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Aerobic rehabilitation program for improving muscle function in Parkinson's disease

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Abstract.
Background: Parkinson's Disease (PD) is characterized by progressive and disabling symptoms. An impaired oxidative metabolism efficiency was supposed to be involved in the systemic impairment. Rehabilitative treatment represents a valid tool in promoting skeletal muscle's adaptations, even if no solid studies on muscle metabolic features are still available.
Objective: To evaluate the efficiency of skeletal muscle oxidative metabolism in PD patients in comparison with age-matched controls and test the role of an intensive aerobic treatment on muscle oxidative metabolism and its clinical effects.
Methods: 60 PD patients and 32 age-matched healthy controls participated. Haematic lactate values were detected during and after a submaximal incremental exercise on treadmill. The number of steps completed during the exercise was recorded. From these patients 10 underwent to an intensive aerobic treatment on treadmill (4 sessions/week for 4 weeks). Haematic lactate values and functional scales were recorded before (T0) and after (T1) treatment.
Results: At rest no significant difference in hematic lactate values between PD and control subjects was found. Lactate blood levels were significantly higher ($p < 0{,}001$) after the aerobic exercise test in PD patients compared to controls. These values remained higher at any time during recovery period ($p < 0{,}001$). No significant relationship between lactate values and the number of completed steps was found. After the rehabilitation treatment haematic value of lactate showed a significant reduction ($p < 0{,}05$) at 0, 5 and 10 minutes of recovery period with a normalization of value at 30'. All functional scales showed an improvement trend at T1, in particular Berg Balance Scale and 6 Meter Walking Test showed a significant reduction ($p < 0{,}001$ and $p < 0{,}05$ respectively).
Conclusion: Our data clearly show an impaired muscle oxidative efficiency in PD subjects. The intensive rehabilitation program on treadmill showed a beneficial effect on muscle oxidative metabolism, endurance and balance, confirming the focal role of rehabilitation in PD patients.

Keyword: Parkinson's disease, muscle oxidative metabolism, rehabilitation

1. Introduction

Parkinson's Disease (PD) is one of the most common chronic neurodegenerative disease, with progressive and disabling symptoms. Generally it is associated with genetic, environmental, and behavioral features, resulting in the main symptoms, such as rigidity, postural instability, progressive bradykinesia, and tremor (Gazibara, 2014). PD is characterized by degeneration of dopaminergic neurons in the nigrostriatal system, with symptoms occurring when the loss of these cells is up to 70% (Birkmayer, 1985; Jellingerk, 1989; Poewe & Mahlknecht, 2009). Currently, the principal drugs for PD treatment just

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provide relief of symptoms and do not control or prevent the disease progression (Tarazi, 2014). No neuroprotective strategies are capable to reduce the functional decline seen in advancing disease and to slow PD progression (Lamotte, 2015).

Nowadays, rehabilitation programs represent a possible alternative approach associated with drug therapy in the long-term management of the disease. Different studies evidenced the benefits of endurance exercise programs in terms of gait performance, mobility and balance abilities, together with cardiorespiratory capacity and quality of life in PD patients (Lamotte, 2015; Brienesse & Emerson, 2013; Nadeau, 2014).

Endurance training could be beneficial through several hypothetical mechanisms (Petzinger, 2013) both central and peripheral. Currently a recent study examined what happens at skeletal muscle level after high-intensity exercise, showing modifications at cellular and subcellular level with improvement of mitochondrial function and oxidative stress (Kelly, 2014). The impairment of oxidative efficiency in PD has been supposed along the years (Mann, 1994; Penn, 1995) and this alteration may be a focal point to take in account. The peripheral oxidative deficit in fact could underlie important symptoms to treat in PD as the sense of weakness and excessive fatigability. Up to now only few studies (Di Monte, 1991; Nakagawa-Hattori, 1992) evaluated blood lactate levels in PD patients, evidencing no difference compared to healthy subjects.

One method to evaluate muscle oxidative metabolism, though non-specific and indirect, is the detection of blood levels of lactate (Di Mauro, 1985). The deficit of muscle oxidative pathways, indeed determines a precocious switch to the anaerobic lactacid way during a prolonged exercise (Thomas, 2004), so the lactacidemia can represent an indirect index of muscle oxidative efficiency.

