A High-Intensity Exercise Boot Camp for Persons With Parkinson Disease: A Phase II, Pragmatic, Randomized Clinical Trial of Feasibility, Safety, Signal of Efficacy, and Disease Mechanisms

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Background and Purpose: The feasibility, safety, and efficacy of a high-intensity multimodal exercise program (aerobic, strengthening, and balance training) have not been well vetted in persons with Parkinson disease (PD). Thus, the primary aim was to determine whether a high-intensity multimodal exercise boot camp (HIBC) was both feasible and safe in persons with PD. The secondary aim was to determine whether the program would produce greater benefit than a usual care, low-intensity exercise program (UC). An exploratory aim was to determine whether these programs affected putative disease-modifying mechanisms.

Methods: Twenty-seven participants (19 men and 8 women) were randomized into 8 weeks of either the HIBC or UC supervised by physical therapists. For feasibility, participation, and meeting, Centers for Disease Control and Prevention (CDC) exercise guidelines were assessed. For safety, adverse events were monitored. For efficacy, the following outcome domains were assessed before and after participation: balance, motor activity, endurance and fatigue, strength, mental health, and quality of life. For disease-modifying mechanisms, circulating brain-derived neurotrophic factor (BDNF) and its genotype, superoxide dismutase, and cytokines (tumor necrosis factor-α, interleukin-6, and interleukin-10) were monitored.

Results: The HIBC was better at attaining CDC guidelines ($P = 0.013$) and spent more minutes in higher-intensity exercise per week ($P < 0.001$). There were no differences in adverse events ($P = 0.419$). The HIBC experienced significant improvements in 7/31 outcomes versus 3/31 in the UC arm. BDNF improved significantly for both groups from pre- to posttests (Ps ≤ 0.041) and an improved anti-inflammatory was observed for both groups.

Discussion and Conclusions: A high-intensity multimodal exercise boot camp was feasible and safe in persons with PD. Compared with usual care, there were no differences in adverse events. Moreover, the high-intensity multimodal exercise program produced more improvement across more domains than usual care. Our results also suggest a possible link between improvement in outcomes and an improved anti-inflammatory milieu.

Video Abstract available for more insights from the authors (see Video, Supplemental Digital Content 1, available at: http://links.lww.com/JNPT/A244).

Key words: *aerobic exercise, balance training, BDNF, cytokines, neuroinflammation*

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INTRODUCTION

Parkinson disease (PD) is a neurodegenerative disease characterized by α-synuclein aggregations called Lewy bodies. The cause of α-synuclein aggregation is unclear, but a complex interaction between oxidative stress and inflammation has been proposed as a potential mechanism.[1-3] Currently, there is no treatment that prevents, slows, or halts the neurodegenerative processes in PD.[4-9] Outside of a cure, finding a neuroprotective treatment is a top priority.[10]

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One neuroprotective candidate is exercise.[11,12] Exercise produces benefits across many body systems, poses few risks, and is relatively inexpensive. In rodent PD models, exercise has been shown to not only decrease symptoms but also to mitigate underlying disease processes.[13-22] In human epidemiological studies, exercise throughout life has been shown to decrease the risk for PD.[23-26] In addition, several meta-analyses and systematic reviews have shown that exercise/physical therapy improves many PD symptoms.[27-30] Exercise may also have positive effects on oxidative stress, which is a prominent feature of PD pathophysiology.[31,32]

Exercise also mitigates the most recalcitrant cardinal sign of PD, postural instability.[33,34] Postural instability often leads to falls and is nonresponsive to PD medications[35] and deep brain stimulation.[36] According to several meta-analyses, the only efficacious treatment for postural instability is balance and strength training exercises.[33,34,37-39] Recent research suggests that high-intensity, challenging balance training is superior to usual care for balance and gait abilities.[40,41]

One potential mechanism that may underlie exercise-induced neuroprotection is brain-derived neurotrophic factor (BDNF), a neurotrophin that increases with exercise.[42-46] BDNF is important in neuroplasticity and may interfere with neuroinflammation and oxidative stress in PD by increasing antioxidant processes, including increasing antioxidant enzymes.[47,48] Taken together, it is possible that a complex interaction among inflammatory processes, BDNF, and oxidative stress may be associated with exercise-induced neuroprotection in PD. Jang et al[49] have shown in a PD mouse model that endurance exercise restores motor function and is linked to the repression of pro-inflammatory cytokines. Therefore, extending our understanding of neuroinflammatory therapies is warranted,[50] as exercise may induce a potentially neuroprotective anti-inflammatory milieu in PD.[51]

The BDNF gene polymorphism, val66met, has been shown to be associated with a decrease in physical activity-dependent BDNF trafficking[52] and is associated with decreased motor performance and neuroplasticity,[53] and impaired motor learning.[54] It may negatively affect rehabilitation and may decrease the positive effects of aerobic exercise on neuroplasticity,[42] and has also been shown to predict poor outcomes in persons with PD.[55] Taken together, these studies suggest the BDNF genotype may explain why some respond well to exercise and others do not. To our knowledge, this has not been explored in a PD exercise trial.

The optimal exercise parameters for persons with PD have not been thoroughly explored. Schenkman et al[56] demonstrated that a high-intensity treadmill training program in de novo PD is feasible and safe. However, only aerobic intensity was explored. Conradsson et al[40,57] demonstrated that a highly intensive balance training program was also safe, feasible, and effective. Hirsch et al[58] reported that high-intensity resistance training combined with balance training afforded more benefit than balance training alone. To our knowledge, a high-intensity multimodal exercise training approach with aerobic, strengthening, and balance components has not been investigated in persons with PD and it stands to reason this approach may afford even greater benefit because it would target a greater breadth of body systems and neurologic mechanisms. Moreover, a multimodal approach is a closer approximation of contemporary physical therapy clinical practice for people with PD. Lastly, continued exploration of high-intensity exercise in persons with PD is warranted since it is considered a primary driver of neuroplasticity.[59]

To address the aforementioned knowledge gaps 4 aims framed this trial. The first primary aim was to test the feasibility of a multimodal high-intensity exercise boot camp (HIBC) in individuals with PD on achievement of US Centers for Disease Control and Prevention (CDC) physical activity guidelines.[60] The second primary aim was to determine whether participation in an HIBC was as safe as a low-intensity, usual care exercise program (UC) based on a modification of the Fitness Counts Exercise Program (FCEP).[61] The secondary aim was to determine whether HIBC participation would produce a signal of efficacy relative to UC across a wide breadth of outcomes (balance, motor activity, endurance and fatigue, strength, mental health, and quality of life) to discover which systems were most responsive to a multimodal exercise approach. The final aim was exploratory on how exercise interacted with putative disease-modifying mechanisms.

