European Journal of Human Movement, 2018: **41**, 149-174

AEROBIC AND RESISTANCE EXERCISES IN PARKINSON'S DISEASE: A NARRATIVE REVIEW

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ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by rigidity, tremor, bradykinesia, and postural instability. Although dopaminergic therapies ameliorate many of the parkinsonian symptoms, especially in the early stages of the disease, as the disease progresses, efficacy of pharmacological therapy is diminished. Therefore, treatment of these symptoms continues to be a challenge. As a result, a significant number of rehabilitation strategies have been explored in order to improve the functional capability in this population. In the last two decades an interest in the role of physical exercise in the treatment of PD has emerged. In the current review we examine two modalities of exercise that have shown beneficial effects in improving motor action, balance, and gait in patients: aerobic training and resistance training. We conclude that although there are promising results suggesting the use of both modalities of exercises for the motor improvement in PD patients, the mechanism underlying these improvements are unknown and more studies with more defined designs and outcome measures are needed to further explore the impact of these two modalities of exercise on PD.

Keywords: Parkinson's disease, aerobic exercise, resistance exercise, brain-derived neurotrophic factor

EJERCICIO AERÓBICO Y DE FUERZA EN LA ENFERMEDAD DE PARKINSON: UNA REVISIÓN NARRATIVA

RESUMEN

La enfermedad de Parkinson (EP) es un trastorno neurodegenerativo progresivo caracterizado por rigidez, temblor, bradicinesia e inestabilidad postural. Aunque las terapias dopaminérgicas mejoran muchos de los síntomas parkinsonianos, especialmente en las primeras etapas de la enfermedad, a medida que la enfermedad progresa, la eficacia de la terapia farmacológica disminuye. Por lo tanto, el tratamiento de estos síntomas sigue siendo un desafío. Como resultado, se ha explorado un número significativo de estrategias de rehabilitación para mejorar la capacidad funcional en esta población. En las últimas dos décadas he emergido un interés en el papel del ejercicio físico en el tratamiento de la EP. En la presente revisión examinamos dos modalidades de ejercicio que han demostrado efectos beneficiosos en la mejora de la acción motora, el equilibrio y la marcha de los pacientes: el entrenamiento aeróbico y el entrenamiento de fuerza. Concluimos que aunque existen resultados prometedores que sugieren el uso de ambas modalidades de ejercicios para la mejora motora en pacientes con EP, el mecanismo subyacente a estas mejoras es desconocido y se necesitan más estudios con diseños y variables bien definidas para explorar el impacto de estas dos modalidades de ejercicio sobre la EP.

Palabras clave: enfermedad de Parkinson, ejercicio aeróbico, ejercicio de fuerza, factor neurotrófico derivado del cerebro

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Submitted: 09/10/2018 *Accepted:* 09/12/2018

INTRODUCTION

Parkinson's disease (PD) is considered the second most common neurodegenerative disorder after Alzheimer's disease and it affects a 0.3% of the entire population in industrialized countries. Standardized incidence rates of reported PD are 10-20 per 100,000 people per year (Twelves, Perkins, & Counsell, 2003). The incidence varies in function of age, gender and ethnicity (Van Den Eeden, 2003). The incidence and prevalence are consistently higher in men than in women and the average age of onset in PD is established at about 60 years old, so it is principally considered to be a disease of the elderly (Wirdefeldt, Adami, Cole, Trichopoulos, & Mandel, 2011). The number of patients with PD is expected to rise considerably in the coming decades due to ageing of the population and longer life expectancy.

For two decades we have been witnessing an exceptional interest in the role of physical exercise in the treatment of PD. This interest is reflected in the exponential increase in the number of articles published on exercise and Parkinson's since 2004, which currently exceed 200 articles a year (in comparison with less than 50 papers before that year). Although no medications are proven to slow PD progression, several epidemiological studies seem to suggest a certain protective effect associated with the practice of exercise or physical activity.

Sasco, Paffenbarger, Gendre and Wing (1992) were the first to suggest a beneficial relationship between physical activity and Parkinson. They conducted a case-control study of PD and physical exercise in a cohort of 50,002 men who attended Harvard College (Cambridge, Mass) or the University of Pennsylvania (Philadelphia) between 1916 and 1950 and they followed up in adulthood for morbidity and mortality data. In adulthood, practice of moderate or heavy sports was linked to a reduced risk of developing PD, although a more precise analysis revealed that there was only a modest non-significant reduction in risk for subjects who performed a moderate amount of physical exercise, but this negative association disappeared at higher levels of physical expenditure.

