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NEUROPROTECTION

REVIEW

Exercise, exerkines, and muscle–brain crosstalk in Parkinson's disease

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder with motor and non-motor symptoms, driven by dopaminergic loss and α-synuclein accumulation. Beyond neurodegeneration, growing evidence highlights skeletal muscle health as a key determinant of prognosis, with sarcopenia and frailty contributing to greater disability, fall risk, and reduced quality of life. This narrative review synthesizes current evidence on the interplay among exercise, muscle status, and exerkine signaling in PD, emphasizing their potential roles in neuroprotection and functional outcomes. A comprehensive literature search in PubMed and SciELO up to October 2025 identified 129 relevant studies, including experimental, observational, and interventional data. Sarcopenia and reduced muscle strength are highly prevalent in PD and independently associated with disease severity, frailty, and falls, while grip strength has emerged as a simple biomarker of progression. Clinical trials consistently show that aerobic, resistance, and multimodal exercise programs improve gait, balance, mood, cognition, and quality of life, with progressive resistance and balance training yielding the greatest motor benefits. At a mechanistic level, skeletal muscle functions as an active endocrine organ, releasing a variety of exercise-induced signaling molecules known as exerkines. These include brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), irisin, cathepsin B, myostatin, and growth/differentiation factor 15 (GDF15). Together, these exerkines facilitate muscle–brain crosstalk and are thought to contribute to the neuroprotective effects of exercise in PD. Through anti-inflammatory, antioxidant, and mitochondrial regulatory pathways, they support dopaminergic neuron survival and promote synaptic plasticity and neuronal resilience. Current international guidelines recommend individualized, multimodal programs integrating aerobic, resistance, and balance training, initiated early and maintained long-term. Exercise represents a promising, nonpharmacological intervention to mitigate neurodegeneration, sarcopenia, and functional decline in PD, although further high-quality studies are needed.

KEYWORDS

exercise, exerkines, handgrip strength, muscle–brain crosstalk, Parkinson's disease, resistance training, sarcopenia

Highlights

- Exercise induces muscle–brain crosstalk via exerkines that regulate neuroinflammation, mitochondria, and dopaminergic survival in Parkinson's disease.
- Sarcopenia and muscle weakness are highly prevalent in PD and strongly linked to greater motor impairment, frailty, and reduced quality of life.
- Aerobic and resistance training improve motor, cognitive, and functional outcomes when personalized and maintained.
- Exerkines are emerging as potential biomarkers and mediators of exercise-driven neuroprotection, but further high-quality studies are needed.

1 | INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor and nonmotor symptoms, driven by dopaminergic neuron loss and α-synuclein accumulation in the substantia nigra. With an estimated prevalence of 572 cases per 100,000 individuals over 45 years PD represents a major and growing global health challenge due to an aging population and the current lack of curative therapies.[1]

In recent years, muscle status, nutrition, and exercise have emerged as key determinants of health and functional outcomes in older adults.[2] Low muscle quantity or quality has been strongly associated with poor prognosis across multiple chronic diseases including cancer, dementia, and other neurodegenerative disorders such as PD.[3,4] Sarcopenia, defined as an age-related decline in muscle mass and strength, is increasingly recognized as a contributor to frailty and disability. Evidence suggests that sarcopenia, particularly loss of muscle mass and strength, may be associated with worse prognosis, increased falls, greater cognitive impairment, and reduced quality of life in patients with parkinsonian syndromes.[4,5] Consequently, lifestyle strategies such as regular exercise, adequate nutrition, and resistance training have been proposed as nonpharmacological approaches to mitigate disease progression and functional decline.

One of the leading hypotheses explaining the protective effects of exercise centers on exerkines, which are bioactive molecules released into circulation in response to physical activity (PA).[6] These molecules, which include cytokines, peptides, and growth factors, mediate interorgan communication and modulate inflammation, metabolism, and neuroplasticity.[7] Various tissues contribute to this systemic signaling network: skeletal muscle (myokines), adipose tissue (adipokines), neurons (neurokines), among others.[8] Increasing evidence suggests that exerkines such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF-1), irisin, cathepsin B, and growth/differentiation factor 15 (GDF15) exert neuroprotective and anti-inflammatory effects, potentially influencing the pathophysiology of neurodegenerative diseases including PD[7,9]

This bidirectional communication between muscle and the brain, often referred to as muscle–brain crosstalk, represents a promising frontier in neurorehabilitation and disease modification.[10] Understanding how exercise-induced molecular changes contribute to neuronal health could open new therapeutic avenues to improve prognosis and quality of life in PD.

