memory Scale Revised - WMS-R (Wechsler, 1997) was used to measure the short-term memory (logical memory I) and episodic declarative memory (logical memory II). In this subtest two stories are told separately. Immediately after hearing each story, the patient states what was remembered and the amount of linguistic units remembered is computed for logical memory I. After 30 minutes, participants are asked to retell the two stories and the points concerning linguistic units remembered are computed for logical memory II.

3. Results

Clinical, functional mobility and cognitive data from pre- and post-tests are outlined in Table 2. The Wilcoxon test did not show significant differences between pre- and post-intervention for H&Y, UPDRS-I, UPDRS-III, MEMS, perseverative errors and episodic logic memory I. The multimodal exercise program was effective in improving UPDRS-II scores, episodic declarative memory II, TUG and PLM.

Dependent variable	Pre-test	Post-test	<i>P</i> value
Clinical			
H&Y (stage)	1.47±0.72	1.53±0.72	0.157
UPDRS-I (score)	3.67±2.69	3.33±2.44	0.301
UPDRS-II (score)	11.07±6.36	9.73±6.04	0.022
UPDRS-III (score)	20.13±12.26	21±14.53	0.728
MEMS (score)	26.2±3.47	25.9±4.35	0.778
Functional mobility			
TUG (s)	10.37±4.54	8.41±2.27	0.002
PLM (s)	4.03±1.42	3.58±0.76	0.013
Cognitive			
Perseverative errors (errors)	6.87±6.83	5.13±7.52	0.151
Logic memory I (score)	14.8±5.02	17.07±5.93	0.132
Logic memory II (score)	8.6±5.95	13.8±6.38	0.005

Table 2. Means and standard deviations for each clinical dependent variable at pre and post-test and *P* value.

Figures 1 and 2 show respectively times to complete all attempts of the TUG and the PLM tests at pre- and post-intervention. The Friedman test showed a significant effect for attempts on TUG at pre-test ($p=0.019$) and post-test ($p=0.047$; not confirmed by the Wilcoxon test, $p>0.05$) and PLM at pre-test ($p<0.001$). Therefore, at pre-test a significantly increase in time to complete TUG (Attempt1 vs Attempt 3 - $Z=2.240$; $p=0.025$) was observed.

During the PLM, patients reduced their time at pre-test (Attempt 1 vs Attempt 3 - $Z=3.678$; $p<0.001$), showing a learning effect. No differences were observed on Attempt 1 and Attempt 2 in all cases.

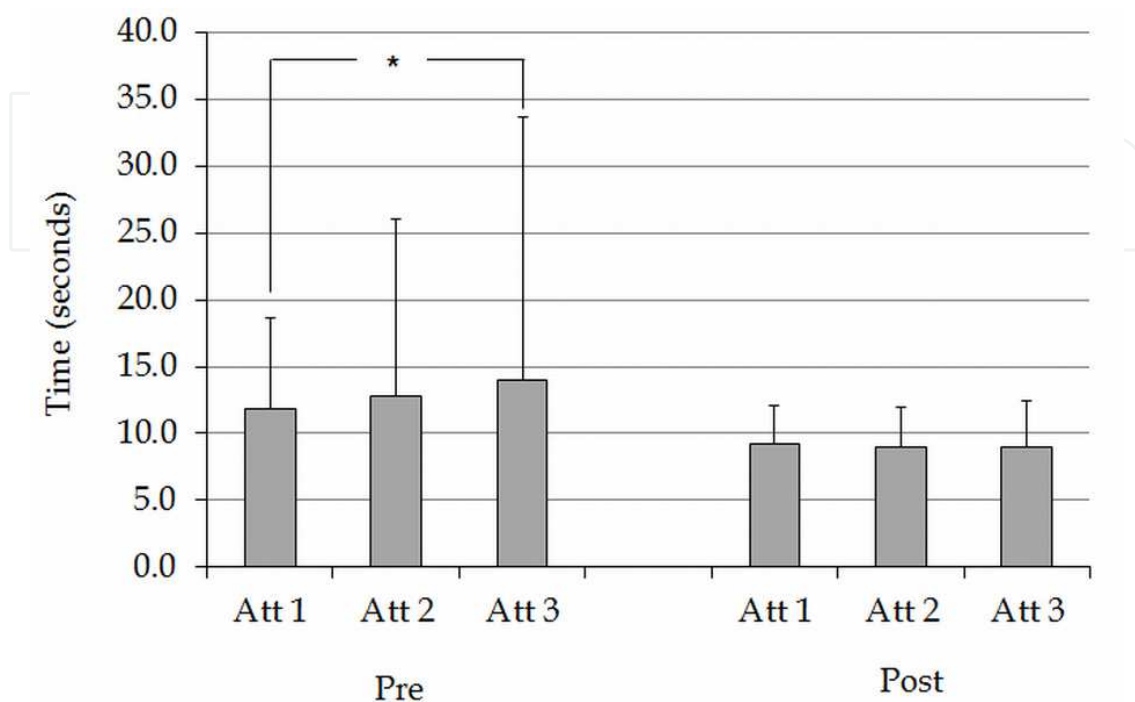


Fig. 1. Mean (+SD) time to complete attempts 1 to 3 (Att1 - Att3) of TUG test at pre- and post-intervention. * $p<0.05$