METHODS

Design Overview

A phase II, pragmatic, randomized, blinded, clinical trial was conducted wherein participants were randomized into one of two 8-week arms, HIBC or UC. Six different boot camps (3 HIBC and 3 UC) were supervised by physical therapists at 2 community gyms. Participants were tested on and off PD medication before, after, and 6 months later. This trial was considered pragmatic because it had few inclusion/exclusion criteria, was designed with input from individuals with PD (unpublished data), and allowed treatment flexibility and autonomy of choice on exercise modality.[62]

Participants

Participants consented under University of Nevada, Las Vegas Institutional Review Board approval. The inclusion criteria included the following: neurologist-diagnosed idiopathic PD, Hoehn and Yahr stages 1 to 3, 45 to 85 years of age, stable on PD medication and/or deep brain stimulation for 3 months prior to trial, no changes in medication or surgical procedures anticipated for trial duration, commitment to attend at least 3 treatments per week, and clearance from primary physician. The exclusion criteria were inability to stand/walk for 10 consecutive minutes; taking medications that interfere with heart rate response to exercise; significant comorbidities that would preclude exercise participation; and regular exercisers ($\geq$3 exercise bouts per week that would produce $>$60% of estimated maximum heart rate). Participants were recruited using public media from July 2014 to March 2015. Of the 87 who expressed interest, 63 were screened, and 27 were randomized (Figure 1). There were no demographic differences between the groups at randomization (Table 1).

BDNF Genotyping

BDNF genotyping was conducted as outlined in Baer et al.[35] Of the 13 completed HIBC participants, 8 were Val/Val

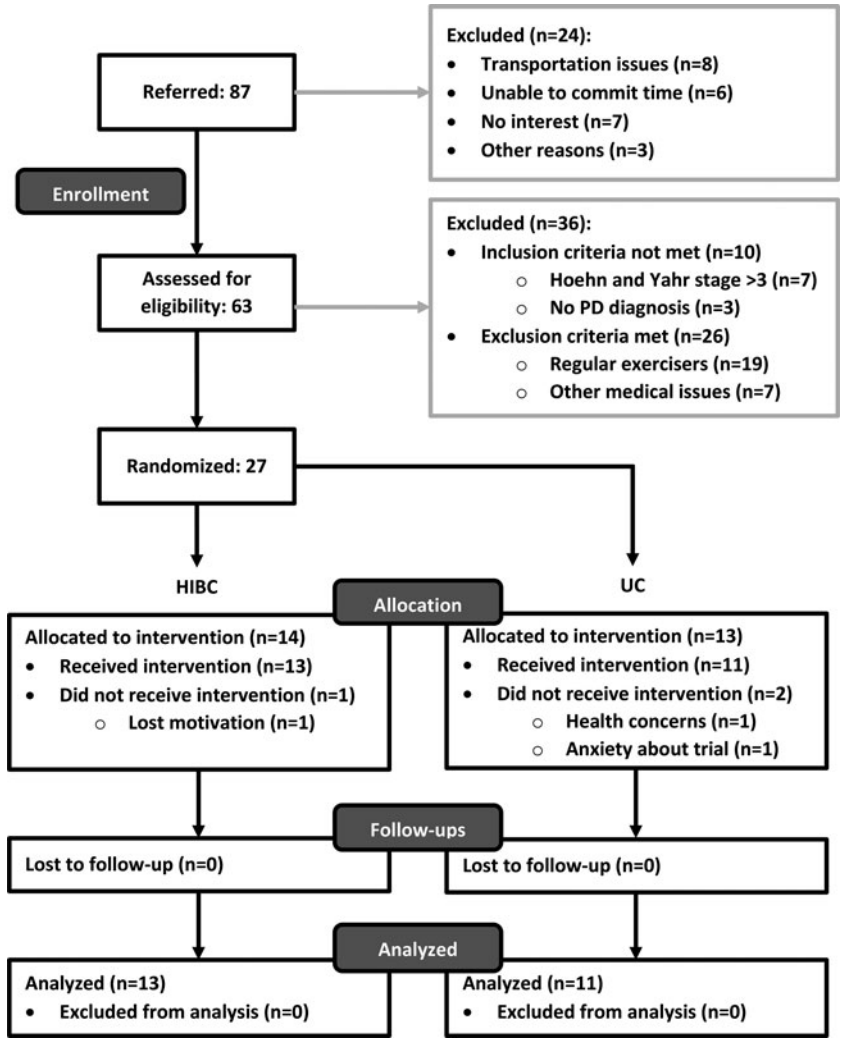

Figure 1. CONSORT flow diagram of participants' progress through the phases of the trial.

and 3 were Val/Met (1 opted out, 1 had poor sample DNA quality). Of the 11 completed UC participants, 7 were Val/Val and 2 were Val/Met (2 opted out). There was no difference in proportions between the 2 groups ($P = 1.000$).

Sample Size

Sample size estimation was based on aim 3, as efficacy was considered important to power future trials and was done using the repeated-measures analysis module (mixed-model factorial analysis of variance) in PASS 14.0 (NCSS, Kaysville, Utah, www.ncss.com/software/pass) at 80% power and $\alpha = 0.05$. To detect an effect size difference of 0.67 (unpublished mini-Balance Evaluation Systems Test [MBT] data from a moderate-high intensity PD group exercise program), 15 participants in each arm were needed. However, based on previous research, we anticipated a 10% to 15% dropout/dropin (participants dropping into another intense community exercise program) rate; thus, 17 to 18 per arm would be needed. Because enrollment projections were not met for the funding timeline, the statistical analyses were changed accordingly (detailed in the Data Analysis subsection).

Randomization and Blinding

After baseline data were collected, participants were block randomized (block size of 8-10 per treatment location; stratified by sex and Hoehn and Yahr stage) into either the HIBC or the UC (Research Randomizer, www.randomizer.org). Participants and outcome assessors were blinded to group assignment and trial aims. Treating therapists were blinded to trial aims and hypotheses.