Accordingly, the aim of this narrative review is to synthesize current evidence on the relationships among exercise, sarcopenia, muscle health, and exerkines in PD, and to outline exercise-based interventions that clinicians can integrate into routine patient care.

2 | METHODS

2.1 | Search strategy and study selection

We searched PubMed and SciELO for studies on PD examining PA/exercise, exerkines, sarcopenia, muscle strength, and muscle mass. The strategy combined MeSH and free-text terms with Boolean operators (AND/OR), including "Parkinson's disease," "exercise," "exerkines," "myokines," "sarcopenia," "muscle strength," "muscle mass," and specific terms (IGF-1, BDNF, irisin, GDF15, myostatin, grip strength, cathepsin B) up to October 2025.

The initial database searches allowed for a preliminary selection of relevant articles, which served as the foundation for further identification of studies through the snowball method. This technique involved reviewing the reference lists of the selected articles and tracking citations of key sources to identify additional literature relevant to the topic.

2.2 | Eligibility criteria

Inclusion criteria included human studies evaluating the impact of PA or exercise on muscle function, sarcopenia, or exerkine signaling in PD onset, progression, or prognosis; experimental, observational, and preclinical studies elucidating mechanisms of muscle–brain crosstalk relevant to PD; and narrative or systematic reviews that contributed mechanistic or clinical context. Exclusion criteria included publications not available in English or Spanish, case reports, conference abstracts, editorials, and studies lacking direct relevance to PD, exercise, or muscle health.

Articles were screened by title, abstract, and full text. Studies examining exerkines such as BDNF, IGF-1, irisin, cathepsin B, myostatin, or GDF15 in relation to

exercise or muscle status in PD were prioritized for inclusion. A total of 129 articles were included.

2.3 | Data synthesis

Given heterogeneity across designs and outcomes, we performed a qualitative narrative synthesis structured around: (1) effects of exercise on motor and non-motor outcomes; (2) associations between muscle mass/strength and PD severity; and (3) exerkine-mediated mechanisms of neuroprotection and potential disease modification.

3 | RESULTS

3.1 | Exerkines involved in PD

Exerkines mediate many of the systemic benefits of exercise, such as anti-inflammatory, metabolic, and neuroprotective effects.[7] Through these signaling pathways, exerkines contribute to inter-organ communication, particularly muscle–brain crosstalk, which plays a central role in the maintenance of neuronal health.[11] While most of the evidence comes from Alzheimer's disease models, emerging data suggest that exerkines also participate in PD pathophysiology, influencing neuroinflammation, mitochondrial function, and dopaminergic survival.[12] The main exerkines implicated in PD include BDNF, IGF-1, irisin, cathepsin B, myostatin, and GDF15. Additionally, other exercise-responsive molecules such as apelin-13, fibroblast growth factor-21 (FGF-21), and musclin have been reported to modulate oxidative stress, glucose metabolism, and neuroprotection in experimental PD models.[13]

In preclinical models of PD, exercise-induced exerkines show distinct but complementary neuroprotective mechanisms that converge on dopaminergic preservation and mitochondrial stability. For example, BDNF enhances synaptic plasticity and neuronal survival by activating tropomyosin receptor kinase B (TrkB) signaling, promoting autophagy, and reducing α-synuclein aggregation.[14–17] Similarly, IGF-1 stimulates the Phosphatidylinositol 3-kinase–protein kinase B–mechanistic target of rapamycin (PI3K–Akt–mTOR) pathway, regulates autophagy, and helps restore tyrosine hydroxylase and dopamine levels, leading to improved motor and cognitive outcomes.[18] Irisin, regulated by peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) and 5′ adenosine monophosphate–activated protein kinase (AMPK), decreases α-synuclein internalization, enhances lysosomal degradation, and preserves striatal dopaminergic integrity.[19,20] Moreover, cathepsin B contributes to α-synuclein clearance and lysosomal function, although its cytosolic accumulation under stress can trigger NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome activation and neuroinflammation.[19,21] In contrast, myostatin upregulation in Parkinsonian muscle promotes inflammation through NF-κB and TNF-α pathways, while endurance exercise suppresses its expression and mitigates muscle atrophy and systemic inflammation.[22] Finally, GDF15, a stress-induced cytokine, protects dopaminergic neurons by maintaining mitochondrial integrity, reducing apoptosis, and activating PI3K–Akt–mTOR and PGC-1α signaling.[23,24] Together, these molecular responses reflect the capacity of exercise to enhance neuronal resilience through anti-inflammatory, antioxidant, and mitochondrial mechanisms. Table 1[25–51] summarizes the effects of these exerkines in response to physical exercise, and Table 2[52–65] describes their correlations with clinical and biomarker findings in patients with PD, with examples of the studies demonstrating the mentioned outcomes. Visual representation of the systemic effects of exercise in PD can be found in Figure 1.