The findings of Sasco et al. (1992) have been replicated in subsequent epidemiologic studies in a total sample of approximately 400,000 subjects. We must highlight the study carried out with 43,368 participants in the Swedish National March Cohort, which reported a detailed description of physical activities including leisure, occupational, household and commuting activities at study enrolment (Yang et al., 2015). During 13 years of follow-up, 286 subjects developed PD. Importantly, subjects who performed more than 6 hours per week of physical activities when enrolled had a 43% lower risk of PD.

However, these studies do not indicate that causality and other factors (such as lifestyle) could explain this relationship between physical activity and

prevalence of the disease. The 2018 report of the Movement Disorder Society on evidence-based medicine concluded there was "insufficient evidence" to support exercise as a treatment that prevents/delays disease progression (Fox et al., 2018). However, in the same report, exercise was classified as "likely efficacious". Exercise interventions included aerobic and resistance training among others. Therefore, although the beneficial effects of exercise on motor performance and general well-being in patients with PD may seem self-evident, the available body of scientific data in this domain is far from conclusive (LaHue, Comella, & Tanner, 2016).

Among the multiple interventions of physical exercise in patients with PD, in recent years, two modalities of exercise have aroused interest to alleviate functional deficits in these patients: aerobic training and resistance training. In the current review, we will critically present the most relevant studies related to aerobic and resistance training in patients with PD. We will discuss the possible mechanisms that underlie the effects reported in these studies and we will suggest new approaches and research directions towards a more robust evidence of physical exercise in PD. Previously, we will make a brief introduction to PD as well as motor symptoms and fitness profile of patients with PD.

A Brief Introduction To Parkinson's Disease

This section describes PD briefly, its motor symptoms as well as the physical fitness profile of patients suffering from this disease. This will provide the reader with a better understanding of the later sections in which the application of aerobic training and resistance training in this pathology are addressed.

Parkinson's disease

PD is a chronic degenerative process caused by the loss of dopaminergic neurons in the substance *nigra*. The first description of the disease was carried out by James Parkinson in 1817, in "*An Essay on the Shaking Palsy*" (Parkinson, 1817).

The aetiology is unknown, but it is believed that various genetic, environmental, as well as aging factors would be involved (Calne, 1989). The effect of all these factors is twofold, the loss of some selective neuronal populations, and the accumulation of abnormal proteins in the neuronal cells and neurites, forming the Lewy bodies, and the Lewy neurites respectively (Forno, 1996). Among the proteins that accumulate we can find alpha-synuclein, which is a major component of the Lewy bodies (Spillantini et al., 1997).

The diagnosis of PD is clinical and it is based on the presence of various motor symptoms such as resting tremor, rigidity, bradykinesia, postural

alterations and freezing phenomena (Daniel & Lees, 1993). However, various non-motor symptoms (NMS) such as pain, depression, anxiety, fatigue, or cognitive alterations among other are also very frequently present in patients with PD, some appearing even before the development of motor symptoms (Stacy, 2009). In addition, these NMS are often very disabling, negatively conditioning the patient's quality of life (QoL) (Martinez-Martin, Rodriguez-Blazquez, Kurtis, Chaudhuri, & NMSS Validation Group, 2011). The differential diagnosis of PD will be established fundamentally with other causes or diseases that cause parkinsonism, and occasionally, some structural and/or functional neuroimaging tests may be useful.

There is no curative treatment at present for PD, although there are several drugs that improve the patient's symptoms both in the early stages of the disease and in those patients in a more advanced stage of the disease. Likewise, research is being carried out on possible therapies that produce an effector that modifies the course of the disease, in order to try to administer these therapies as early as possible with the intention of slowing down or delaying neuronal loss and the secondary symptoms caused by this loss (Schapira & Olanow, 2004). Among the non-pharmacological therapies, surgery is currently a useful treatment option in some patients with advanced PD. On the other hand, another type of non-pharmacological therapies such as physiotherapy, physical exercise, speech therapy or cognitive stimulation are equally fundamental, in such a way that the most appropriate management of the disease is probably through a multidisciplinary approach (A'Campo, Wekking, Spliethoff-Kamminga, Stijnen, & Roos, 2012).

Motor features

Motor features mainly comprise the four cardinal signs of PD (resting tremor, bradykinesia, rigidity and gait disturbances/postural instability), plus a widespread number of other motor abnormalities, called secondary motor symptoms, such as dysarthria, hypophonia, dysphagia or sialorrhoea, between others. In addition, flexed posture, gait disorders and freezing (motor blocks) have been included among classic features of PD (Shahed & Jankovic, 2007).

a) Bradykinesia

From a purist perspective, bradykinesia refers to slowness of movement, akinesia refers to poverty of spontaneous movement and the term hypokinesia means smaller amplitude of movement. However, in the literature the term bradykinesia tends to group all these motor features within the same construct. Bradykinesia encompasses difficulties with planning, initiating and executing movement with performing sequential and simultaneous tasks (Berardelli et al., 2001). Bradykinesia is the motor sign that appears to correlate best with

degree of dopamine loss, due to the potential correlations with disease severity and response to treatment (Rodriguez-Oroz et al., 2009).