The first aim of our study is to evaluate skeletal muscle oxidative efficiency, through hematic lactic acid assay before and after an aerobic exercise, in a large cohort of PD patients. The second aim is to evaluate the role of an aerobic and intensive rehabilitation program on skeletal oxidative metabolism and its clinical effects.

2. Materials and methods

60 PD patients (mean age ± SD: 67.4 ± 8.8 yrs), diagnosed using the UK PD Society Brain Bank, were recruited and compared to 32 sex and age-matched control subjects (mean age ± SD: 66.6 ± 5.6 yrs). PD patients were rated using the section III of the Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn and Yahr Scales in the off-state; major cognitive dysfunction was excluded by applying the Mini-Mental State Examination. Subjects with cardiovascular disorders were not included in the study. Antiparkinsonian therapy did not change in the last 6 months prior to the enrollment (patient's clinical details are shown in Table 1). Body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) was calculated for both group (25.91 ± 4.42 in PD vs 24.01 ± 3.32 in controls).

Each subject performed a submaximal incremental test on a calibrated, electronically braked treadmill (Runrace HC 1200, TechnoGym, Forlí, Italy).

They were instructed to refrain from exercise they were unaccustomed to, at least in the two days before the exercise session. They were advised to wear comfortable clothes and shoes with low heels or trainers and to eat a light meal no less than two hours before arrival. After careful explanation of the procedures, informed consent was obtained from all the subjects.

The exercise protocol consisted of 2-min steps, at a constant speed of 3 Km/h. The grade was 0 at the beginning and it was increased 2.5% each step. The test was stopped if patients reached the 75% of the theoretically calculated maximum heart rate (220-patient's age) (Jones, 1982). In this way the work was maintained in predominantly aerobic conditions (Bertolucci, 2014). All subjects were informed that the exercise could be stopped at any time.

The following parameters were evaluated:

– Haematic lactate values, by venous blood samples collected at rest, at the end of the exercise and during recovery period (5', 10' and 30' after the end of the exercise);

Table 1
Clinical and demographic details for the study population ($n = 60$)

Patients	Mean Values
Age	67,4 ± 8,80 years
Gender	38 men and 22 women
BMI	25,91 ± 4,42
Hoen & Yahrd stage	2,72 ± 0,89
PD duration	6,16 ± 3,92 years
UPDRS III	31,05 ± 13,71
MMSE	25,55 ± 1,66
Daily Levodopa Equivalent Dose	628,81 ± 172,90 (mg/die)

– Cardiac and ventilatory parameters, in particular heart rate and oxygen saturation of arterious haemoglobin (Radiometer Pulse Oximeter, Radiometer Copenaghen, Copenaghen, Denmark).

Blood samples were collected in EDTA tubes. Samples were withdrawn from the antecubital vein by venipuncture and immediately centrifuged after blood withdrawal, frozen and stored at –20°C until analysis. Lactate concentrations were measured by an enzymatic determination at a temperature of 25°C (Sigma Chemical Co., St. Louis, MO, USA).

These data were analyzed with standard statistical methods used to calculate mean and standard deviation (SD). The evaluation of the differences between mean values of the PD patients and controls, used as reference value, were performed using the z-test. Statistical significance was set at $p < 0.001$.

Moreover 10 of these 60 patients (8 men and 2 woman) were enrolled for an intensive rehabilitation program. These patients were not significantly different for age (71.7 ± 5.9 years), UPDRS III (26.3 ± 9.7) and cognitive impairment (MMSE 28.6 ± 1.3). To be included in rehabilitation group (RG), subjects were required to be medically stable, able to walk a 10 m distance at without an assistive device. All baseline assessments were done by the same investigator approximately 1 hour after antiparkinson medication, with the patients in the on state when they were moving freely and easily without dystonia, excessive rigidity or tremor. The functional status of RG patients was assessed before (T0) and after (T1) treatment using: (i) the Berg Balance Scale (BBS), a scale of ability to maintain balance, either statically or while performing functional movements. It comprises 14 observable tasks common to everyday life measured on a 5 point ordinal scale (Bronstein & Pavlou, 2013); (ii) Timed Up and Go Test (TUG): in this test subjects are asked to stand up from a chair, walk for 3 meters, walk back and sit down again, while the time necessary to complete the exercise is recorded (Schoene, 2013); (iii) 10-Meter Walking Test (10mWT): for this test, participants must ambulate 10 meters while being timed so that their walking speed may be calculated. A "flying start" is used where the subject may accelerate 2 meters before entering the timed 10-meter distance and 2 meters to decelerate afterwards. Speed is only calculated for the 10-meter distance between the "end zones" (Morganti, 2013); (iv) Six-minute walk test (6MWT): subjects were instructed to "walk as far as possible in six minutes". Subjects walked up and down a 25 m walkway without encouragement (Dalgas, 2013).