Interventions

Detailed description of both groups is shown in Table 2 and general exercise instructions are in Supplement A (see Supplemental Digital Content 2, available at: http://links.lww.com/JNPT/A245). Protocol fidelity was addressed through: pretrial training sessions, standardized protocol manual, protocol flowsheets in participant charts, and e-mail/phone reminders. Because this was a pragmatic trial, therapists in

Table 1. Characteristics of Trial Participants After Randomization Using Mann-Whitney With Means and Standard Deviations—Age, PD Duration (Years From Diagnosis), PD Medications (Levodopa-Equivalent Daily Dose), UPDRS III—and χ^2 Analyses With Proportions (Gender, Hoehn and Yahr, Fall History)

Characteristic	HIBC (n = 14)	UC (n = 13)	*P* Value
Age, y	63.5 ± 10.9	64.6 ± 6.0	0.778
Sex			
Male	10	9	0.793
Female	4	4	
PD duration	4.92 ± 5.1	4.70 ± 3.9	0.910
PD medications–LEDD	419.3 ± 389.2	476.7 ± 300.0	0.686
Hoehn and Yahr stage			
Stage 1	2	3	0.339
Stage 2	10	7	
Stage 3	2	3	
Faller history in the last year			
Faller	6	7	0.431
Nonfaller	8	6	
Faller history in the last month			
Faller	11	10	0.759
Nonfaller	3	3	
Fall injury that required medical attention in last year			
Injured faller	3	2	0.759
Nonfaller	11	11	
UPDRS III at baseline (on-medication)	27.5 ± 10.7	36.5 ± 15.0	0.392
UPDRS III at baseline (off-medication)	34.1 ± 12.3	38.8 ± 15.1	0.140

Abbreviations: HIBC, high-intensity multimodal exercise boot camp; LEDD, levodopa-equivalent daily dose; PD, Parkinson disease; UC, a usual care, low-intensity exercise program; UPDRS, Unified Parkinson's Disease Rating Scale.

both arms had leeway to control the intensity and/or the exercise modality provided it fit within trial parameters. Participants had some autonomy of choice for exercise modality. Home exercise was encouraged for both groups (see Supplement A, Supplemental Digital Content 2, available at: http://links.lww.com/JNPT/A245, for home exercise instructions).

HIBC (Experimental Arm)

The HIBC was held 4 days of the week and participants had flexibility to attend 3. In the aerobic component, 70% to 80% of the estimated maximum heart rate (EMHR) was chosen because it is moderate intensity and appropriate for aerobic training. An intensity of more than 80% is closer to anaerobic threshold and, thus, would be difficult to do for extended periods. We encouraged treadmill for the aerobic component because it is functional and improves clinically relevant gait parameters.[29]

UC (Usual Care, Low-Intensity, Control Arm)

UC was a modification of the FCEP, which is a low-intensity, sitting/standing exercise program. Participants committed to attend at least 3 of 4 days per week. This program followed the FCEP closely for the first 2 weeks. Thereafter, low-intensity, suboptimal weight training was implemented.

Outcome Measures and Follow-up

Outcomes for Aims 1 (Feasibility) and 2 (Safety)

For aim 1, 5 feasibility targets were assessed: attendance (majority of participants would average at least 3 sessions per week), aerobic intensity (majority of participants would complete at least 150 minutes per week of moderate-intensity exercise; 70%+ of EMHR), strengthening (majority of participants would average at least 2 days per week of strengthening exercises of the major muscle groups), attrition (dropout rate below 15%), and intrinsic motivation (participants would have average Intrinsic Motivation Inventory[63] scores ≥4 on positively worded items and <4 on negatively worded items on 5 dimensions—interest/enjoyment, perceived competence, effort/importance, pressure/tension, and value/usefulness—with Likert response choices: 1 = not true at all, 7 = very true). In addition, participants rated the following trial-specific statements using the same anchors: I felt safe doing the exercises at the gym; I thought the trainers provided adequate supervision; I am motivated to continue exercising; I feel comfortable doing the exercises on my own now; and the exercise in this trial was intense.

Heart rate was monitored using H7 Polar Heart Rate Sensors (Polar Electro Oy, Kempele, Finland) and an iPad (Apple Inc, 1 Infinite Loop, Cupertino, California) application that allows real-time heart rate display of multiple users (Polar Team, Polar Electro Oy, Kempele, Finland). Time spent in each of the 5 EMHR zones (zone 1: 50%-60%; zone 2: 60%-70%; zone 3: 70%-80%; zone 4: 80%-90%; zone 5: 90%-100%) was tracked.

The safety aim would be met if there were no differences in adverse events between the 2 arms. Adverse events (eg, strains/sprains, delayed onset muscle soreness, cardiovascular events, and falls) were tracked. Falls outside of the treatment were also tracked to ascertain whether treatment-related fatigue made participants more vulnerable to injuries or falls in the intersessions.

Outcomes for Aim 3 (Signal of Efficacy)

Since this was a pilot trial to power a larger trial, a broad net of outcomes was cast under the following domains:

- *Balance*. Balance performance was assessed using the MBT,[64-67] and self-efficacy was assessed using the Activities-Specific Balance Confidence Scale[68,69] and the Catastrophization About Falls Questionnaire.[70,71]
- *Motor activity.* Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ),[72,73] the Movement Disorder Society Unified Parkinson's Disease Rating Scale motor subscales (MDS-UPDRS III),[74] and the Fear of Falling Avoidance Behavior Questionnaire.[75-77]
- *Endurance and fatigue.* Endurance and fatigue were assessed using the 6-minute walk test (6MWT)[78,79] and the Parkinson Fatigue Scale.[80,81]
- *Strength.* This was assessed functionally using the 30-second sit-to-stand test (STS).[82-84] Bone strength and body composition (fat percentage, lean muscle mass) were also collected (see Supplement B, Supplemental Digital Content 1, available at: http://links.lww.com/JNPT/A246).

