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LITERATURE REVIEW

The Beneficial Role of Intensive Exercise on Parkinson Disease Progression

ABSTRACT

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In the last decade, a considerable number of articles has shown that exercise is effective in improving motor performance in Parkinson disease. In particular, recent studies have focused on the efficacy of intensive exercise in achieving optimal results in the rehabilitation of patients with Parkinson disease. The effects of intensive exercise in promoting cell proliferation and neuronal differentiation in animal models are reported in a large cohort of studies, and these neuroplastic effects are probably related to increased expression of a variety of neurotrophic factors. The authors outline the relation between intensive exercises and neuroplastic activity on animal models of Parkinson disease and discuss the clinical results of different intensive strategies on motor performance and disease progression in patients with Parkinson disease.

Key Words: Parkinson Disease, Intensive Rehabilitation, Neuroplasticity

Parkinson disease (PD) is a neurodegenerative and progressive disease that represents a heavy burden in western countries: the incidence among individuals 65 yrs or older is 160 per 100,000 person-years, with a prevalence of 950 patients per 100,000 persons.[1]

A variety of drugs has been developed and is currently used to control the disability related to the disease: levodopa, dopamine (DA) agonists, monoamine oxidase B inhibitors, and catechol-O-methyltransferase inhibitors.

All these drugs act on the dopaminergic nigrostriatal system, although it has been established that other pathways are involved in PD: cholinergic, serotoninergic, and noradrenergic circuits are affected as well.[2,3]

Patients with PD have a sedentary lifestyle, which worsens balance and gait disturbances, the most important signs related to nondopaminergic pathways.[4] In addition, some nonmotor symptoms such as depression, fatigue, apathy, and constipation play an important role in reducing physical activity in these patients. Thus, a vicious circle sets up with deterioration of physical fitness, which, in turn, leads to a more rapid disease progression[5] (Fig. 1).

In the last decade, a considerable number of articles have shown that exercise is effective in improving gait, balance, freezing, and motor performance in PD.

In particular, recent studies have focused on the association between a diminished PD risk and moderate to vigorous activities in preceding years as well as on the efficacy of intensive exercise in achieving optimal results in the rehabilitation of patients with PD.[6–8]

Here, the authors briefly describe the rationale of this therapeutic approach and show the efficacy of intensive rehabilitation treatment on patients with PD.

EXPERIMENTAL DATA

The neuroprotective effects of intensive exercise on animal models of PD are reported in a large cohort of studies, although these results have not been confirmed by all researchers[9–11] (Tables 1–2). A relation between the distance run and cell proliferation has been found in mice using a wheel running device,[12,13] and enhancement of hippocampal neurogenesis by running is a well demonstrated phenomenon.[14–16] Exercise not only increases the number of new neurons but also influences the morphology of individual newly born cells, suggesting that the benefits of exercise are qualitative as well as quantitative.[17,18]

Moreover, long-term potentiation, an electrophysiologic basis for learning and memory, is influenced by using running wheels or a treadmill.[19–21]

Besides promoting neurogenesis, intensive exercise is able to counteract neurodegeneration. In animals with cerebral lesions produced by 6-hydroxydopamine or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), the intensive use of a