The RG participated in a four-week exercise program (4 session/week) for a total of 16 sessions. Each session, lasting about 1 hour and 15 minutes, was divided into different phases: an initial phase of active and active-assisted exercises for stretching and maintaining joint ROM, promoting postural stability and static and dynamic balance. In the second phase, patients performed the aerobic training on a treadmill. The initial rate was set considering the 80% speed previously reached at 10mWT (Morganti, 2005) by each patient and a progressive increase of 0.2 km/h according to patient tolerance was set, up to maintaining aerobic conditions (between 65 and 80% of theoretical maximum rate calculated as: 220 – patient's age). Therefore, each patient was monitored during treatment and a dedicated physical therapist encouraged him to walk with long strides trying to maintain a good posture. Data were examined before (T0) and after the treatment (T1).

The non-parametric Wilcoxon signed-rank test was applied. Significance of statistical tests was set at $p < 0.05$.

3. Results

3.1. At rest

No significant difference in haematic lactate values between PD and control subjects was found (mean ± SD 1.71 ± 0.60 vs 1.67 ± 0.55 mmol/l, respectively) ($z = –0.81$ $p > 0.001$) (Table 2).

Table 2
Haematic lactate values between PD and control subjects during different stages of treadmill treatment: at rest (Baseline); at the end of treadmill training (Final value) and during Recovery (at 5, 10 and 30 minutes). The lactate clearance is expressed in mean values (mean ± SD)

			Recovery		
	Baseline	Final value	5'	10'	30'
PD	1.71 ± 0.60	$4{,}53 \pm 1.90$	4.06 ± 2.13	3.50 ± 1.72	2.27 ± 0.95
Controls	1.67 ± 0.55	2.61 ± 0.86	3.17 ± 1.40	2.65 ± 1.12	1.80 ± 0.86

3.2. Stop

At the end of the exercise, the haematic lactate was significantly higher in PD (4.53 ± 1.90 mmol/l) than in controls (2.61 ± 0.86 mmol/l) ($z = -16.86$ $p < 0.001$) (Table 2). The mean duration of the exercise was six steps in PD and eight steps in controls.

3.3. Recovery

At 5', lactate values were 4.06 ± 2.13 mmol/l in PD and 3.17 ± 1.40 mmol/l in controls ($z = -4.93$ $p < 0.001$). At 10' lactate was 3.50 ± 1.72 mmol/l in PD and 2.65 ± 1.12 mmol/l in controls ($z = -5.61$ $p < 0.001$). At 30' after the end of the exercise values tended to normalize but remained significantly higher in PD (2.27 ± 0.95 mmol/l in PD vs 1.80 ± 0.86 mmo/l in controls) ($z = -4.22$ $p < 0{,}001$) (Fig. 1; Table 2).

No significant relationship between lactate values and number of steps completed during the exercise was found.

3.3.1. Rehabilitation group

The mean value of basal haematic lactate level did not show significant difference at two time (2.49 ± 9.80 vs 1.47 ± 0.51 mmol/dl T0 vs T1 respectively), while at the end of the exercise, lactacidemia was significantly lower ($p < 0.05$) at T1 than T0 (4.75 ± 1.59 vs 3.12 ± 0.98 mmol/dl T0 vs T1 respectively). This value was significant maintained lower ($p < 0.05$) also at 5' (4.12 ± 1.58 vs 2.78 ± 0.75 mmol/dl T0 vs T1 respectively) and 10' (3.61 ± 1.72 vs 2.39 ± 0.66 mmol/dl T0 vs T1 respectively) during recovery and then it normalized to 30' (2.56 ± 1.08 vs 1.69 ± 0.45 mmo/dl T0 vs T1 respectively) (Fig. 2).