Table 2. Basic Treatment Details of the HIBC and UC Exercise Boot Camp Arms

	HIBC	UC
Frequency	3 of 4 d per week	3 of 4 d per week
Session duration	90 min	60 min
Program length	8 wk	8 wk
Supervision ratio	1:3-5	1:3-5
Aerobic component	*30 min of moderate-high intensity aerobic exercise at 70%-80% of EMHR* Goal: accumulate 150 min of aerobic exercise per week A. Exercises (therapist and participant discretion, preference to the treadmill): a. Treadmill, overground walking on the indoor track, stair climber, bike, recumbent bike, rowing machine B. Progression: a. Wk 1-2: minimum of 6 bouts of 5 min b. Wk 3-4: minimum of 3 bouts of 10 min c. Wk 5-8: minimum of 2 bouts of 15 min or 1 bout of 30 min	*15 min of aerobic exercise at 50%-65% of EMHR* Goal: accumulate 150 min of aerobic exercise per week A. Exercises (therapist and participant discretion, preference to the treadmill): a. Treadmill, overground walking on the indoor track, stair climber, bike, recumbent bike, rowing machine B. Progression: a. Wk 1-2: minimum of 3 bouts of 5 min b. Wk 3-4: minimum of 2 bouts of 7.5 min c. Wk 5-8: minimum of 1 bouts of 15 min
Strength component	*30 min of strengthening the major muscle groups of the trunk and upper/lower extremities* A. 1RM method was used to estimate the proper intensity (http://www.exrx.net/Calculators/OneRepMax.html) and was recalculated every 2 wk of the trial. B. Dosing: a. Wk 1-2: 50%-70% (3 sets of 10-14 repetitions) b. Wk 3-4: 60%-80% (3 sets of 8-12 repetitions) c. Wk 5-8: 70%-80% (3 sets of 8-10 repetitions) C. Suggested exercises (therapist and participant discretion) a. Chest (eg, chest press and bench press) b. Back (eg, rows and lat pull-downs) c. Trunk (eg, crunches, rotations, and back extensions) d. Upper extremity (eg, bicep curls and triceps extensions) e. Lower extremity (eg, leg press, lunges, squats, knee extension, hip abduction/adduction, step-ups, and heel raises)	*15 min of strengthening the major muscle groups of the trunk and upper/lower extremities* A. Strength training in the first 2 wk followed by the standing, seated, and lying-strengthening program detailed in the Fitness Counts Exercise Program. a. Dosing: 1 set of exercises, 10-15 repetitions B. Starting in wk 3, free weights and machines were introduced. a. 1RM method was used to determine the suboptimal intensity. b. Dosing: 1 set of 10-15 repetitions at no more than 50% of their 1RM C. Suggested exercises (therapist and participant discretion) a. Same as the HIBC.
Balance component	*15 min of balance training* A. Example exercises: a. Anticipatory postural control i. Single-leg stance ii. Tandem stance iii. Medicine ball toss b. Reactive postural control i. External perturbations c. Dynamic gait i. Carioca and side-step walking ii. Walking with change in speed, head turns, and stepping over obstacles d. Sensory orientation i. Eyes open and closed ii. On and off compliant surfaces	*10 min of balance training* A. Exercise: a. Step touch task
Range of motion and stretching component	*15 min of active rest and stretching* A. <3-min breaks, if needed, were interspersed throughout the 90-min training session. B. Breaks were intended to be active and include some stretching or range-of-motion task (at discretion of the therapist and participant). C. Hydration was encouraged.	*10 min of stretching* Hold stretches (gentle pull, subpain threshold) for 10-30 s for the following: A. Axial skeleton (neck, low back, chest) B. Upper extremity (shoulder, elbow, wrist, hand) C. Lower extremity (hip, knee, ankle)
Rest component	None	*10 min of rest* 1- to 3-min breaks were interspersed throughout the session and hydration was encouraged.

Abbreviations: EMHR, estimated maximum heart rate; HIBC, high-intensity multimodal exercise boot camp; 1RM, 1-repetition maximum; UC, a usual care, low-intensity exercise program.

- *Mental health* (Beck Depression Inventory[85-87]) and *quality of life* (Parkinson's Disease Questionnaire-39[88-90]) were also collected (see Supplement C, Supplemental Digital Content 4, available at: http://links.lww.com/JNPT/A247).

Outcomes for Aim 4 (Disease Mechanisms)

To determine the impact on putative neuroprotective mechanisms in PD, levels of circulating BDNF, superoxide dismutase (an antioxidant enzyme), and cytokine concentrations (tumor necrosis factor-α [TNFα], interleukin [IL]-6, and IL-10) were quantified using enzyme-linked immunosorbent assays. Blood BDNF levels were considered an approximation of brain BDNF levels, as it is known to cross the blood-brain barrier.[91] Cytokines have been recently suggested as potential biomarkers for PD.[92,93] TNFα is a primary pro-inflammatory cytokine and a known contributor to neurodegeneration in PD.[94] IL-6 and IL-10 are well characterized as anti-inflammatory cytokines. To evaluate inflammatory milieu, the IL-10/TNFα ratio was used with higher values suggestive of a more anti-inflammatory state. Exercise has been shown to improve the IL-10/TNFα ratio in rats.[95] Blood was extracted via a finger stick between 48 and 72 hours from active participation in the trial or strenuous activity. Peripheral increases in BDNF due to exercise are transient and return to baseline after 15-60 minutes of rest postexercise.[45] However, we were interested in resting levels, which is thought to be related to up-regulation of BDNF gene transcription.[45] All enzyme-linked immunosorbent assays were supplied by eBioscience (Bender MedSystems, Vienna, Austria) and conducted according to manufacturer's protocol.

An additional exploratory piece of this trial was the analysis of participant improvement with exercise based on BDNF genotype. Participants were grouped by genotype and their improvement was compared to the performance-based assessments in aim 3: MBT, MDS-UPDRS III, 6MWT, and STS.

Data Analysis

Data were analyzed using SPSS, version 24.0 (IBM SPSS Statistics for Windows, Armonk, New York) and $\alpha = 0.05$. Between-group comparisons for aims 1 and 2 were analyzed using the Fisher exact test for proportions and Mann-Whitney analyses for means. Because of the small sample size, aims 3 and 4 were analyzed with nonparametric, within-group comparisons rather than between-group comparisons. Cohen's d ($d = \frac{\text{Mean}_{\text{pre}} - \text{Mean}_{\text{post}}}{\text{Standard deviation}_{\text{pooled}}}$) was used for effect sizes. To detect whether motor performance improvements were associated with biological mechanisms, blood change scores (BDNF, SOD, and cytokines) were correlated (Spearman's ρ) with performance-based change scores for the overall sample. BDNF genotype (val/val and val/met) was compared using the same performance-based change scores. Due to a small sample size and similar proportions in both arms, the groups were combined and genotype difference were analyzed using Mann-Whitney analyses. BDNF genotype was also used to see whether there were associations with BDNF, SOD1, and cytokine levels using Mann-Whitney analyses on the pre- and posttest scores as well as the change scores. Because aim 4 was exploratory, it was analyzed with a lower threshold ($\alpha = 0.10$) to detect a signal that would warrant further investigation.

RESULTS

Feasibility

Attendance—Target Met for Both Groups

A majority of participants in both groups met this target (HIBC: 11 of 13 met the goal; UC: 7 of 11 met the goal), $P = 0.357$, with a mean overall attendance over the 8 weeks of 22.9 ± 3.6 days for the HIBC and 20.5 ± 8.8 days for UC.

Aerobic Intensity—Target Not Met in the Clinic But Was for the HIBC When Home Exercise Was Added

The HIBC spent more minutes per week on average in each of the zones 3 to 5 (Table 3). More participants in the HIBC met the aerobic intensity goal of 150 minutes of moderate-intensity exercise per week (8 out of 13) than UC (2 of 11), $P = 0.090$.

Strengthening—Target Met for the HIBC

All 13 participants in the HIBC met the strength training target whereas 0 out of 11 in UC did, $P < 0.001$.