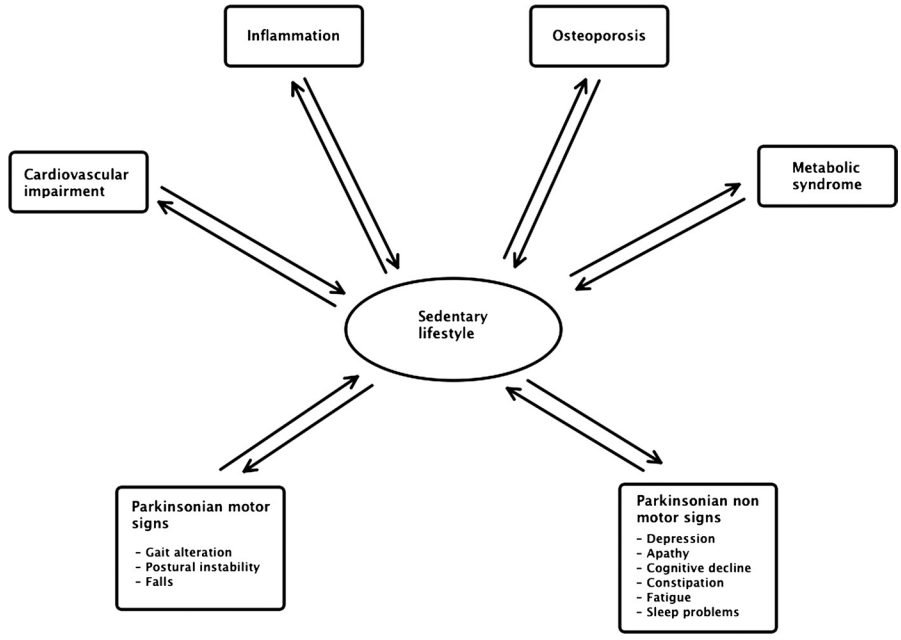

FIGURE 1 *Lack of exercise in Parkinsonian patients sets up various adverse reciprocal multiplicative effects, both at the central and peripheral levels. These effects, in turn, worsen the motor and nonmotor PD symptoms, and a vicious circle ensues (modified from Speelman et al., 2011).*

TABLE 1 Effects of exercise on plasticity in an animal model of PD

Enhancement in hippocampal neurogenesis[9–11]
Influence on the morphology of individual newly born cells[12,13]
Modulation of long-term potentiation[14–16]
Preservation of both tyrosine hydroxylase–positive fibers in the striatum and the substantia nigra as well as of vesicular monoamine transporter and DA transporter levels[17–22]
Increase in DA availability, especially within the dorsolateral striatum[23]
Increase in D_2 DA receptors in the striatum[24]
Reduction in levels of presynaptic glutamate inside the striatal terminals[25]
Internalization of the AMPA postsynaptic receptor[26–28]
Increase in GDNF levels inducing sprouting from dopaminergic neurons into the nigrostriatal system and increasing levels of DA, noradrenaline, and serotonin[39]
Increase in BDNF levels increase DA concentration and tyrosine hydroxylase activity in the striatum[22,40]

AMPA is defined as alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid.

treadmill or running wheels led to improvement in motor performance as compared with animals that did not use these devices; indeed, the latter actually experienced worsening of their parkinsonian symptoms. Both in the unilateral and bilateral models of PD, intensive treadmill exercise produced improvement in motor symptoms, which was related to a reduction in neurochemical deficit: preservation of both tyrosine hydroxylase–positive fibers in the striatum and the substantia nigra as well as of vesicular monoamine transporter and DA transporter levels.[22–27] Increased DA availability, especially within the dorsolateral striatum, has been found in an MPTP mice model after intensive exercise with a motorized treadmill.[28]

After basal ganglia injury, DA binding to the D_2 receptor alone may elicit a robust response that may be attributed to its increased sensitivity after lesioning. An increase in D_2 DA receptors in the striatum of MPTP-treated mice performing high-intensity treadmill exercises was demonstrated by means of positron emission tomography imaging.[29] An exercise-induced increase in D_2 receptor expression coupled with an increase in the synaptic availability of DA may be sufficient to elicit increased dopaminergic neurotransmission and improved motor function. Overall, these findings show that intensive exercise, through a neurorestorative mechanism, exerts beneficial effects on DA transmission in mice models of PD.

Moreover, intensive exercise acts not only on dopaminergic neurotransmission.