Functional scales as BBS (49.6 ± 4.85 vs 52.3 ± 3.50) and 6MWT (261.7 ± 27.61 vs 314 ± 52.25 meters) showed a significant improvement at T1 ($p < 0.001$ e $p < 0.05$ respectively). Other scales did not show significant changes although there was a trend towards improvement in all these parameters (Fig. 3).

4. Discussion

Data obtained in the present study show significantly higher blood lactate levels in PD patients compared to control subjects after aerobic stress. These values remained significantly higher at any time during recovery period in PD subjects, even if a trend toward normalization after thirty minutes was observed. Interestingly, after the four-week aerobic training we showed an improvement in functional scales and a significant reduction of lactacidemia at the aerobic test.

Lactic acidemia results from enhanced glycolitic activity, accumulation of pyruvate and reduction of pyruvate to lactate by lactate dehydrogenase (LDH) at the expense of nicotinamide adenine dinucleotide (NADH). This parameter was taken into consideration by other authors, in order to explore *in vivo* the oxidative metabolism efficiency both in healthy individuals and in different pathologies, such as myopathies (Taivassalo, 2001).

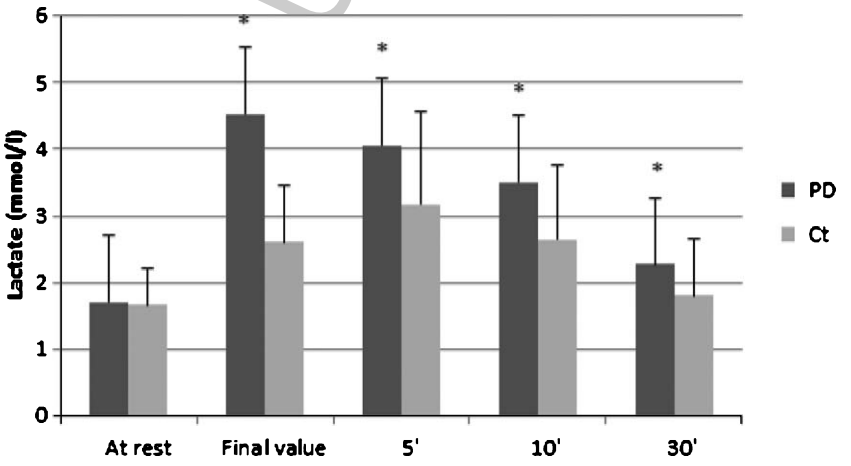

Fig. 1. Lactate clearance in PD and controls. Absolute mean values (mmol/l) at rest, at the end of the exercise and during recovery (*$p < 0.001$).

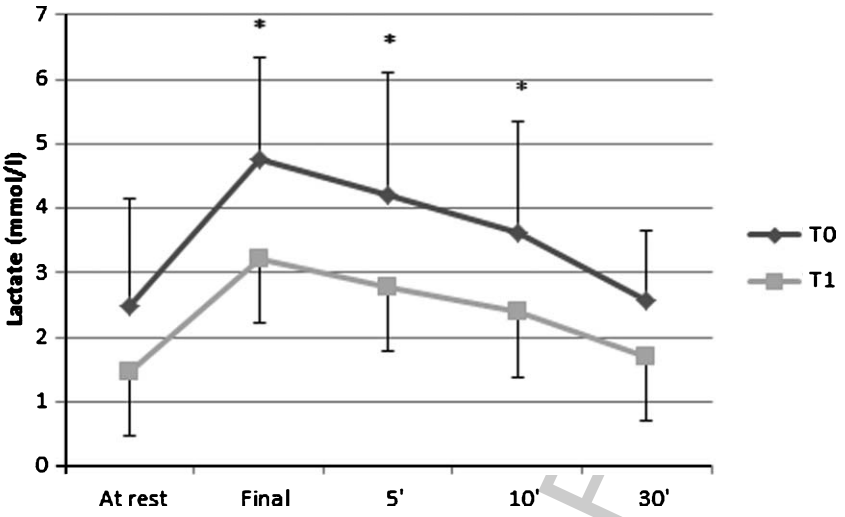

Fig. 2. Lactate clearance in RG before (T0) and after (T1) treatment. Absolute mean values (mmol/l) at rest, at the end of the exercise and during recovery ($^{*}p < 0.05$).