b) Classic tremor

Classic tremor is the most common and easily recognized symptom of PD. It is characterized by a low frequency rhythmic oscillation within a bandwidth of 4 or 6 Hz that occurs at rest (Shahed & Jankovic, 2007). Hand-tremors are described as a supination-pronation tremor ('pill-rolling'), but rest tremor in PD can also involve the lips, chin, jaw and legs. This type of tremor is pathophysiologically separated from the bradykinesia and rigidity, and the response of tremor to dopaminergic agents is less than in bradykinesia (Jellinger, 2012). It is now understood that classical tremor in PD is mediated by an abnormal oscillatory activity in an extensive motor network that involves the basal ganglia (BG), cerebellum, thalamus, and motor cortex (Hallett, 2014).

c) Rigidity

Rigidity is essentially an increase in resistance to passive movement. It was thought for years that rigidity is related to an enhancement of stretch reflex excitability (Cantello et al., 1991). It is known that rigid patients present an enhanced cortical excitability, coupled with the dopamine depletion and an increased BG output (Rodriguez-Oroz et al., 2009). However, how the BG changes associated with dopamine depletion modify the excitability of stretch reflex mechanisms has not been clarified.

d) Postural stability and gait disorders

Parkinson's patients have difficulties with balance in both sitting and standing and also to walk. When PD patients are standing, they adopt a flexed posture, with the body inclined slightly forward, with flexed knees and the arms in front of the body (Hanakawa et al 1999). PD gait is mainly characterized by the inability to generate an appropriate stride length (Morris, Iansek, Matyas, & Summers, 1996). Associated disturbances include a reduced gait speed, reduced arm swing (Wood, Bilclough, Bowron, & Walker, 2002), increased stride-to-stride variability, increased double limb support time, gait instability, stooping, difficulty turning, and forward-flexed posture (Ebersbach, Moreau, Gandor, Defebvre, & Devos, 2013; Huang et al., 2012). In advanced stages, more complex gait disturbances may often appear, including motor blocks, festination and disequilibrium. These entire gait features cause significant disability resulting in falls, immobility, and loss of independence (Bloem et al., 2016). Falls are considered one of the most serious complications of motion in PD, with an incidence of 70% during a 1-year follow-up, and recurrent falls occurred in approximately in 50% of the cases (Bloem,

Hausdorff, Visser, & Giladi, 2004; Okuma, 2014). Disturbances of gait are one of the classical features in PD, which appear in almost all patients and often lead to loss of QoL (Ebersbach et al. 2013). Gait difficulties become progressively more levodopa-resistant, and thus are considered the hallmarks of the advanced stages in PD. Therefore the main focus of physical rehabilitation is to improve the gait deficits in PD.

Physical inactivity in Parkinson's disease

The amount of physical activity is highly related with a wide list of health benefits and the lack of such activity is a major cause of chronic diseases. This is more dramatic when we refer to patients with PD, since the decrease of physical activity in these patients can worsen the symptoms associated to the disease.

The knowledge of the physical behaviour profile in PD patients and the reasons to explain their physical activity are of importance since these will allow us to develop more rational strategies and programs to engage these patients in physical activities. However, the physical behaviour profile in PD is far from being known. Although, it has been suggested that Parkinson's patients show lower levels of physical activity in comparison with healthy age-matched subjects, the number of studies describing the physical activity in PD patients is limited. A retrospective study (Fertl, Doppelbauer, & Auff, 1993) exploring the engagement of PD patients and controls in physical activities and sports reported that until the occurrence of the first symptoms, PD patients did not differ from controls. However, during the course of the disease, a striking reduction in physical activity (but not a complete abandonment of sports) was found.

Chastin et al. (2010) analysed the sedentary behaviour in 17 PD patients and 17 age-matched controls during a period of 7 days using a wearable accelerometer to record bouts of sitting, lying, upright stance and walking. Their results showed that the total inactivity time was similar between groups although the bouts of inactivity tend to last longer than those of controls. The author suggests that with this behaviour patients try to conserve energy to maximize function, which is in agreement with other studies that showed a more spread out daily physical activity in PD patients than in healthy subjects (Busse, Pearson, Van Deursen, & Wiles, 2004; Rochester et al., 2006; van Hilten et al., 1993). Other studies using objective measures of physical activity did not find differences between PD patients and controls (Rochester et al., 2006; van Hilten et al., 1993). However, Busse et al. (2004) reported a significant lower number of steps during a 7 day period in PD patients in comparison with healthy subjects. In addition, the number of steps taken per day, as well as the average steps per minute in the most active hour was lower in individuals with

more severe PD, as defined by Hoehn & Yahr scale (Skidmore et al., 2008). Thus, although activity monitoring using accelerometry provides an objective method of quantifying activity in an ecological context (Rochester et al., 2006), the different variables recorded in each study (e.g. number of steps, number of walking periods, duration of walking periods) can account for these discrepancies between the mentioned studies. Moreover, several other physical activities can be more difficult to quantify using these activity monitors (van Nimwegen et al., 2011).