Treadmill exercise is also able to reverse the increased levels of presynaptic glutamate inside the striatal terminals in MPTP-treated mice[30] and to modulate the AMPA [alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid] postsynaptic receptor responsible for fast excitatory neurotransmission in the central nervous system[31]; the effect is a diminished synaptic strength and the relief from overactivation in the basal ganglia circuits.[32,33]

These neuroplastic effects of intensive exercise are probably related to increased expression of a variety of neurotrophic factors[34–37] (Fig. 2). In particular, brain-derived neurotrophic factor (BDNF) and glial-derived neurotrophic factor (GDNF) are the most likely growth factors involved in this process. BDNF is a key component of a number of aspects of neuroplasticity (neurogenesis, synaptogenesis, and cell survival),[38] whereas GDNF has been shown to promote the survival and the differentiation of DA neurons and to maintain the survival of adult catecholaminergic neurons in mice.[39,40] BDNF and GDNF exert protective effects against MPTP and 6-hydroxydopamine.[41–43] GDNF administration into the nigrostriatal system induces sprouting from dopaminergic neurons and increases levels of DA, noradrenaline, and serotonin,[44] whereas BDNF increases DA concentration and tyrosine hydroxylase activity in the striatum.[27,45]

TABLE 2 Inefficacy of exercise on neuroplasticity

O'Dell SJ, Gross NB, Fricks AN, et al: Running wheel exercise enhances recovery from nigrostriatal dopamine injury without inducing neuroprotection. *Neuroscience* 2007;144:1141–1151.
Al-Jarrah M, Pothakos K, Novikova L, et al: Endurance exercise promotes cardiorespiratory rehabilitation without neurorestoration in the chronic mouse model of Parkinsonism with severe neurodegeneration. *Neuroscience* 2007;149:28–37
Pothakos K, Kurz M, Lau Y-S: Restorative effect of endurance exercise on behavioral deficits in the chronic mouse model of Parkinson's disease with severe neurodegeneration. *BMC Neurosci* 2009;10:6

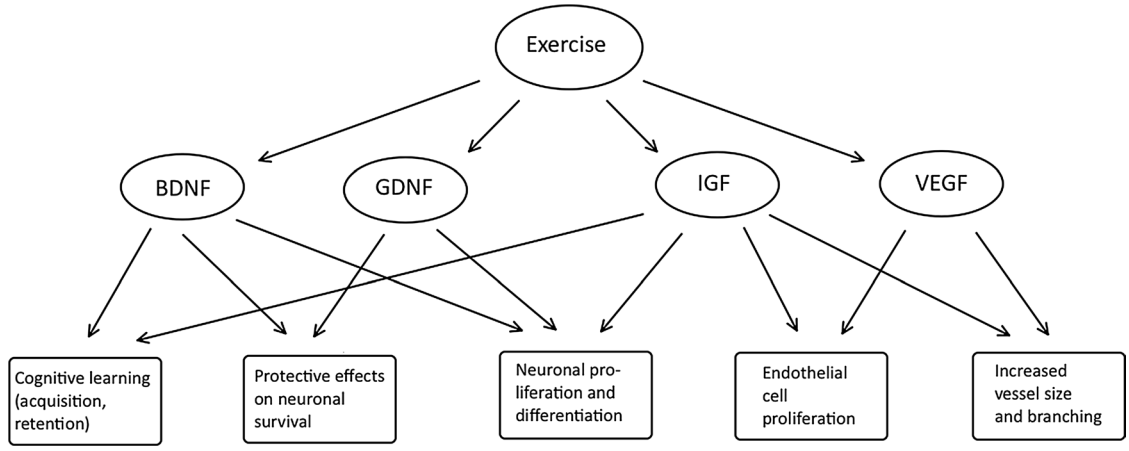

FIGURE 2 *Through growth factor production, exercise can regulate neurogenesis, angiogenesis, neuroplasticity, and learning. BDNF, GDNF, insulin growth factor-1 (IGF), and vascular endothelial growth factor (VEFG), derived from central and peripheral sources, modulate exercise-dependent effects on the brain (modified from Cotman et al., 2007).*