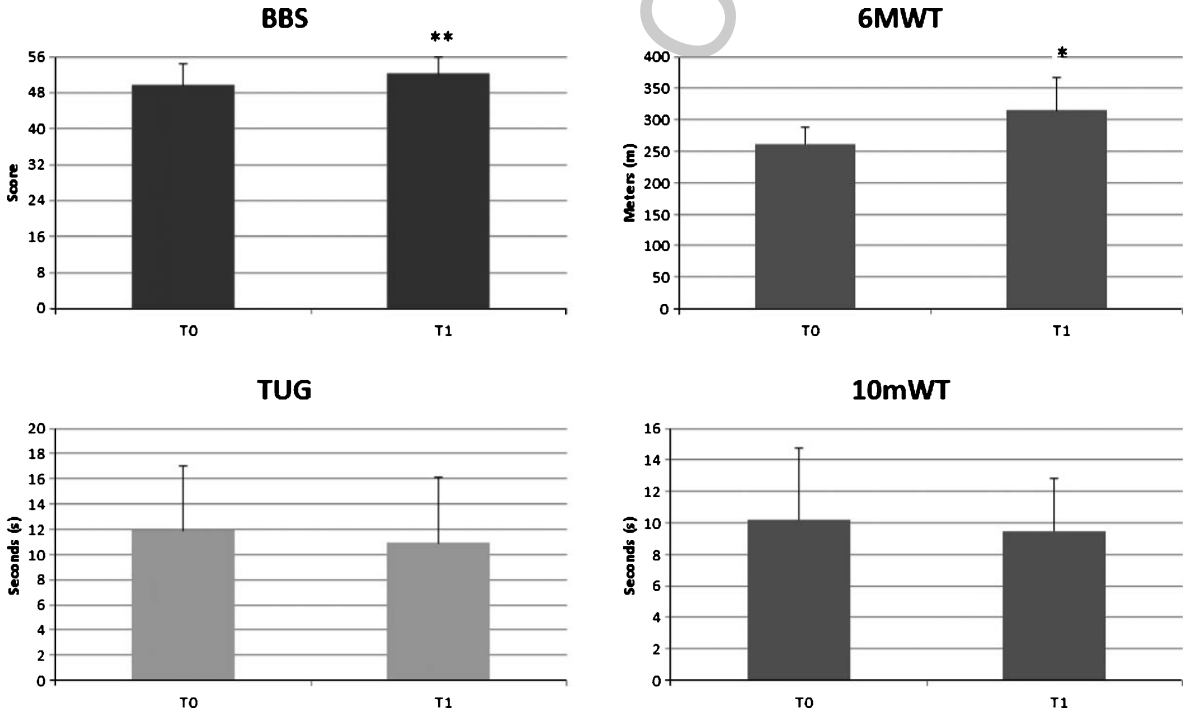

Fig. 3. RG functional scales before (T0), after (T1) the treatment ($^{*}p < 0.05$; $^{**}p < 0.001$).

An impaired muscles oxidative efficiency in Parkinson's disease has been supposed along the years. Di Monte et al. (1991) assessed resting lactic acidemia in a small cohort of PD vs healthy controls in basal conditions showing any significant difference in blood lactate levels between the two groups. Nevertheless, Nakagawa-Hattori et al. (1992) evaluated blood lactate and pyruvate concentrations at the basal resting state, during and after a minimal exercise on a bicycle ergometer in 15 PD patients and 5 age-matched controls: no significant difference was noted in blood lactate and pyruvate

levels at the basal resting state and during the aerobic test when PD patients were compared to the control group. Nevertheless, 6 of 15 patients revealed a slight exercise-induced increase in lactate levels. Interestingly, our results provide apparently discordant data from Nakagawa-Hattori's study. Probably this difference could be due to the small sample size of patients considered in the aforementioned investigation. On the contrary, our aerobic test was performed in a large cohort of PD patients and furthermore oxidative metabolism was stressed with a prolonged exercise.

Based on these data we can speculate that the metabolic consequences of skeletal muscle oxidative impairment in PD patients are adequately compensated when patients are at rest or perform gentle exercise.