Attrition—Target Met for both Groups

Only 3 of 27 dropped out (HIBC: 1/14, 7.1%; UC: 2/13, 15.4%).

Intrinsic Motivation—Target Met for Both Groups

Intrinsic Motivation Inventory scores were in the higher range: exercise was interesting and enjoyable (HIBC = 6.0 ± 0.9; UC = 5.9 ± 1.1, $P = 0.947$), felt competent to perform the exercise (HIBC = 5.3 ± 1.3; UC = 5.3 ± 1.7, $P = 0.751$), put forth a good effort (HIBC = 6.2 ± 0.8; UC = 5.9 ± 1.2,

Table 3. Means, Standard Deviations, and *P* Values of the Comparisons Between the HIBC and the UC of the Weekly Minutes Averaged in Each Estimated Heart Rate Zone During the Intervention, Including a Combination of Zones 3 to 5, the HEP Averages, and the Combination of Zones 3 to 5 With the HEP

	Zone 1 (50%-60%)	Zone 2 (60%-70%)	Zone 3 (70%-80%)	Zone 4 (80%-90%)	Zone 5 (90%-100%)	Zones 3 + 4 + 5 (≥70%)	HEP (Moderate-Vigorous)	Zones 3 + 4 + 5 + HEP
HIBC	28.6 ± 22.2	98.7 ± 20.1	87.6 ± 38.4	11.3 ± 11.1	0.5 ± 1.2	99.3 ± 7.1	110.2 ± 73.3	221.1 ± 86.8
UC	63.8 ± 28.3	48.0 ± 35.0	6.3 ± 9.9	0.8 ± 2.1	0.0 ± 0.1	7.1 ± 11.8	75.2 ± 91.4	83.1 ± 92.4
	$P = 0.005$	$P = 0.001$	$P < 0.001$	$P < 0.001$	$P = 0.006$	$P < 0.001$	$P = 0.152$	$P = 0.001$

Abbreviations: HEP, home exercise program; HIBC, high-intensity multimodal exercise boot camp; UC, a usual care, low-intensity exercise program.

$P = 0.696$), did not feel pressure or tension (HIBC = 2.4 ± 1.2; UC = 2.1 ± 1.3, $P = 0.357$), and felt that activity was of value and useful (HIBC = 6.4 ± 0.6; UC = 6.3 ± 1.4, $P = 0.584$). Participants felt safe (HIBC = 6.6 ± 0.9; UC = 6.0 ± 1.8, $P = 0.261$), thought the trainers provided adequate supervision (HIBC = 6.8 ± 0.5; UC = 6.8 ± 0.4, $P = 0.785$), were motivated to continue exercising (HIBC = 6.3 ± 1.2; UC = 6.1 ± 1.9, $P = 0.817$), felt comfortable doing the exercises independently (HIBC = 5.9 ± 1.4; UC = 6.5 ± 0.5, $P = 0.587$), and felt the exercise was intense (HIBC = 4.8 ± 1.3; UC = 4.3 ± 1.8, $P = 0.587$).

Safety

There were no differences in the total number of adverse events per participant (HIBC = 1.3 ± 2.0; UC = 0.5 ± 0.9, $P = 0.268$). There were 2 falls by 1 HIBC participant, 1 at the gym (safely lowered to the ground), and 1 on the way home from the gym that resulted in a broken finger. The most common adverse event was pain (excluding delayed onset muscle soreness), but in all cases they were considered minor and resolved without treatment. There were a couple of episodes of dizziness that resolved with rest. There were no differences for delayed onset muscle soreness averages on a scale of 0 to 10 (HIBC = 0.01 ± 0.04; UC = 0.09 ± 0.18, $P = 0.552$) and falls at home (HIBC = 8.3 ± 26.4; UC = 0.1 ± 0.3, $P = 0.641$). There was 1 outlier in the HIBC group, a regular faller before the trial, who reported 92 falls at home during the trial. With that participant's score winsorized to the next nearest value, the mean for the HIBC dropped considerably (HIBC = 1.3 ± 3.1).

Signal of Efficacy

Balance, motor activity, endurance, and fatigue and strength domain results are presented in Table 4. Effect sizes for those variables are detailed in Figure 2. Body composition and bone mineral density results are included in Supplement B (see Supplemental Digital Content 3, available at: http://links.lww.com/JNPT/A246). Mental health and quality-of-life results are included in Supplement C (see Supplemental Digital Content 4, available at: http://links.lww.com/JNPT/A247). The HIBC group had statistically significant improvements in 7 outcomes: MBT both on and off medication (P s ≤ 0.027), IPAQ moderate physical activity ($P = 0.004$), MDS-UPDRS III scores on medication ($P = 0.022$), 6MWT on medication ($P = 0.017$), Parkinson Fatigue Scale ($P = 0.033$), and hip bone mineral density ($P = 0.047$). The UC group had statistically significant improvements in 3 outcomes: IPAQ vigorous activity ($P = 0.026$), 6MWT on medication ($P = 0.015$), and STS on medication ($P = 0.026$).

Disease Mechanisms

Pre- and postdata are detailed in Table 5. Correlations for the change scores of blood concentrations (BDNF, SOD, and cytokines) and the change scores of the performance-based assessments (MBT, MDS-UPDRS III, 6MWT, and STS) are detailed in Table 6.

There were no differences between the val/val and val/met genotypes for all outcome measures except the 6MWT in the on phase ($P = 0.06$) (see Supplement D, Supplemental Digital 5, available at: http://links.lww.com/JNPT/A248). There were no differences in blood concentrations (BDNF, SOD, and cytokines) and performance-based assessments based on BDNF genotype (see Supplement D, Supplemental Digital Content 5, available at: http://links.lww.com/JNPT/A248).

DISCUSSION

Results of this pilot study suggest that a high-intensity multimodal exercise program in persons with PD is feasible and safe, which is consistent with a meta-analysis of studies related to intensive exercise in persons with PD.[96] Despite similar levels of participation, HIBC participants were more likely to attain CDC aerobic and strength guidelines than UC participants. Participants in both arms had a positive experience and felt their programs were safe and enjoyable. Interestingly, both groups perceived that their exercise program was intense with no difference between them. This suggests that relying solely on self-report of intensity may not give an accurate representation of exercise capacity since the intensities were clearly different.