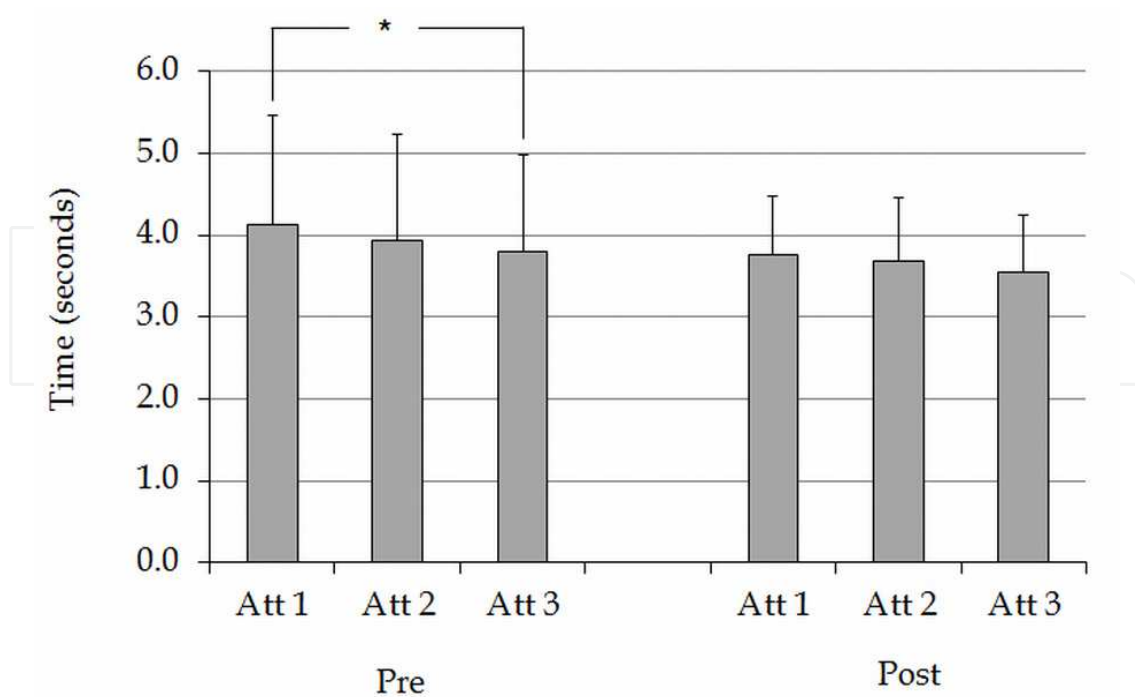


Fig. 2. Mean (+SD) time to complete attempts 1 to 3 (Att1 - Att3) of PLM test at pre- and post-intervention. * $p<0.05$

4. Discussion

The purpose of this chapter was to demonstrate the effectiveness of a long-term multimodal exercise program in improving clinical parameters, functional mobility and cognitive function in people with PD. Our results show a clear maintenance in the disease stage and severity with an increase on balance control and functional mobility. Also, the maintenance of both the executive functions and the short-term memory was observed.

Even with an expected increase in the disease stage and severity (H&Y scale), patients that were enrolled in our 6-months multimodal exercise program maintained their disease and motor impairments (Table 1). Since PD is a neurodegenerative and progressive disorder (Olanow et al., 2009) it would be expected that after the intervention period these patients would present a reduction in their motor performance as also observed by others (Hackney & Earhart, 2010). Alves et al. (2005) found an increase of 3.2% in the H&Y score for each year. However, as shown in Table 2, our multimodal training program was successful to maintain both UPDRS I and UPDRS III sub-scores and to decelerate the increment in H&Y score, since it was observed only a 0.04% raise in 6-months.

In this way, we can speculate that exercise promotes at least in part, a protective role on dopaminergic neuronal loss and on the disease impairments. Several studies had pointed out a positive exercise effect on brain function, as neural growth (Zigmond et al., 2009), higher neurotransmitters use efficiency (Petzinger et al., 2010) and angiogenesis (Hirsch & Farley, 2009). According to Tajiri et al. (2010), exercise can enhance synaptic plasticity with a re-construction of cortical path network on PD induced rat models. Therefore we can suggest that exercise played some role, not yet fully understood (Hirsch & Farley, 2009), in the protection of dopaminergic neural loss.