In addition, Tajiri et al.[27] have recently shown that rat models of PD performing intensive treadmill exercise experience upregulation of BDNF and GDNF in the striatum compared with rats that do not exercise. These findings are consistent with those of another study by Lau et al.,[46] who showed that intensive treadmill exercise raises the level of endogenous BDNF and GDNF in the substantia nigra and the striatum. Moreover, it has been recently hypothesized that the protective action of treadmill exercise is not caused by anti-inflammatory effects but rather by the activation of the BDNF signaling pathway.[47]

THE CLINICAL EVIDENCE

Several studies have already shown the efficacy of rehabilitation in improving quality-of-life, strength, balance, and gait in patients with PD,[48–53] and some studies have also shown that the improvements after rehabilitation persist in the medium term.[41,54,55] However, all these studies adopted a global treatment program that amounted to 6–18 hrs, distributed within 6–12 wks (1–1.5 hrs per week).

Recently, an intensive, specific exercise with a therapeutic approach that adheres to the principles of neuroplasticity has been indicated as one possible solution to improve rehabilitation outcome for people with PD.[56,57]

Intensity of treatment depends on frequency and duration of treatment, number of repetitions, and difficulty/complexity of exercises. A treatment is generally considered intensive when involving 2–3 hrs of physical exercise per week, for 6–14 wks, that is, a total of 12–42 hrs of treatment.[57–62]

A meta-analysis on the efficacy of exercise on the prevention of falls in older people recognized that the soundest improvements are achieved with programs using a higher dose of exercise: the criterion for a minimal effective exercise dose would equate to a program[63] running twice a week for 25 wks.

A few previous studies assessed intensive exercise treatment of patients with PD (Table 3).

The relevance of the exercise intensity in PD rehabilitative treatments was established in a recent article.[64] In this work, a group of patients with PD in the early stages of the disease followed three different treatment programs: zero, low, and high treadmill intensity. It turned out that only the patients following the high-intensity treatment program showed a significant improvement in motor performance. Similarly, only the patients exercising at a high treadmill intensity showed a lengthening of the cortical silent period after transcranial magnetic stimulation, suggesting that intensity of exercise is a crucial parameter when activity-dependent neuroplasticity is required in addition to improved motor performance.

Similar conclusions have been reached by other authors adopting different procedures, but with analogous emphasis on exercise intensity.[62,65]

An intensive rehabilitation treatment with a greater amount of hours of treatment was able to improve motor performance in patients with PD in an intermediate stage of the disease (stage 3 Hoehn-Yahr).[66] This improvement was also evaluated by means of metabolic parameters, a more quantitative outcome. At the end of treatment, the improvement in clinical scores was associated with an increase in energy consumption during the 6-min walk test, an indicator of greater speed in the

recruitment of motor units and of the ability to maintain this recruitment over time. The authors hypothesized that these improvements may be related to high-intensity exercise promoting activity-dependent neuroplasticity.

Duncan and Earhart[67] evaluated the efficacy of a 12-mo tango program on 62 patients randomly assigned to an Argentine tango program twice a week or a control group (no intervention). They found that, at the end of the study, the experimental group showed a significant reduction on Movement Disorder Society–Unified Parkinson Disease Rating Scale (UPDRS)–3 score, whereas there was no significant change in the control group. The importance of this article lies in considering the effectiveness of a continuous intensive treatment on disease progression. This could be an important strategy to counteract the sedentary lifestyle of patients with PD.

A longer treatment (16 mos) was evaluated by Schenkman and colleagues[68] in a study that compared two different supervised exercise programs and a home-based control exercise program. Unfortunately, the participants were in different stages of the disease (Hoehn-Yahr stages 1–3), and this could bias the efficacy of the different treatments. The authors found a significant improvement in walking economy in patients who underwent an aerobic treatment (using treadmill, bike, or elliptical trainer) at the end of the study.