Our data suggest that intensity may matter as the participants in the HIBC group experienced improvements across more domains than the UC participants. Of the 31 outcome measures, HIBC participants improved in 7 whereas UC participants improved in 3 (see Table 4 and Supplement B, Supplemental Digital Content 3, available at: http://links.lww.com/JNPT/A246). The effect size of many of the nonsignificant outcomes indicates that they were underpowered especially in the HIBC group where effect sizes were quite large. HIBC effect sizes were in the positive direction (improvement) in 26 of the 31 outcomes (4 negative direction [worsened], 1 unchanged) whereas in UC there were 20 positives and 11 negatives. There were no statistically significant deteriorations in any outcome for either group. While results from the outcome measures do not give unequivocal evidence that the HIBC was better, they do provide a signal of efficacy that they may be. These findings are consistent with meta-analyses on high-intensity exercise for PD,[96] physical therapy for PD,[27] and balance training in persons with PD.[33] However, it should be noted that few participants in both arms improved beyond the minimal detectable change for outcome measures with PD-derived minimal detectable change values (see Supplement E, Supplemental Digital Content 6, available at: http://links.lww.com/JNPT/A249). In light of this, these results should be interpreted with some caution.

Despite the positive experience from participants in both arms, there was little exercise engagement in the 6-month posttrial period. Imparting a behavioral change regarding participation in regular exercise was a secondary focus, and the lack of participation after the trial is concerning. One inclusion criterion was that participants were "nonexercisers": this may have created a selection bias in our trial. Because participants were nonexercisers, they may have had a low expectation from exercise, which has been reported as the strongest barrier to engaging in exercise among those with PD.[97]

Strength improvements were observed only for UC. The resistance training was more intensive in the HIBC, so this lack of improvement is perplexing. However, the only strength measure was the STS test and, in retrospect, it may not have

Table 4. Mean, Standard Error, and 95% Confidence Interval for Each Outcome Variable Associated With the Balance, Motor Activity, Endurance and Fatigue, and Strength Domains for Each Treatment Arm

Domain	Variable	Arm	Pretest Mean ± SE; 95% CI	Posttest Mean ± SE; 95% CI	6 mo Mean ± SE; 95% CI	Pre- to Posttest *P* Value	Posttest to 6 mo *P* Value
Balance	MBT on (scale range 0-28) Higher score = better balance performance	HIBC	25.3 ± 1.5; 22.1-28.4	26.9 ± 1.4; 23.9-29.8	26.3 ± 1.5; 23.1-29.5	0.016[a]	0.157
		UC	21.3 ± 1.4; 18.3-24.2	22.3 ± 1.3; 19.5-25.0	22.5 ± 1.4; 19.5-25.5	0.598	1.000
	MBT off (scale range 0-28) Higher score = better balance performance	HIBC	23.0 ± 1.3; 20.1-25.9	24.9 ± 1.3; 22.1-27.7	24.4 ± 1.2; 21.9-27.0	0.027[a]	0.157
		UC	19.8 ± 1.6; 16.3-23.4	20.8 ± 1.6; 17.4-24.2	21.2 ± 1.4; 18.1-24.3	0.112	0.596
	ABC (scale range 0%-100%) Higher score = more confidence with balance	HIBC	86.2 ± 3.0; 77.8-94.6	88.0 ± 2.7; 73.7-102.2	79.7 ± 5.7; 65.1-94.4	0.359	0.0504
		UC	79.7 ± 4.7; 71.4-88.1	77.5 ± 9.1; 63.2-91.8	77.7 ± 8.0; 63.1-92.4	0.594	0.906
	CAFS (scale range 3-12) Higher scores = more catastrophization about falls	HIBC	4.9 ± 0.7; 3.4-6.4	5.2 ± 0.7; 3.7-6.7	5.2 ± 0.7; 3.5-7.0	0.524	1.000
		UC	6.7 ± 0.7; 5.1-8.2	7.1 ± 0.7; 5.6-8.6	6.3 ± 1.0; 4.6-8.1	0.271	0.236
Motor activity	IPAQ—vigorous, min/wk	HIBC	77.8 ± 35.9; 15.5-140.1	411.1 ± 309.3; -56.4-878.6	168.9 ± 116.3; -13.3-351.1	1.000	0.109
		UC	33.3 ± 20.9; −29.0 to 95.6	90.0 ± 40.0; −377.5 to 557.5	86.7 ± 35.2; −95.5 to 268.8	0.026[a]	1.000
	IPAQ—moderate, min/wk	HIBC	86.1 ± 49.6; −14.0 to 186.2	218.9 ± 74.5; 104.9-332.9	236.1 ± 127.2; −114.1 to 586.3	0.004[a]	0.441
		UC	85.6 ± 44.8; −14.6 to 185.7	26.1 ± 15.5; −87.9 to 140.1	245.6 ± 195.9; −104.6 to 595.7	0.225	0.225
	IPAQ—walk, min/wk	HIBC	135.6 ± 42.1; 17.9-253.2	581.1 ± 454.9; −104.1 to 1266.3	333.9 ± 193.8; 19.1-648.7	0.450	0.833
		UC	312.2 ± 66.2; 194.6-429.8	153.3 ± 44.6; −531.8 to 838.5	217.8 ± 80.9; −97.0 to 532.6	0.069	0.515
	IPAQ—sit, min/wk	HIBC	507.8 ± 81.2; 340.5 to 675.0	464.8 ± 46.1; 335.6-594.0	453.3 ± 56.7; 284.8-621.9	0.735	0.671
		UC	363.4 ± 76.5; 196.2-530.7	376.2 ± 72.8; 247.0-505.4	393.3 ± 97.1; 224.8-561.9	0.752	0.767
	MDS-UPDRS III on (scale range 0-132) Higher score = more symptoms	HIBC	25.8 ± 4.7; 15.7-35.8	17.1 ± 3.9; 8.8-25.4	16.3 ± 4.8; 6.0-26.5	0.022[a]	0.888
		UC	35.6 ± 4.4; 26.1-45.0	28.4 ± 3.7; 20.6-36.3	24.2 ± 4.5; 14.6-33.9	0.0504	0.123
	MDS-UPDRS III off (scale range 0-132) Higher score = more symptoms	HIBC	32.3 ± 5.0; 21.8-42.9	24.4 ± 5.0; 13.7-35.1	23.6 ± 4.5; 13.9-33.2	0.0502	0.673
		UC	36.5 ± 5.3; 25.3-47.7	33.1 ± 5.3; 21.8-44.5	35.0 ± 4.8; 24.7-45.3	0.106	0.888
	FFABQ (scale range 0-56) Higher score = more avoidance behavior	HIBC	8.9 ± 4.3; −0.220 to 18.0	7.0 ± 4.3; −2.2 to 16.2	8.5 ± 4.0; −0.093 to 17.1	0.153	0.391
		UC	12.3 ± 4.0; 3.8-20.9	11.3 ± 4.1; 2.7-20.0	11.6 ± 3.8; 3.5-19.7	0.624	0.944

(*continues*)