An alternative and complementary approach for the study of physical activity is the use of validated physical activity questionnaires. Using the LASA (Longitudinal Aging Study Amsterdam) Physical Activity Questionnaire (LAPAQ), van Nimwegen et al. (2011) compared the physical activity between 699 PD patients and 1959 healthy controls in the largest study of this kind conducted in PD patients so far. The LAPAQ (Stel et al., 2004) is a relative new physical activity questionnaire for older persons based on both the Modified Baecke Questionnaire for Older Adults (Voorrips, Ravelli, Dongelmans, Deurenberg, & Van Staveren, 1991) and the Zutphen Physical Activity Questionnaire (Caspersen, Powell, & Christenson, 1985). The LAPAQ covers frequency and duration of different activities during the previous 2 weeks such as walking outside, cycling, gardening, light and heavy household activities, and a maximum of two sport activities (Stel et al., 2004). The results of this study showed that PD patients were physically less active with a reduction of 29% compared to controls. In addition, the loss of time spent on activities was most obvious in patients with greater disease severity (van Nimwegen et al., 2011).

Most of the above-mentioned studies support the hypothesis of a significant reduction of physical activity in PD patients. Several factors have been explored in order to explain this reduction. Fatigue, motor disabilities and disease severity have been the logical factors.

Fatigue has been defined as an intense feeling of tiredness, lack of energy and a feeling of being exhausted. Fatigue is a very common and severe problem in PD and, with the exception of its epidemiology, the nature and aetiology of this symptom is unknown (Friedman & Abrantes, 2012). Fatigue affects approximately two thirds of patients and it is reported as the most severe symptom in 15-33% of patients, and as one of the three worst symptoms in 50% of patients. Although fatigue is associated with depression and sleep disorders, it is also common in patients who do not suffer from these conditions. Neither does it seem to be directly associated with a greater severity of the disease.

The association found between fatigue and dynamic activity suggests that patients who experience higher levels of fatigue are less physically active. However, the total explained variance of dynamic activity by fatigue alone was small, suggesting that fatigue is only a minor factor in the complex of

behavioural aspects that affect the amount of physical activity in patients with PD (Elbers et al., 2009). While disease severity, gait and disability in daily living predicted part of the inactivity, a portion of the variance remained unexplained, suggesting that additional determinants may also affect daily physical activities in PD (van Nimwegen et al., 2011).

Interestingly, when PD patients were classified as "exercisers" or "nonexercisers" based on their responses to the Stages of Readiness to Exercise Questionnaire, self-efficacy rather than disability was most strongly associated with regular exercise. Patients with higher exercise self-efficacy were more likely to engage in exercise compared with those with low exercise self-efficacy, regardless of the disease severity (Ellis et al., 2011).

Cardiovascular system in Parkinson's disease

Several studies have examined aerobic capacity in subjects with PD. Maximal or peak aerobic capacity (VO2peak) is evaluated during a maximal effort graded exercise test usually conducted on a cycling ergometer or a treadmill (Katzel et al., 2011; Protas, Stanley, Jankovic, & MacNeill, 1996). Measurement of VO2peak is reliable and repeatable in subjects with mild to moderate PD, thereby validating the use of this parameter for assessing the effects of exercise interventions on cardiorespiratory fitness (Katzel et al., 2011). Overall, the results for VO2peak in PD have been mixed. Some studies reported VO2peak values that were generally 20% lower in PD than in age-matched controls (Katzel et al., 2011), while others find not differences between those groups (Canning, Alison, Allen, & Groeller, 1997; Saltin & Landin, 1975). It is possible that substantial heterogeneity in the VO2peak and walking speeds in PD subjects account for this discrepancy across studies. Nevertheless, it seems that there is not correlation between disease severity and VO2peak, at least for individuals with mild to moderate PD (Canning et al., 1997; Christiansen, Schenkman, McFann, Wolfe, & Kohrt, 2009).