3.2 | Muscle health and PD

3.2.1 | Decline in muscle mass and body composition changes in PD

Muscle mass declines more rapidly in individuals with PD than in normal aging, and sarcopenia is strongly associated with advanced disease stage, greater motor impairment, and reduced gait performance.[66–68] Alterations in body composition are also common, as reduced body mass index, unintentional weight loss, and loss of lean mass correlate with higher disability and worse prognosis.[66,69,70] Notably, weight loss may emerge early in the disease course and has been linked to increased energy expenditure, reduced nutritional intake, and metabolic alterations, including gut microbiota dysregulation.[71,72]

3.2.2 | Muscle strength, functional performance, and prognostic value

Handgrip strength is a simple, reliable bedside measure and a core criterion for diagnosing sarcopenia, and is consistently reduced in individuals with PD.[73] Lower handgrip strength predicts disease progression and future PD risk: reduced upper-limb strength correlates with greater disease severity[74] and higher lifetime PD risk, including observations that men with low strength in late adolescence are more likely to develop PD decades later.[75,76] A study by da Luz et al. demonstrated that handgrip strength also correlates inversely with Unified Parkinson's Disease Rating Scale (UPDRS) part II and III scores, supporting its role as a biomarker of functional independence and disease severity.[74] Direct assessments of strength and muscle function provide prognostic information beyond the motor items included in UPDRS-III.[67,77]

In addition to isolated strength, skeletal muscle impairment associated with PD also includes reductions in power, endurance, and metabolic efficiency, contributing to slower gait, shorter stride length, postural instability, and increased fall risk.[73,78,79] These deficits lead to mobility limitation, sedentary behavior, and loss of independence, ultimately worsening quality of life.[80,81]

TABLE 1 Effects of exercise on exerkines in Parkinson's disease.

Exerkine	Exercise-related effects	Studies
BDNF	Increased circulating levels with physical exercise, especially acute aerobic exercise, even in patients with neurodegenerative diseases.	Romero Garavito et al.[25]; Edman et al.[26]; Dinoff et al.[27]; Huang et al.[28]; Szuhany et al.[29]; Coelho et al.[30]
IGF-1	Increased circulating levels especially with resistance exercise.	Jiang et al.[31]; Rodríguez-Gutiérrez et al.[32]; Vale et al.[33]; Annibalini et al.[34]
	No clear association between exercise load characteristics and serum IGF-1 changes were observed	Alcantara et al.[35]
Irisin	Increased levels more significantly with acute aerobic exercise than with acute anaerobic exercise.	Kazeminasab et al.[36]
	Increased significantly with resistance training and combined training.	Mohammad Rahimi et al.[37]; Kim et al.[38]
	No difference on serum levels regarding intensity of aerobic exercise or type of exercise.	Fox et al.[39]
	Increased levels immediately after a high-intensity interval exercise and declined 1 h after.	Torabi et al.[40]; Huh et al.[41]; Nygaard et al.[42]
Cathepsin B	Transient increased levels with physical exercise, especially high-intensity interval exercise, that return to baseline in 30–90 min.	Ji et al.[43]
	Open-skill exercises (e.g., fencing, which require cognitive engagement) result in higher basal and post-exercise cathepsin B levels than closed-skill exercises (e.g., swimming).	Gökçe et al.[44]
Myostatin	Consistent decreased levels with resistance and aerobic training.	Ataeinosrat et al.[45]; Khalafi et al.[46]; Bagheri et al.[47]; Hittel et al.[48]
GDF15	Increased circulating levels more significantly with vigorous aerobic exercise than with resistance exercise.	Klein et al.[49]; Campderrós et al.[50]; Kleinert et al.[51]

Abbreviations: BDNF, brain-derived neurotrophic factor; GDF15, growth differentiation factor 15; IGF-1, insulin-like growth factor 1.