The characteristics of the multimodal exercise program were responsible for increase stability of these patients. All exercises were focused on the patients' impairments, as bradykinesia, unbalance, difficulties to perform sequential movements and changing movement directions. Therefore, we can affirm that the 10-20% of reduction in time to complete TUG and PLM tests (Table 2) was due, at least in part, to the intervention features, such as the group sessions and long-term duration. The program effect was enough to approach the patients' performance to healthy elderly (8.8 to 9.1 seconds - Alfieri et al., 2010). The reduction presented by our subjects is highly superior to that observed on both healthy elderly (Alfieri et al., 2010: 8-12%; Arai et al., 2009: 8%) and people with PD (Sage & Almeida, 2009: 6-8%). In this way, our data are particularly important, since the improvement in balance control reduces the risk of falling and therefore, reduces patients' mortality and morbidity (Lee & Chou, 2006).

It is believed that physical capacities such as strength, flexibility, aerobic resistance and others were worked properly during our multimodal exercise program, allowing subjects to improve functional capacity and decrease their time spent to perform the TUG and PLM tests. We can also suggest that aerobic resistance was also improved by our intervention program. Before the program, subjects presented an increase on time to complete TUG in different attempts, suggesting the presence of fatigue (Garber & Friedman, 2003). However, after the 6-months intervention period, this time was maintained during different attempts (Figure 1). Also, subjects performed TUG and PLM tests with a lower variability at post-test in comparison to pre-test (Figures 1 and 2), showing an improvement on stability.

The multimodal exercise program also improved the episodic declarative memory, despite the physical exercise did not change the executive function and short-term memory

performance. However, studies have shown that the annual rate of clinical decline in people with PD is between 3.5% (Alves et al., 2005) and 11.2% (García-Ruiz et al., 2004). So, the maintenance of the scores in executive functions and short-term memory in the period of six months is also an important outcome for the patient.

The different memory systems depend on different anatomical structures. The short-term memory is located in the hippocampus and adjacent cortical areas of the temporal lobe, while episodic declarative memory is related to the medial temporal lobe, anterior thalamic nucleus, mammillary bodies, fornix, and prefrontal cortex (Robertson, 2002; Budson & Price, 2005). People with PD do report declarative memory loss but they do not report implicit memory loss, which suggests a problem of memorization strategy (Appollonio et al., 1994). To retrieve some information, people can use declarative memory, which requires conscious effort and attention, or implicit memory (typically unconscious), which is automatically accessed (Johnson et al., 2005). Due to degeneration of dopaminergic and cholinergic neurons in the nigrostriatal pathway in PD, cognitive behavior and the control of motor action are impaired. Therefore, the anatomical damages due to the disease can explain why episodic memory is the most affected (Calabresi et al., 2006). Our results showed that the episodic declarative memory (logical memory II) was more sensitive for the exercise. Perhaps, the exercise may achieve most impaired memory areas in PD patients.

As a study limitation we can not forget that all these results are applicable for subjects in the initial stages of the disease as those evaluated by our group. Also, it is important to remember that a control group was not assessed and therefore there is a need to evaluate if some of these results were not related to learning or aging effects. However, our research group is already performing another study to fulfill this need.

5. Conclusion

As conclusion we can affirm that exercise as proposed by our group – a multimodal exercise program of long duration – plays an important role on the quality of life in people with PD by improving or maintaining their clinical parameters, functional mobility and cognitive function. This program has the capacity to decelerate the disease advance. This is particularly true when the disease stage and impairments are considered, as also seen in memory. These exercise effects are believed to be due to neuroprotection mechanisms not yet fully understudied and to an increase of all components of the functional capacity.

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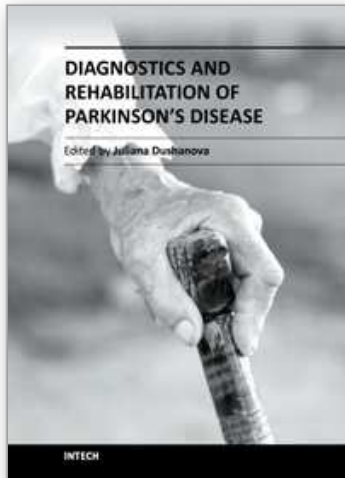
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Diagnostics and Rehabilitation of Parkinson's Disease presents the most current information pertaining to news-making topics relating to this disease, including etiology, early biomarkers for the diagnostics, novel methods to evaluate symptoms, research, multidisciplinary rehabilitation, new applications of brain imaging and invasive methods to the study of Parkinson's disease. Researchers have only recently begun to focus on the non-motor symptoms of Parkinson's disease, which are poorly recognized and inadequately treated by clinicians. The non-motor symptoms of Parkinson's disease have a significant impact on patient quality of life and mortality and include cognitive impairments, autonomic, gastrointestinal, and sensory symptoms. In-depth discussion of the use of imaging tools to study disease mechanisms is also provided, with emphasis on the abnormal network organization in parkinsonism. Deep brain stimulation management is a paradigm-shifting therapy for Parkinson's disease, essential tremor, and dystonia. In the recent years, new approaches of early diagnostics, training programmes and treatments have vastly improved the lives of people with Parkinson's disease, substantially reducing symptoms and significantly delaying disability. Written by leading scientists on movement and neurological disorders, this comprehensive book should appeal to a multidisciplinary audience and help people cope with medical, emotional, and practical challenges.

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