Interestingly, one study indicated that patients with PD were unable to exercise as long as the age-matched controls before reaching VO2max, even though there were no significant differences in VO2max between both groups (Stanley, Protas, & Jankovic, 1999). This could suggest that individuals with PD may be less efficient during exercise (Stanley et al., 1999). This is in line with the findings that indicate that walking economy, defined as the rate of oxygen consumed per distance during walking, is less efficient in PD patients compared with healthy subjects (Christiansen et al., 2009). Alterations in walking performance, such as increased stride length variability and reduced gait speed, and changes related to PD motor symptoms of tremor, rigidity, hypokinesia, and postural instability could increase the total energy cost in this population.

Cardiovascular autonomic dysfunction is a non-motor feature in PD, affecting 40% of Parkinson's patients in advanced stages, but it can also be present in patients in earlier stages (Velseboer, de Haan, Wieling, Goldstein, & de Bie, 2011). Also known as orthostatic hypotension or autonomic failure, this autonomic dysfunction can lead to sudden reductions in blood pressure during daily activities significantly affecting the QoL. Few studies have explored if blood pressure increases appropriately during exercise or if exercise accentuates orthostatic hypotension in PD patients with autonomic dysfunction, which is of relevance for safety reasons (Low et al., 2014; Mavrommati et al., 2017). The current available literature indicates that, in PD patients with autonomic dysfunction, exercise-induced hypotension can occur with the magnitude of the exercise response being related to the severity of the autonomic dysfunction (Low, Vichayanrat, Iodice, & Mathias, 2014). In addition, exercise does not appear to worsen orthostatic hypotension in this sample of Parkinson's patients (Low et al., 2014). However, in this study the exercise test protocol involved supine cycling and thus, it remains to be explored whether those results can be replicated in other kind of exercises. In a randomized controlled trial (Mavrommati et al., 2017), PD subjects without autonomic dysfunction participated in an exercise programme of 48 sessions over a 24-week period (2 sessions per week). Each session, which lasted 60 min, consisted of the following: 30 min of aerobic training (plus an initial 10 min warm-up) [55%–85% age-predicted HRmax (220 - age)] followed by 30 min of resistance training (resistance was selected so that 10 repetitions could be performed). The results indicate that i) PD patients present lower elevations in heart rate and blood pressure during exercise; ii) they improved movement in response to exercise; iii) there was a trend to reduce HR in response to training, suggesting an improved efficiency of the cardiovascular system; and iv) there was a positive effect on reducing blood pressure after 3 and after 6 months. The authors suggest that PD patients have a reduced aerobic response during exercise and rely on anaerobic metabolism for their capacity gains. In addition, cardiovascular changes are normal whereas respiratory changes are not, indicating cardiovascular adaption to exercise occurs in the absence of effects on metabolic systems.

Muscle strength in Parkinson's disease

Several reviews have addressed the so-called muscle weakness (Cano-De-La-Cuerda, Pérez-De-Heredia, Miangolarra-Page, Muñoz-Hellín, & Fernández-De-Las-Peñas, 2009; Falvo, Schilling, & Earhart, 2008) and detailed information of the studies included in those reviews is available for the reader. The ability to exert force in patients with PD has not been sufficiently explored although there is agreement that certain manifestations of strength are impaired in this

disease. In fact, some authors suggest that a loss of muscle strength could be a primary symptom inherent to the disease (Kakinuma, Nogaki, Pramanik, & Morimatsu, 1998), although more studies are needed to confirm this assertion.

Most of the studies comparing the force production capabilities between patients with PD and healthy subjects agree in showing a reduction in the rate of force development in subjects with PD (Pääsuke et al., 2004; Pääsuke, Mõttus, Ereline, Gapeyeva, & Taba, 2002). Persons with mild-to-moderate PD display disparities in the rate of force development, even without deficits in maximal force (Hammond, Pfeiffer, LeDoux, & Schilling, 2017).

Unlike the rate of force development (RFD), the effect of the PD on the maximum voluntary contraction (MVC) is not clear (Falvo et al., 2008). There are studies that indicate a lower MVC in these patients (Inkster, Eng, MacIntyre, & Stoessl, 2003; Pääsuke et al., 2004, 2002) while other studies show no differences in comparison with healthy age-matched subjects (Hammond et al., 2017). Recently, it has been reported that PD patients not only show lower maximal force production but also show higher force variability in the hip flexors, ankle plantar flexors and dorsiflexors (muscles that are critical for effective ambulation) in comparison with healthy age-matched subjects (Skinner, Christou, & Hass, 2019).

The inability to produce force at a rate comparable to controls has been suggested to be a downstream effect of central dysfunction of the motor pathway in PD (Hammond et al., 2017). This could also be true for the MVC. Using the interpolated twitch test, voluntary activation level and twitch force were quantified on the quadriceps muscle by exercise-induced changes in MVC (Huang et al., 2017). The results of this study showed that voluntary activation level was lower in the PD group than in the healthy control group, suggesting that weakness originated from central fatigue in the PD group. This is in line with a previous study showing that Parkinson fallers are affected by strength impairments arising from the central nervous system and not from the peripheral muscle contractile capacity, even at early stages of the disease and young age (Moreno Catalá, Woitalla, & Arampatzis, 2013).