TABLE 2 Exerkine correlation with clinical and biomarker findings in Parkinson's disease.

Exerkine	Clinical correlates/biomarker evidence	Studies
BDNF	Reduced nigral BDNF in PD	Wolf et al.[52]
	Inhibition of nigral BDNF in animal models induces parkinsonian features	Zhang et al.[53]
	Exercise-induced increase linked to neuroplasticity and improved UPDRS motor scores.	Marston et al.[54]
IGF-1	Higher serum IGF-1 in early PD	Bernhard et al.[55] Godau et al.[56]
	Correlates with fewer non-motor symptoms (anxiety, depression, fatigue, cognitive impairment)	Gu et al.[57]; Shi et al.[58]; Shi et al.[59]
Irisin	Reduced circulating irisin in PD	Shi et al.[60]
	Low levels correlate with worse UPDRS-III and MoCA scores	
	Higher irisin linked to preserved striatal ^{18}F-DOPA uptake	
Cathepsin B	Higher CatB linked to lower PD risk PD does not alter circulating CatB	Yusufujiang et al.[61]; Lu et al.[62]
Myostatin	No direct PD evidence; indirect data suggest that exercise-induced myostatin suppression may help preserve muscle mass and function	Hjorth et al.[63]
GDF15	Elevated serum/CSF GDF15 in PD Age-dependent variability but potential disease biomarker	Miyaue et al.[64]; Yao et al.[65]

Abbreviations: 18F-DOPA, fluorine-18–labeled L-DOPA; BDNF, brain-derived neurotrophic factor; CatB, cathepsin B; CSF, cerebrospinal fluid; GDF15, growth differentiation factor 15; IGF-1, insulin-like growth factor 1; MoCA, Montreal Cognitive Assessment; PD, Parkinson's disease; UPDRS-III, Unified Parkinson's Disease Rating Scale part III.

3.2.3 | Sarcopenia, frailty, and fall risk in PD

Sarcopenia and frailty frequently coexist in people with PD, representing overlapping syndromes of reduced physiological reserve. Reported prevalences range from 30% to 35%,[82] and their coexistence amplifies vulnerability to falls, disability, and hospitalization.[82–84] Notably, Moreno Catalá et al. demonstrated that reduced lower-limb muscle strength correlates with impaired postural stability and increased fall risk in PD; in their study, weaker knee extensors and plantar