Table 4. Mean, Standard Error, and 95% Confidence Interval for Each Outcome Variable Associated With the Balance, Motor Activity, Endurance and Fatigue, and Strength Domains for Each Treatment Arm (*Continued*)

Domain	Variable	Arm	Pretest Mean ± SE; 95% CI	Posttest Mean ± SE; 95% CI	6 mo Mean ± SE; 95% CI	Pre- to Posttest *P* Value	Posttest to 6 mo *P* Value
Endurance and fatigue	6MWT on, m	HIBC	491.9 ± 32.5; 403.0-580.9	527.0 ± 32.3; 444.5-609.6	515.1 ± 39.7; 395.0-635.2	0.017[a]	0.484
		UC	418.3 ± 48.8; 329.4-507.2	453.7 ± 43.9; 371.1-536.3	440.4 ± 68.5; 320.3-560.5	0.015[a]	0.779
	6MWT off, m	HIBC	456.7 ± 42.2; 365.7-547.8	495.0 ± 51.9; 382.9-607.1	484.6 ± 46.4; 384.4-584.9	0.0505	0.674
		UC	394.6 ± 45.1; 297.2-491.9	440.9 ± 55.5; 321.1-560.7	442.7 ± 49.6; 335.5-549.9	0.093	0.612
	PFS (scale range 1-5) Higher scores = more fatigue	HIBC	3.2 ± 0.4; 2.3-4.2	2.9 ± 0.3; 2.2-3.7	2.8 ± 0.3; 2.1-3.5	0.033[a]	0.889
		UC	2.7 ± 0.4; 1.8-3.6	2.3 ± 0.3; 1.6-3.0	2.8 ± 0.3; 2.1-3.5	0.208	0.0499[a]
Strength	STS on, n	HIBC	11.5 ± 2.0; 7.3-15.7	12.1 ± 1.8; 8.3-15.9	12.6 ± 2.2; 8.0-17.2	0.154	0.336
		UC	7.3 ± 1.9; 3.4-11.3	9.0 ± 1.7; 5.4-12.6	9.2 ± 2.0; 4.9-13.6	0.026[a]	0.713
	STS off, n	HIBC	9.1 ± 1.5; 5.8-12.4	10.6 ± 1.6; 7.1-14.0	11.2 ± 1.7; 7.6-14.8	0.151	0.196
		UC	8.0 ± 1.6; 4.5-11.5	9.1 ± 1.7; 5.4-12.8	9.6 ± 1.8; 5.8-13.4	0.234	0.317

Abbreviations: ABC, Activities-Specific Balance Confidence Scale; CAFS, Catastrophization About Falls Questionnaire; CI, confidence interval; FFABQ, Fear of Falling Avoidance Behavior Questionnaire; HIBC, high-intensity multimodal exercise boot camp; IPAQ, International Physical Activity Questionnaire; MBT, mini-Balance Evaluation Systems Test; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; PFS, Parkinson Fatigue Scale; SE, standard error; 6MWT, 6-minute walk test; STS, sit-to-stand test; UC, a usual care, low-intensity exercise program.

[a]Statistically significant at $P < 0.05$.

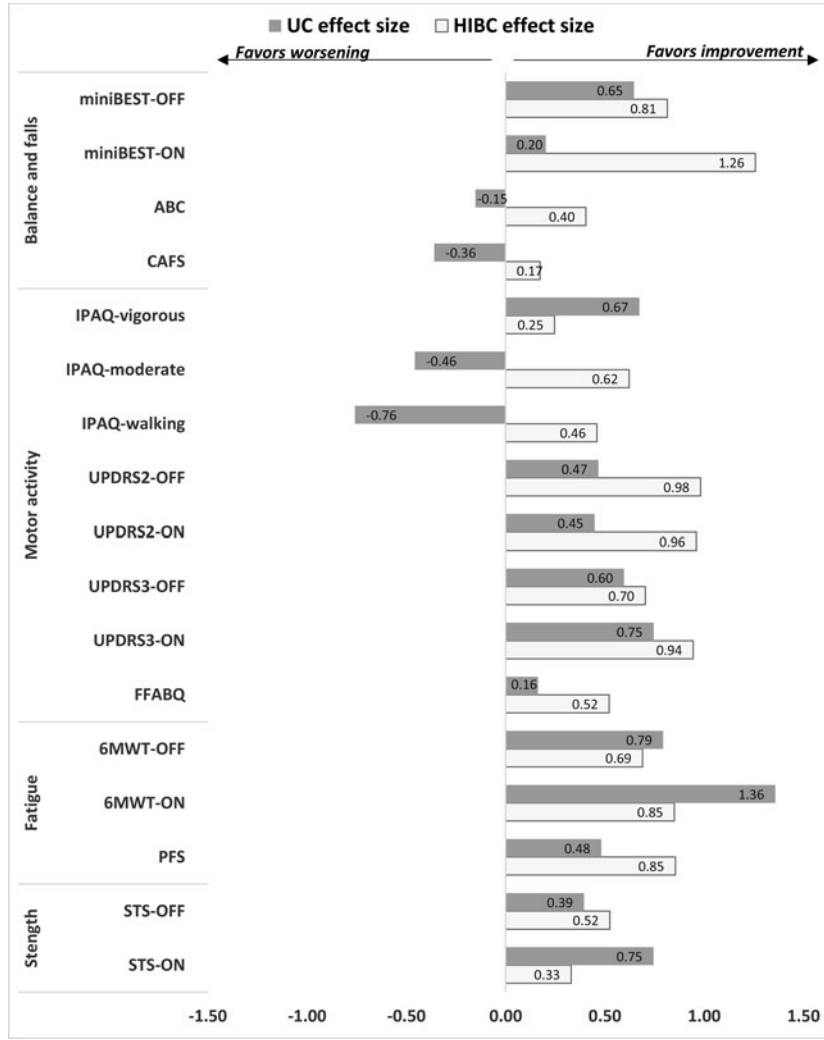

Figure 2. Effect sizes (Cohen's *d*) for the HIBC and UC for pre- to post on all of the outcome measures. A positive effect size value suggests improvement; conversely, a negative effect size value suggests worsening of the outcome over time. HIBC, high-intensity multimodal exercise boot camp; UC, a usual care, low-intensity exercise program.

been appropriate for PD because it is a timed-task. Since PD is impacted by bradykinesia, this may have introduced unwanted variance into the assessment. We recommend that future studies use a nontimed strength test. Also, from a design perspective and to avoid task-specific improvements, using a strength test that was utilized as an exercise in only one treatment arm (UC) is also confounding.