It is important is to emphasize the role that both the maximum strength and RFD can play in situations of imbalance, fundamentally at the level of the lower extremities. High RFD is crucial in order to achieve high levels of force and speed during the movement, since the maximal RFD determines the force that can be generated in the early phase of muscle contraction (Aagaard, Simonsen, Andersen, Magnusson, & Dyhre-Poulsen, 2002) while sufficient force would be crucial to modify the center of mass over the base of support. Therefore, optimal maintenance of the maximum force levels and RFD is even more relevant in Parkinson's patients, who have a high incidence of falls.

Whether resistance training is the ideal intervention to achieve those goals is discussed in a latter section.

AEROBIC TRAINING IN PARKINSON'S DISEASE

Aerobic exercise (also known as cardio) is physical exercise of low to high intensity that depends primarily on the aerobic energy-generation process. Under this premise any type of exercise that is in this range of intensity could be considered aerobic exercise. For example, in a review (Shu et al., 2014) on the effect of aerobic exercise in PD it was concluded that aerobic exercise showed immediate beneficial effects in improving motor action, balance, and gait in patients with PD. However, this review included activities such as dancing, tai chi or gait training with rhythmic support, activities that may involve other potentially therapeutic mechanisms in this pathology. This is of relevance to objectively examine the impact of aerobic exercise and isolate it from the effect that other potential players may have on the motor treatment of this pathology. In fact, the authors of the revision recognize that it is difficult to extract accurate information regarding the contribution of aerobic exercises in patients with PD because multiple exercise therapies were often involved (Shu et al., 2014).

One of the most relevant studies on aerobic exercise in PD has been a randomized clinical study of 3 types of exercise (Shulman et al., 2013) performed in a total of 77 patients distributed in a group of lower-intensity treadmill training (reaching up to 50 min at 40% to 50% of heart rate reserve), higher-intensity treadmill training (up to 30 min at 70% to 80% of heart rate reserve) and stretching and resistance training. For the treadmill training groups, mechanical work was equated. After 36 sessions of training distributed in 3 weekly sessions for 3 months, it was found that each type of exercise resulted in different types of benefits. Interestingly, the lower-intensity treadmill exercise was the single most effective training exercise for gait and fitness. This study leads to interesting questions such as the specificity of the exercise, or how different modalities of exercise can lead to different kind of improvements. In addition, it seems that to improve the gait in PD subjects, high intensities of training are not necessarily needed. We should emphasize that the training of the gait was conducted walking on a treadmill, so it is questionable that these findings are reproducible by walking on the ground. In fact, in a study from our lab, 22 PD patients were randomly assigned to a treadmill or overground gait training group (Bello et al., 2013). After 15 training sessions all subjects improved their walking speed. However, the treadmill training program, but not the overground program, led to an improvement in the stride length at the preferred and maximal walking speed. This study provides evidence of a specific therapeutic effect of treadmill

training on Parkinsonian gait and questions that the effects reported in the mentioned study are the result of an aerobic training in itself.

The rationale of using aerobic exercise in patients with PD would be their possible contribution to the neuroplasticity of the nervous system. By neuroplasticity we can understand the brain's ability to form and modify synaptic connections. There are numerous studies that have addressed the effect of aerobic exercise on neuroplasticity, although most of these have been carried out with animals [see review in Ahlskog (2018)]. Those studies have shown an improvement in the performance of tasks related to spatial memory and the recognition of objects after an aerobic training (i.e. 1 hour of treadmill exercise for 5 months) (Rhyu et al., 2010). Changes in hippocampal neurogenesis (increased neurons) in rats after long-term aerobic training have been documented, as well as an increase in brain factors mediating the neuroplasticity process (Gibbons et al., 2014).