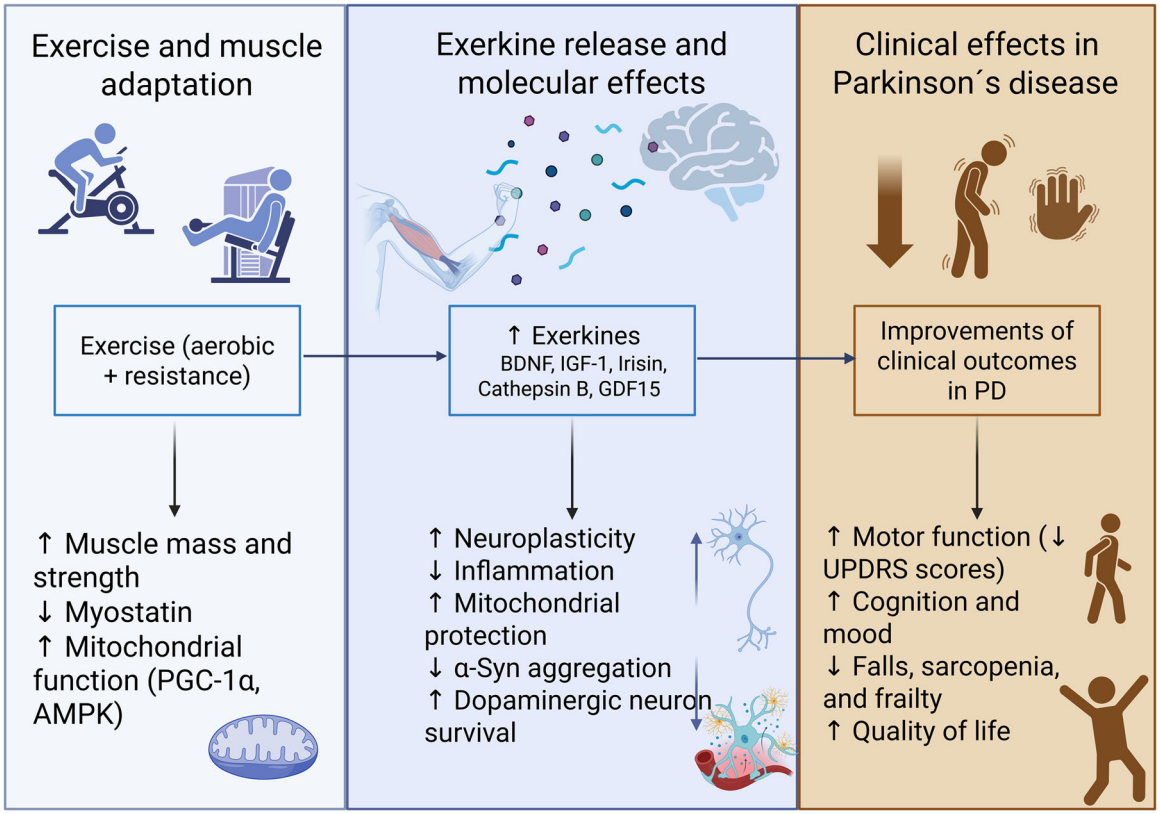

FIGURE 1 Aerobic and resistance exercise promote muscle hypertrophy, increased strength, reduced myostatin expression, and enhanced mitochondrial function. These adaptations stimulate the release of exerkines such as BDNF, IGF-1, irisin, cathepsin B, and GDF15, which exert neuroprotective actions including improved neuroplasticity, reduced inflammation, enhanced mitochondrial protection, decreased α-Syn aggregation, and increased dopaminergic neuron survival. Together, these molecular effects contribute to clinically relevant benefits in Parkinson's disease, including improved motor function (reduced UPDRS scores), better cognition and mood, lower risk of falls, sarcopenia and frailty, and enhanced quality of life. AMPK, 5′ adenosine monophosphate–activated protein kinase; BDNF, brain-derived neurotrophic factor; GDF15, growthdifferentiation factor 15; IGF-1, insulin-like growth factor-1; PGC-1α, proliferator-activated receptor gamma coactivator 1-alpha; α-Syn, α-synuclein; UPDRS, Unified Parkinson's Disease Rating Scale.

flexors accurately identified fallers, emphasizing the relevance of targeted strength and balance training.[85] Moreover, reduced muscle strength and probable sarcopenia, identified through SARC-F screening and objective strength assessments, have been consistently associated with a higher risk of falls and disability in PD.[77,84] These findings are consistent with meta-analyses demonstrating significant reductions in muscle strength and power compared with age-matched controls.[73] Altogether, muscular, neurological, and systemic deficits establish a self-perpetuating cycle of declining physical performance, inactivity, and further muscle loss, reinforcing the bidirectional link between frailty and disease progression.[86]

3.2.4 | Exercise-driven muscle–brain molecular interactions in PD

At a mechanistic level, skeletal muscle functions as an active endocrine organ that releases exerkines capable of modulating neural and systemic processes. Molecules such as BDNF, IGF-1, irisin, cathepsin B, and GDF15 have been implicated in pathways supporting neuroplasticity, dopaminergic integrity, and inflammatory regulation.[16–18,20,23] Exercise-induced increases in circulating BDNF and IGF-1 correlate with motor and cognitive improvements, while cathepsin B may facilitate α-synuclein clearance and promote synaptic maintenance.[57,87,88] Recent preclinical studies in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) models show that irisin activates Sirtuin 1, leading to deacetylation of hypoxia-inducible factor 1-alpha (HIF-1α)/PGC-1α, normalization of lactate metabolism in dopaminergic neurons, and enhanced mitochondrial function.[89] Together, these findings support the existence of a muscle–brain signaling axis that contributes to the beneficial effects of exercise in PD, although robust translational evidence in humans remains limited.