Ellis et al.[8] studied the efficacy of a multidisciplinary and intensive program in 68 inpatients with PD, who spent 15–21 hrs a week following an exercise program that included physical therapy, occupational therapy, and speech therapy. After 21 days of treatment, all patients showed statistically significant improvements in all evaluated outcomes: the Functional Independence Measure, timed up and go test, 2-min walk test, and finger-tapping test. Unfortunately, no follow-up was reported, and the study included the optimization of drug therapy, which introduced an important bias preventing the assessment of the true efficacy of the rehabilitation treatment alone. Nevertheless, ten patients who did not change the drug dosage showed a statistically significant improvement in Functional Independence Measure scores.

Another study addressing inpatient rehabilitation programs was a randomized controlled trial investigating the difference between two different treatments: one that included movement strategies and another that included only physical exercise.[69] The authors found that, after treatment (5–16 sessions lasting $\leq$45 mins for 2 wks), the patients enrolled in the group practicing movement strategies showed a significant improvement[70] in UPDRS scores, 10-m walk test, 2-min walk test, balance pull test, and the PD Questionnaire–39. However, after 3 mos, some improvement in the performance was lost. The authors hypothesized that treatment lasting on an average of 9 hrs was not able to induce long-term changes in movement performance and suggested more prolonged therapeutic programs.

To address the specific value of intensive rehabilitation programs in detail, a randomized, parallel group study in patients with PD was recently performed.[71] A first group after an intensive inpatient exercise program was compared with a group only pharmacologically treated. To obtain uniform evaluations and to reduce the confounding variables, all the patients belonged to the same stage of the disease (stage 3 Hoehn-Yahr). The patients enrolled in the physical sessions underwent very intensive treatment (3 hrs daily, 5 days per week, for 4 wks, reaching a total of 60 hrs of treatment) that included physical exercises; occupational exercises; and the use of a number of devices, such as a stabilometric platform and a treadmill with auditory and visual cues.[72] In particular, all patients walked on a treadmill for at least 30 mins a day. The study included a 12-mo follow-up and the evaluation of Levodopa dosage at the beginning and at the end of treatment. At discharge, the group that underwent the rehabilitative treatment showed an improvement in UPDRS II, III, and total scores. At follow-up, the same group showed significantly lower UPDRS scores. Moreover, the experimental group reduced the total Levodopa dosage, whereas the control group needed to increase Levodopa dosage without any improvement in UPDRS scores. After 1 yr, a second intensive treatment in the experimental group led to additional significant improvement in all UPDRS scores.

A significant reduction of balance impairment and falls has been found in patients with PD who underwent a Tai Chi intensive program.[73] The patients, treated 2 hrs per week for 24 wks, showed better results in different scales (maximum excursion and directional control, UPDRS, and number of falls) in comparison with the control group treated with resistance or stretching rehabilitation program. These improvements were maintained at 3-mo follow-up. A bias in the study was related to the fact that the patients were in different stages of the disease (Hoehn-Yahr stages 1–4: patients with and without balance problems). Moreover, no data are provided on the dose of the drug at the end of treatment and follow-up.