Perhaps the most studied factor has been the brain-derived neurotrophic factor (BDNF), with numerous studies that have linked the practice of physical exercise with an increase in BDNF levels [see review in De Assis, Gasanov, de Sousa, Kozacz, & Murawska-Cialowicz (2018)]. This is of relevance since it is well established that in PD patients there is a depletion of BDNF in blood serum, which typically helps support existing neurons and encourages the growth of synapses (Scalzo, Kümmer, Bretas, Cardoso, & Teixeira, 2010). There have been attempts to restore this depletion via directly infusing BDNF although they have been unsuccessful as BDNF is not able to cross the blood–brain barrier (Nagahara & Tuszynski, 2011). Therefore, a potential alternative way to restore BDNF would be through exercise, which has been shown to increase BDNF levels in the blood serum (Da Silva, Domingues, De Carvalho, Allodi, & Correa, 2016; Gerecke, Jiao, Pagala, & Smeyne, 2012; Tang, Chu, Hui, Helmeste, & Law, 2008). However, several studies have shown an increase in BDNF serum levels in PD subjects after exercise (Angelucci et al., 2016; Frazzitta et al., 2014) but other studies indicate that although exercise can improve PD patient's motor deficits, it does not slow down or stop the progressive aspect of PD [see review in Bega, Gonzalez-Latapi, Zadikoff, & Simuni (2014)]. Therefore, while exercise would be beneficial to PD patients for controlling the motor symptoms, it does not necessarily facilitate restoration of the nigrostriatal pathway (Churchill et al., 2017). This interesting dichotomy suggests that exercise is facilitating motor recovery through either other neurotransmitter circuits or non-neuronal mechanisms and this could be allowing the brain to compensate for the dopamine depletion (Petzinger et al., 2015).

RESISTANCE TRAINING

The effectiveness of resistance training in improving motor symptoms in patients with PD has been investigated in several systematic reviews (Falvo et al., 2008; Ramazzina, Bernazzoli, & Costantino, 2017; Roeder, Costello, Smith, Stewart, & Kerr, 2015). Resistance training performed against external resistance is well tolerated and appears to be a suitable physical activity to improve both physical parameters and QoL parameters of PD subjects. However, these findings should be interpreted with caution due to the relatively high risk of bias of most studies (Roeder et al., 2015). In addition, only a few selected studies assessed the improvement of muscle strength, making it difficult to establish a correlation between resistance training and the improvements made (Ramazzina et al., 2017; Shu et al., 2014). Moreover, high variation was evident across studies in the training durations, frequencies, modes, volumes, intensities and progressions. This makes it difficult to identify characteristics of effective resistance training interventions and to provide evidence-based guidelines at the present time (Roeder et al., 2015). Details of training doses in those studies can be found in Roeder et al. (2015).

The longest intervention is reported in the study of Corcos et al. (2013), in which they assessed the effects of 2 years of progressive resistance training (PRET) in mild-to-moderate PD patients. PRET was significantly more efficacious at improving movement velocity and isometric muscle strength than a multimodal exercise regime that used stretching, balance, breathing, and non-progressive resistance exercises. Further analysis from the same cohort published in later publications indicated that PRET partially restores the triphasic electromyographic pattern and improves movement velocity (David et al., 2016). Additionally, the improvement in the triphasic electromyographic pattern and muscle strength was significantly associated with improvement in peak velocity. The authors suggest that that resistance exercise can drive neurophysiological changes that underlie the improvement in movement velocity in PD (David et al., 2016). Interesting, strength gains did not appear to transfer to gait, even though both PRET and the multimodal exercise program improved off-medication fast gait velocity and improved cadence in all conditions evaluated (off-/on-medication, comfortable/fast speed) (Rafferty et al., 2017).

Recently, new modalities of resistance training such as instability resistance training (Silva-Batista et al., 2017) or high-speed resistance training (Ni & Signorile, 2017) have been used in patients with PD. The former modality seems to be more effective than traditional resistance training in improving neuromuscular parameters such as root mean square and mean spike frequency of electromyographic signal, peak torque and rate of torque

development of the knee extensors and plantarflexors during maximum ballistic voluntary isometric contractions (Silva-Batista et al., 2017).

Different reasons have been pointed out that justify introducing resistance training in patients with PD. In PD, motor cortices are not fully activated due to the secondary abnormal drive from the BG to the thalamus (Albin, Young, & Penney, 1989). This impaired cortical activation can lead to an inability to sufficiently activate motoneuron pools, thereby affecting recruitment and discharge rate (Falvo et al., 2008). Therefore, resistance training may be of therapeutic value to individuals with PD to enhance neural drive to the agonist as well as decrease coactivation, both contributing to improved strength and movement control (Falvo et al., 2008). However, it is questionable that resistance training may act on the same cortical mechanism that is impaired in PD, especially when it has been reported that resistance training changes the functional properties of spinal cord circuitry in humans, but does not substantially affect the organisation of the motor cortex (Carroll, Riek, & Carson, 2002). Another argument to support the use of resistance training in PD is the possible relationship of strength levels and performance in daily activities such as walking or getting up from a chair. Although numerous studies have shown that increased strength translates into gait improvements in healthy elderly subjects, this has not been shown conclusively in patients with PD. Therefore, the rationale of the use of resistance training in EP is still under debate.