3.2.5 | α-Synuclein pathology and direct muscle involvement

PD-related muscle dysfunction may also reflect local α-synuclein pathology. Aggregated α-synuclein, the hallmark of Lewy bodies, has been detected in skeletal muscle, particularly at the neuromuscular junction.[90] Yang et al. demonstrated in mouse models with induced α-synuclein overexpression that its accumulation in motor neuron axons and neuromuscular junctions triggers mitochondrial oxidative stress, impairs neuromuscular transmission, and disrupts muscle regeneration, ultimately leading to muscular atrophy.[91]

3.3 | Effects of exercise in PD

3.3.1 | Effects of exercise on motor symptoms in PD

Aerobic and resistance training consistently improve motor disability and functional mobility. Adapted exercise programs enhance walking capacity, balance, and quality of life,[92] while progressive resistance training reduces UPDRS-III scores and increases strength in previous RCTs.[93] Remote, supervised home-based aerobic training in RCT settings also improves motor severity with high adherence.[94] Additionally, low-intensity modes such as yoga and Tai Chi are less potent for motor outcomes but still improve posture, flexibility, and balance.[95] Umbrella and systematic reviews further confirm overall improvements in motor severity, particularly with dance- and gait/balance-focused interventions.[96,97]

3.3.2 | Effects of exercise on non-motor symptoms in PD

Regular exercise is associated with reduced apathy and fatigue[98] and slower cognitive decline.[99] Aerobic and interval training improve executive function, cognition, mood, and fatigue across several RCTs,[100–103] and some studies also report structural brain changes consistent with cognitive preservation.[100,102,104] Umbrella reviews indicate that combined, sensorimotor, dance-based, and Tai Chi programs are especially effective for cognition, mood, sleep, and overall quality of life, though methodological heterogeneity remains.[96,105]

3.3.3 | Personalized exercise interventions

Tailoring programs to functional needs enhances adherence and outcomes.[106] Multimodal and individualized interventions combining aerobic, resistance, balance, and flexibility training yield superior gains in mobility, motor severity, and quality of life.[107,108] King et al. demonstrated that individually supervised exercise improves balance and everyday function more than group or home-based programs in patients with comorbidities.[109] However, Zippenfening et al. found similar improvements in functional performance between personalized and group training after 6 months, suggesting multiple effective delivery models.[110]

3.3.4 | Physiotherapy and technology-enabled rehabilitation

Physiotherapy is central to PD care, optimizing mobility, reducing falls, and preventing complications. Structured delivery systems like ParkinsonNet improve coordination and outcomes,[111] although trials such as PD REHAB have questioned cost-effectiveness.[112]

Digital tools, including tele-rehabilitation, smartphone-guided exercise, virtual-reality and exergaming balance training, and wearable biofeedback, are feasible, safe, and well-accepted, with demonstrated improvements in gait, balance, engagement, and long-term participation.[113–116] These approaches enhance accessibility and support continuous personalized rehabilitation.

3.4 | Guidelines and recommendations for PA and exercise in PD

Exercise is now recognized as a core therapeutic component in PD, with most modalities offering meaningful benefits; therefore, programs should be individualized based on functional needs and patient preference.

The American Physical Therapy Association (APTA, 2022) strongly recommends individualized multimodal exercise with moderate–high intensity aerobic and progressive resistance training, complemented by balance-focused, community-based interventions like Tai Chi and dance, implemented early and sustained over time.[117]

The European Physiotherapy Guideline advises structured and progressive exercise combining aerobic, resistance, balance, and task-specific training, performed 2–3×/week for 30–60 min over 10–24 weeks. Treadmill training enhances gait, while tango-based dance and Tai Chi improve balance and functional mobility.[118]

Spanish guidelines support supervised aerobic and strengthening programs in early–moderate PD and highlight progressive resistance training as the modality with the greatest long-term functional benefit.[119]

Ni et al. recommend treadmill or cycling (2–5×/week), resistance training (2–3×/week), and balance-gait programs (3×/week), with Tai Chi, yoga, and dance effective particularly when incorporating external cues; supervised and task-specific training yields the most durable results.[120]