TABLE 3 Clinical trials with intensive rehabilitation protocols

	H-Y	Design Study	Rehabilitation Treatment	Treatment Dose
Fisher et al., 2008	1-2	Randomized controlled; 30 patients in 3 groups, outpatients	Treadmill with body-weight support (HI), traditional PT (LI), and educational treatment (0I)	8 wks, 24 sessions for groups HI and LI and 6 sessions for 0I
Ellis et al., 2008	2-3-4-5	Open study, no control group; 68 patients, inpatients	Auditory cues, PT, cognitive movement strategies, occupational therapy, speech therapy	3 hrs per day, 5 or 7 days per week, 3 wks
Morris et al., 2009	2-3	Randomized controlled; 28 patients in 2 groups, inpatients	Movement strategy training, traditional PT	14 sessions of 45 mins for the movement strategies group and 13 sessions of 45 mins for the PT group
White et al., 2009	2-3	Randomized controlled; 108 patients in 3 groups, outpatients	Auditory cues, PT, occupational therapy, speech therapy	Group 1: no rehabilitation treatment; groups 2 and 3: 3 or 4.5 hrs of interdisciplinary treatment per week for 6 wks
Ebersbach et al., 2010	1-2-3	Randomized controlled; 60 patients in 3 groups, outpatients	LSVT BIG training, Nordic walk, domestic exercises	4 hrs per week for 4 wks for BIG for group 1, two hours per week for 8 wks for Nordic walk for group 2, one hour of domestic exercises for group 3
Frazzitta et al., 2012	3	Randomized controlled; 50 patients in 2 groups, inpatients	Treadmill with auditory and visual cue, stabilometric platform, PT, occupational therapy	3 hrs per day, 5 days per week for 4 wks for group 1, no rehabilitation treatment for group 2
Duncan and Earhart, 2012	1-2-3-4	Randomized controlled; 62 patients in 2 groups, outpatients	Argentino tango program *vs.* no intervention	54 wks, 2 sessions per week
Schenkman et al., 2012	1-2-3	Randomized controlled; 121 patients in 3 groups, outpatients	Flexibility/balance, aerobic exercise home-based exercise	70 wks, from 5 to 7 days of session per week, approximately 1 hr per session
Li et al., 2012	1-2-3-4	Randomized controlled; 195 patients in 3 groups, outpatients	Tai Chi, resistance training, stretching training	24 wks, 2 sessions of 60 mins per week
Shulman et al., 2012	1-2-3	Randomized controlled; 67 patients in 3 groups, outpatients	Higher-intensity treadmill, lower-intensity treadmill, stretching, and resistance exercise	Higher: 30 mins, 3 times per week for 3 mos. Lower: 50 mins, 3 times per week for 3 mos. Stretching: 3 sessions, 3 times per week for 3 mos

0I indicates zero intensity; CSP, cortical silent period; F-U, follow-up; FIM, Functional Independence Measure; FOGQ, Freezing of Gait Questionnaire; H-Y, Hoehn-Yahr stages; HI, high intensity; LI, low intensity; MDS, Movement Disorder Society; PDQ39, Parkinson disease quality of life; PT, physical therapy; UPDRS, Unified Parkinson Disease Rating Scale; LVST, Lee Silverman Voice Treatment.

Shulman et al.[74] suggested the importance of a combination of treadmill training and resistance exercise to obtain a greater benefit in patients with PD. The authors, in their randomized clinical trial, showed that an intensive treadmill treatment at 40%–50% of heart rate reserve achieved greater improvement in gait speed in comparison with an intensive treadmill training at 70%–80% of heart rate reserve, whereas only stretching and resistance exercises improved muscle strength.

CONCLUSIONS

There is a general consensus about improvements of physical exercise in both performance and quality-of-life in patients with PD.

The presence of a large cohort of studies on animal models focusing on the neuroplastic action of the treadmill and intensity of exercise collides with a small number of clinical studies on patients with PD.

These also do not show uniformity in the choice of rehabilitation strategy and outcome.

Often, these studies do not consider a follow-up and bring little information on drug therapy.

Despite these gaps, the intensive multidisciplinary rehabilitation emerges as key in the treatment of PD. The beneficial effect of the intensive use of the treadmill on plasma and cerebrospinal fluid levels of several growth factors is responsible for neurotransmitter and cellular changes shown in animal models of PD. Because the treadmill has