NEW APPROACHES AND RESEARCH DIRECTIONS

The study of the effects of physical exercise, not only for the resistance and aerobic training, in PD presents numerous challenges that make it difficult to know the impact of exercise on the prevention / treatment of the disease and also the mechanisms underlying these possible effects.

Randomized controlled trials

The realization of clinical randomized controlled trials to explore whether exercise slows down the neurological deterioration that occurs in PD is very complex due to several factors such as the relatively slow deterioration of the patients, which implies excessively long periods of intervention and monitoring (Ahlskog, 2018). This makes it difficult for measure outcomes not to be contaminated by changes in medication, changes that are relatively frequent in many patients. In addition, long periods of intervention also demand adherence to exercise by participating patients, which in itself can be a challenge (Ahlskog, 2018).

Specific vs generalized benefits

Exercise interventions have been effective in improving several gait parameters and, as a result, the QoL of PD patients. However, these improvements may have been the result of a general beneficial effect of exercise rather than a specific improvement of the motor symptomology in this pathology. Without undermining the importance of these improvements for the functionality of these patients, it is necessary to know which type of exercise has specific effects on the symptoms of this disease in order to develop more effective interventions. For instance, we have previously mentioned that gait pattern in PD subjects is characterized by a specific deficit of the internal regulation of the stride length, while the cadence control is intact (Morris, Iansek, Matyas, & Summers, 1994). In other words, for an equal value in speed or cadence the stride length is always lower in PD subjects. Therefore, the regulation of stride length must represent one of the main goals in rehabilitation interventions in PD subjects. However, most of the studies that evaluate the efficacy of rehabilitation and exercise interventions use, independently, changes in stride length, cadence or speed as the main outcome measures (Kwakkel, de Goede, & van Wegen, 2007). Thus, although, increases in gait speed may reflect a functional improvement, these do not necessarily reflect an amelioration of PD symptomatology. In addition, due to the age-associated progressive loss of physical function, it is difficult to elucidate which rehabilitation approach has a specific impact in PD rather than a generalized benefit from exercise (Ambrus, Sanchez, & Fernandez-Del-Olmo, 2018). We propose that the study of the stride length-cadence may help to establish the specific therapeutic effect of an intervention, in order to optimize the rehabilitation strategy (Ambrus et al., 2018). Therefore, the selection of appropriate outcome measures is another relevant issue in the study of the effects of physical exercise in PD.

Outcome measures

The heterogeneity of motor symptoms in PD and their effects on the functional capacity of the patients with PD leads to a large number of variables and measurement protocols that make the interpretation of results very complex. To establish the outcome measures in a study must depend on whether the objective is simply to capture disease burden, or to use it as a surrogate marker of pathology (Lord, Galna, & Rochester, 2013). This highlights the need for interventional studies to indicate a priori the expected results for the primary and secondary outcome measures.

Several previously cited reviews in the current manuscript indicate that only a few selected studies assessed the improvement of muscle strength (Ramazzina et al., 2017) or cardiovascular measures in response to resistance

training and aerobic training programs, respectively. Despite the encouraging results of those studies, it is difficult to establish a correlation between resistance and aerobic training and the improvements made and to clarify the nature of those improvements.

Cued training

Martin in 1967 was the first to prove how a series of coloured lines arranged on the floor perpendicular to the direction of walking improved the ambulatory characteristics of PD patients. The first therapeutic application was conducted by Thaut et al. (1996) who subjected patients with PD to a training program consisting of walking in synchrony with a rhythmic auditory stimulus. The training lasted for 3 weeks, after which there was an improvement in the speed, amplitude and cadence of the gait and muscle activation pattern. In addition, this improvement was significantly greater in comparison to a group of patients who performed the same training, but without rhythmic auditory stimulation. Similar results have been obtained in numerous studies that have indicated an immediate, short- and long-term positive effect in the gait of PD patients after interventions that used visual signals, rhythmic auditory signals or proprioceptive cues (by walking on a treadmill). It has been suggested that external sensory cues can provide the necessary trigger in PD to switch from one movement component to the next, bypassing defective internal pallidocortical projections, possibly via the lateral premotor cortex, which controls externally guided movements (Alexander, DeLong, & Strick, 1986; Penney & Young, 1983). It is important to note that most of the studies that assess the impact of aerobic exercise on PD have been performed using a treadmill. This makes us question whether the effects on the progress reported in these studies are due to aerobic work and not to the unique effects of the treadmill and thus, other intervention strategies are necessary to evaluate the effect of aerobic training.

CONCLUSIONS

Physical exercise in the form of aerobic training or resistance training seems to be effective in the motor treatment and in improving the functional capacity of patients with PD, although the mechanisms underlying these improvements are still unknown. More studies are needed with more defined designs and outcome measures to further explore the impact of these two modalities of exercise on PD.

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