Table 3 summarizes effective aerobic and resistance protocols for PD.[121–125]

4 | DISCUSSION

This narrative review integrates current evidence on the relationships among exercise, muscle health, and exerkine signaling and their relevance to motor and non-motor outcomes in PD. Across multiple studies, both aerobic and resistance training are consistently associated with improvements in motor, not-motor symptoms and daily functioning. In addition, there is increasing recognition that muscle is not merely a passive target of disuse or disease-related decline, but a biologically active tissue capable of influencing neural function. This perspective reframes exercise in PD from compensatory rehabilitation toward a potential disease-modifying approach, even though definitive causal confirmation is not yet available. Personalization,

TABLE 3 Examples of effective aerobic and resistance training interventions for patients with Parkinson's disease.

Study	Frequency	Intensity	Time	Type
Aerobic training				
Alberts et al.[121]	3 sessions per week, sustained long-term to maintain benefits.	60%–80% HRR or 70%–85% HRmax, or 14–17 on the RPE scale; increase effort if conversation is easily possible.	30–40 min per session, plus 5–10 min for warm-up and cool-down.	Aerobic exercise such as walking or stationary cycling; choose safe, enjoyable, and sustainable activities.
Kim et al.[122]	3–5 days per week, starting at 3 and progressing to 5.	Moderate (RPE 13/20), 60%–80% HRpeak or 40–60% HRR/VO_2R.	20–30 min per session, gradually progressing up to 60 min.	Walking, treadmill, cycling, or aquatic exercise; focus on safe, enjoyable, and sustainable modes.
Schootemeijer et al.[123]	3–5 sessions per week; training duration in studies ranged from 6 to 24 weeks.	Moderate to high intensity, typically 60%–85% of HRmax, 60%–80% VO_2max, or 50–80% HRR; higher intensities produce greater improvements in fitness and motor outcomes.	30–45 min per session, progressing up to 60 min.	Continuous, rhythmic activities engaging large muscle groups, such as treadmill walking, cycling, or similar aerobic modalities.
Resistance training				
Kim et al.[122]	2–3 days per week, starting at 2 and progressing to 3; include rest days between sessions.	40%–50% 1-RM initially, progressing to 60%–80% 1-RM.	1–3 sets of 8–12 repetitions per exercise; 8–10 exercises per session.	Multi-joint exercises targeting major muscle groups (e.g., legs, core, upper limbs) using weights, bands, or machines.
Chung et al.[124]	2–3 sessions per week.	Moderate intensity, typically 40%–80% of one-repetition maximum (1-RM).	Not specified	Progressive resistance exercises using machines, weights, or body weight; focus on lower limbs, sometimes including trunk and upper body muscles.
Strand et al.[125]	3 sessions per week for 12 weeks.	Strength: 3 × 8 at 80% 1-RM; Power: 3 × 6 at 50% 1-RM; Hypertrophy: 3 × 12 at 70% 1-RM.	~60 min per session, including warm-up and cool-down.	Machine-based exercises (leg press, chest press, leg curl, seated row, hip adduction, lat pull-down, triceps push-down, biceps curl).

Abbreviations: 1-RM, one-repetition maximum; HR, heart rate; HRmax, maximum heart rate; HRR, heart rate reserve; HRpeak, peak heart rate; RM, repetition maximum; RPE, rating of perceived exertion; VO_2max, maximal oxygen uptake; VO_2R, oxygen uptake reserve.

continuous monitoring, and continuity of care appear to be crucial. For this, integrating digital tools may further enhance outcomes, particularly in settings where in-person access is limited. Current international guidelines reflect this shift, recommending structured, multimodal exercise integrated early and maintained throughout the disease course.[120,126]

A key implication of these findings in PD is the potential to modify the exerkine profile. Both acute and long-term training increase circulating BDNF, IGF-1, and irisin.[29,31,36] In PD, lower BDNF and irisin levels and altered IGF-1 profiles are linked to greater motor and non-motor impairment, while higher IGF-1 and irisin concentrations relate to better cognitive and affective outcomes.[52,57,60] GDF15 has also emerged as a potential biomarker of disease burden and progression.[64,65] These associations support a model in which exercise-induced exerkine responses partially counteract deficits in trophic support, neuroinflammation, and mitochondrial stress, consistent with preclinical evidence for BDNF, IGF-1, and irisin.[55,88,89] However, substantial heterogeneity in exercise protocols and sampling methods, along with small, short-term studies, limits links to hard clinical outcomes.