TABLE 3 *(Continued)*

Outcome Measures	Pharmacologic Therapy	Results	F-U
UPDRS, self-selected and fast walking, sit-to-stand test, CSP	Evaluated and stable during study but specific data not reported	Only people in the HI group improved spatiotemporal gait parameters, kinematics of gait, and performance of sit-to-stand task	No
FIM instrument, timed up and go test, 2-min walk test, finger-tapping test	Evaluated and modified during study	Statistically significant improvement across all outcome measures	No
UPDRS II and III, 10-m walk test, timed up and go test, 2-min walk test, balance pull test, PDQ39	Evaluated and stable during study but specific data not reported	The movement strategy group showed improvements in the UPDRS, 10-m and 2-min walk, balance, and the PDQ39. The PT group showed improvement only in the PDQ39	3 mos
Activity monitor and 2-min walk test	Evaluated and stable during study but specific data not reported	Higher doses resulted in significant improvement in 2-min test for subjects with low baseline and improvement in walking activity for subjects with high baseline walking activity	No
UPDRS III, PDQ39, 10-m walk test, timed up and go test	Evaluated and stable during study but specific data not reported	Improvement of UPDRS III, 10-m walk test, and timed up and go test in BIG group	No
UPDRS II, III, and total	Evaluated and stable during 4 wks of treatment, evaluated as Levodopa-eq at the beginning and at the end of the study	Improvement of UPDRS II and III at t he end of treatment	12 mos
MDS-UPDRS-1-2-3, FOGQ, MiniBESTest balance test, gait parameters	No data	Statistically significant improvement across all outcome measures in the Tango group	No
Physical Functional Performance Balance and walking economy, UPDRS 2-3, PDQ39	No data	Improvement in walking economy at 16-mo follow-up in patients who underwent aerobic treatment	No
Limits of stability test, UPDRS 3, gait parameters, number of falls	Evaluated and stable during study but specific data not reported	Tai Chi group improved in limits of stability test and all secondary outcomes. Lowered incidence of falls in Tai chi group in comparison with stretching	3 mos
Gait speed, cardiovascular fitness, muscle strength	Evaluated but specific data not reported	Lower- and higher-intensity treadmill improved cardiovascular fitness but only lower-intensity improved gait speed. Only stretching and resistance improved muscle strength	No

been shown to be effective in improving gait disturbances also in patients with PD,[75] it can be hypothesized that similar neurochemical modifications happen in humans, and future studies should be designed to evaluate this hypothesis in both early and advanced stages of disease. Moreover, exercise has a peripheral effect on improving cardiovascular health, lipid-cholesterol balance, energy metabolism, glucose

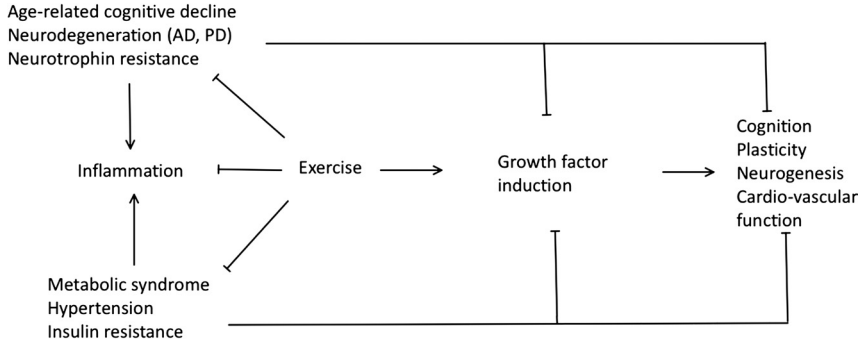

FIGURE 3 *Apart from its beneficial effect on brain health through growth factor induction, exercise also reduces peripheral risk factors for cognitive decline and motor inability, such as hypertension, insulin resistance, and inflammation (modified from Cotman et al., 2007). PD indicates Parkinson disease; AD, Alzheimer disease.*

use, insulin sensitivity, and inflammation[76,77] (Fig. 3). Several guidelines have been proposed, each by a different group, suggesting different exercises and devices.[78,79] The following move of the authors is to establish, on the basis of the evidence of the literature, the best exercise program and the best intensity that ensures optimal results. New randomized controlled intensive trials with a greater number of patients, an appropriate follow-up, and an evaluation of pharmacologic therapy should be planned to elucidate the efficacy of rehabilitation, the maintenance of benefits over time, and the probable neuroplastic action on the human brain.

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