However the pathogenesis of the oxidative metabolism dysfunction in Parkinson's disease is still open to controversy. Several assumptions were proposed in order to justify the reduced oxidative capacity in PD patients, such as an age-dependent dysfunction (Ghosh, 2011; Petersen, 2003; Short, 2005). Our data seem to disagree with this idea, as far as control subjects were age-matched with PD patients. Indeed, in the past, different clinical trials confirmed the frequently observed mitochondrial respiratory failure in skeletal muscle of PD patients (Blin, 1994; Winkler-Stuck, 2005).

On these basis we cannot disregard the relevance of a mitochondrial dysfunction in these patients. Different evidences supported the hypothesis that PD imply a systemic biochemical disorder involving energy metabolism both in central (Bowen, 1995; Mann, 1994) and in peripheral tissue (Penn, 1995). Blin et al. (1994) demonstrated a deficit in muscle mitochondrial complex I activity in PD patients compared to age-matched controls, highlighting this widespread alteration. Moreover the debated presence of a mild mitochondrial defect in skeletal muscle of PD patients was also confirmed by Winkler-Stuck et al. (2005). These results are consistent with the hypothesis that mitochondrial electron transport chain deficits could play an important role in PD and that the associated lactate elevation is a sign of metabolic oxidative stress. Anyway it seems important to underline the potential role played by the described reduced mobility in PD individuals (Garber & Friedman, 2003). In fact the finding of normal haematic lactate levels at baseline does not seem to indicate a primitively mitochondrial problem, because generally mitochondrial myopathies present increased levels of lactate even at rest (Bertolucci, 2014). However the evidence of mitochondrial respiratory failure and reduced oxidative enzymes in skeletal muscles induced by inactivity is well known in literature (Hauschka, 1987; Krieger, 1980). These data could partially explain our results, confirming the influence of reduced mobility and joint stiffness on skeletal muscle metabolism in PD patients.

Another factor to be taken into account in PD patients is the effect of antiparkinsonian drugs on muscle oxidative metabolism. Adams and colleagues (2008) showed that levodopa/benserazide elicits a switch from lipid to carbohydrate metabolism both in adipose than in skeletal tissue. The mechanism is still unclear but it could partly justify our data, because all of our patients were taking stable antiparkinsonian therapy.

An important result of our study, although preliminary, is the effectiveness of an aerobic intensive treatment. In fact after the four-week training the selected patients showed an improvement in functional tests, that was statistically significant for the BBS and the 6MWT. Moreover the RG presented a significant reduction of lactacidemia after aerobic test. These data show that the aerobic training on a treadmill can be an important rehabilitation tool to improve balance and endurance with a positive influence on patients' quality of life.

Although this is a pilot study on 10 patients, our study confirms the findings of other studies. Nadeau et al. (2014) described the positive effects of a 24-week treadmill training on gait performance, pointing out an improvement in walking speed, spatio-temporal gait parameters, walking endurance and health-related quality of life. Along this line, different studies evidenced its beneficial effects on cardiorespiratory capacity, endurance, as expected, but also on functional abilities (Brienesse & Emerson 2013), while balance-related activities seemed to be less modified by this intervention (Lamotte, 2015).

To our knowledge, only few studies focused their attention on muscle modification after physical exercise. Recently, Kelly et al. (2014) tested the muscle adaptability to high-intensity exercise training in PD subjects, evidencing by biopsy that persons with moderate PD present favorable changes in skeletal muscle at the cellular and subcellular levels, correlated with an improvement in motor performances.

In this study we focused our attention on skeletal muscle metabolism in PD patients and on how an aerobic and intensive rehabilitation program can act on

through a minimally invasive test. Despite the exiguity of our sample and the lack of a control group, the modifications in oxidative muscle metabolism and the improvement in motor function and physical capacity after training highlight the importance of the muscle in the evaluation and treatment of PD.

On these basis, the evaluation of muscle oxidative efficiency in PD subjects may represent a critical point to be considered in order to design specific rehabilitation protocols, thus focusing on muscle function as a target of intervention.

5. Conclusion

In conclusion these data underline the central role of skeletal muscle as a target of training interventions. Our study clearly shows that patients with PD may present muscle modifications, characterized by impaired oxidative capacity. The intensive rehabilitation program on treadmill showed a beneficial effect on endurance and balance, confirming the focal role of rehabilitation in PD patients.

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