Patients with PD are generally advised to accumulate at least 150 min per week of moderate-to-vigorous aerobic activity such as brisk walking, cycling, swimming, or dancing combined with 2 to 3 weekly sessions of

resistance training targeting major muscle groups.[126,127] Complementary activities that prioritize balance, agility, and flexibility, such as Tai Chi, yoga, or functional multitask exercises, are recommended several times per week, while daily stretching helps maintain joint mobility and postural alignment. Exercise prescription should follow principles of progressive overload, task specificity, safety supervision, and enjoyment to optimize adherence. Early implementation ideally at diagnosis or in the mild stages is recommended, as maintenance of strength, endurance, and balance may help preserve independence and delay disability. When access to in-person physiotherapy is limited, tele-rehabilitation and wearable feedback systems can provide feasible alternatives for ongoing support.[128]

Despite a strong evidence base, important limitations persist. Existing exercise guidelines remain generalized and rarely stratify recommendations by disease stage, comorbidity profile, or physical capacity. European guidance, last updated in 2014, does not reflect recent developments in neurorehabilitation.[107] Most trials are short-term, single-center, and underpowered to evaluate long-term outcomes. Considerable heterogeneity in intervention type, supervision, and participant characteristics complicates synthesis. Mechanistic evidence linking exerkines to clinical change remains preliminary, as most human studies involve small samples and short follow-up durations. In addition, the feasibility of structured PA is limited for a substantial proportion of individuals with PD. In geriatric patients, participation is frequently hindered by fear of falling and low expectation of benefit, both of which reduce engagement in supervised exercise programs.[129] By contrast, among younger individuals with PD, reduced adherence is more often attributed to logistical constraints, including time limitations and inconvenience.[129]

4.1 | Future directions

Future research should prioritize long-duration, adequately powered trials that stratify exercise prescriptions by disease stage, phenotype, and comorbidity profile. Integrating mechanistic biomarkers such as circulating exerkines, muscle imaging, and wearable-based physiological metrics, may clarify how exercise influences neural and muscular pathways. Standardizing intervention protocols and reporting frameworks will improve comparability across studies. Additionally, combining digital health technologies with personalized exercise algorithms could enhance adherence, expand access, and enable real-time monitoring of progression. Finally, translational studies are needed to determine whether modulating specific muscle-derived signaling pathways can slow neurodegeneration or modify long-term clinical trajectories in PD.

5 | CONCLUSIONS

Exercise and preservation of muscle strength are essential components of PD management. Multimodal exercise programs incorporating aerobic, resistance, and balance training are associated with functional and psychosocial benefits across disease stages. Future work should refine stage-specific exercise dosing, develop validated biomarkers of muscle–brain signaling, and integrate digital tools to sustain adherence. Such efforts are needed to determine whether exercise and muscle preservation may influence long-term clinical milestones. Exercise represents a plausible therapeutic pathway in PD with the potential to affect neuroinflammation, sarcopenia progression, and quality of life, warranting continued investigation.

AUTHOR CONTRIBUTIONS

Salomón Páez-García: Conceptualization (equal); formal analysis (equal); investigation (equal); methodology (equal); project administration (equal); writing—original draft (equal). **Edgar Alvarado**: Formal analysis (equal); investigation (equal); methodology (equal); writing—review and editing (equal). **Alejandro Cuevas**: Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal). **Laura Valverde**: Data curation (equal); formal analysis (equal); investigation (equal); methodology (equal). **Eduardo Salinas**: Data curation (equal); formal analysis (equal); methodology (equal); writing—review and editing (equal). **Kevin O'Hara-Veintimilla**: Conceptualization (equal); project administration (equal); supervision (equal); writing—review and editing (equal). **María Cruz Rodríguez-Oroz**: Conceptualization (equal); project administration (equal); supervision (equal); writing—review and editing (equal). **Miguel Germán Borda**: Conceptualization (equal); project administration (equal); supervision (equal); writing—review and editing (equal).

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The authors declare no conflict of interest.

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Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICS STATEMENT

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