Plasma BDNF improved significantly for both groups and then dropped to lower levels at 6 months compared with baseline. The increase in BDNF is consistent with a recent meta-analysis, which concluded that BDNF increases with exercise in persons with PD.[46] BDNF levels have also been reported to remain elevated for up to 28 days following exercise[98]; however, the length of increase following exercise remains to be determined, as we observed a return to baseline levels at the 6-month follow-up. Research has shown that BDNF is associated with motor impairment and will decrease over time in individuals with PD,[99] and the decrease observed at 6 months may reflect disease progression. Lastly, because there were so few BDNF-met allele carriers, it was likely underpowered and inappropriate to make inferences.

Because inflammatory cytokines promote the death of dopaminergic neurons, they have been implicated in the pathophysiology of PD.[100,101] While there are several animal PD model studies evaluating the interaction between cytokines and exercise,[49,102-104] we are aware of only 2 human PD trials.[105,106] Cadet et al[106] reported that a cycling program increased IL-10, but had no effect on IL-6; we noted a similar trend in our data. Zoladz et al[105] found TNFα to be reduced by 7% as a result of a cycling program. We did not find this reduction in our data; however, our results are consistent with other exercise studies in elderly women,[107] patients with multiple sclerosis,[108] and sedentary and active older adults.[109] Despite starting at a more favorable inflammatory status, an increase of 48% in the IL-10/TNFα ratio was observed in the HIBC, which suggests that it may have created a better

Table 5. Mean, Standard Error, and 95% Confidence Interval for serum BDNF, SOD1, TNFα, IL6, IL10, and IL10/TNFα for Each Treatment Arm

Variable	Arm	Pretest Mean ± SE; 95% CI	Posttest Mean ± SE; 95% CI	6 mo Mean ± SE; 95% CI	Pre- to Posttest *P* Value	Posttest to 6 mo *P* Value
BDNF, pg/mL	HIBC	1960.2 ± 424.2; 1065.3-2855.1	2580.7 ± 391.4; 2025.0-3676.4	365.9 ± 56.3; 247.1-484.6	0.041[a]	0.005[a]
	UC	960.3 ± 447.1; 17.0-1903.6	1697.5 ± 412.5; 827.1-2567.8	279.8 ± 59.3; 154.6-405.0	0.021[a]	0.008[a]
SOD1, ng/mL	HIBC	0.60 ± 0.02; 0.55-0.65	0.60 ± 0.07; 0.46-0.74	0.55 ± 0.03; 0.53-0.64	0.533	0.173
	UC	0.58 ± 0.03; 0.53-0.64	0.68 ± 0.07; 0.53-0.83	0.62 ± 0.05; 0.53-0.72	0.161	0.173
TNFα, pg/mL	HIBC	5.4 ± 3.1; −1.2 to 12.0	5.3 ± 2.6; −0.0.2 to 10.8	8.3 ± 4.5; −1.2 to 17.7	0.807	0.093[a]
	UC	12.3 ± 3.5; 4.9-19.7	12.3 ± 2.9; 6.1-18.4	14.9 ± 5.0; 4.3-25.5	0.889	0.674
IL6 (pg/ml)	HIBC	9.9 ± 1.9; 6.0-13.8	10.7 ± 4.8; 0.5-20.9	8.8 ± 2.6; 3.4-14.3	0.286	0.139
	UC	9.3 ± 2.0; 5.1-13.4	16.5 ± 5.1; 5.7-27.2	9.8 ± 2.7; 4.0-15.5	0.110	0.008[a]
IL10, pg/mL	HIBC	8.4 ± 1.8; 4.5-12.2	11.7 ± 1.8; 8.0-15.4	7.9 ± 1.4; 4.9-10.9	0.071[a]	0.169
	UC	5.1 ± 1.9; 1.1-9.2	11.4 ± 1.9; 7.5-15.4	9.9 ± 1.5; 6.7-13.1	0.066[a]	0.441
IL10/TNFα, ratio	HIBC	1.53 ± 1.02; 0.80-2.26	2.35 ± 1.22; 1.58-3.12	1.43 ± 1.11; 0.64-2.22	0.050[a]	0.114
	UC	0.66 ± 0.49; 0.25-1.07	1.55 ± 1.40; 0.38-2.72	1.54 ± 1.55; 0.24-2.84	0.093[a]	0.889

Abbreviations: BDNF, brain-derived neurotrophic factor; CI, confidence interval; HIBC, high-intensity multimodal exercise boot camp; IL, interleukin; SE, standard error; TNFα, tumor necrosis factor-α; UC, a usual care, low-intensity exercise program.
[a]Statistically significant at $P < 0.10$.

anti-inflammatory milieu. A recent meta-analysis reports elevated levels of IL-6, IL-10, and TNFα in persons with PD compared with healthy controls, which suggests an inflammatory response in PD.[110] Based on this meta-analysis and our results, research on exercise-induced inflammatory changes in PD is warranted.

It is worth noting trends in Table 6 that suggest correlations between motor outcome changes and changes in BDNF, SOD1, and cytokine concentrations. Of particular note, 3 of the 4 outcomes for both BDNF and IL10/TNFα showed a trend toward more association (ie, higher correlation) in the off-medication state than in the on state (Table 6). And, in most cases, those correlational trends were in opposite directions (ie, one was a positive correlation while the other was negative). These data suggest that off-medication motor improvements were associated with more BDNF and a better inflammatory milieu. Presumably, these positive associations were masked in the on state by the symptomatic benefit from the medication. Consistent with this notion is that most PD neuroprotection trials consider the off state as the primary outcome because it is a better indicator of the true, unaltered disease state. However, since the on-medication state is a better reflection of day-to-day status in persons with PD, it is also important to consider.

Limitations

Due to the sample size, the feasibility and safety comparisons should be interpreted with caution. However, one should bear in mind that the exposure between the 2 groups was different (HIBC: 90 minutes per session; UC: 60 minutes per session). Excluding regular exercisers was designed to prevent a ceiling effect but made enrollment difficult because many PD volunteers tend to be active. Another weakness was that 8 weeks may not have been long enough to drive meaningful changes in the outcomes and promote behavioral change. It should also be noted that the CDC goal for 150 minutes was not met for most participants with just the HIBC or UC programs at the gym; it required the addition of the home exercises. In addition, it should be noted that the in-gym exercises were monitored using heart rate monitors whereas the home exercise was self-reported.

Table 6. Spearman's Correlation Coefficients for the Change Scores (Post- Minus Pretest) of Blood Concentrations (BDNF, SOD1, and Cytokines) and the Change Scores (Post- Minus Pretest) of the Performance-Based Assessments (MBT, MDS-UPDRS III, 6MWT, STS) for All Participants Regardless of Group Membership

		BDNF	SOD1	TNFα	IL6	IL10	IL10/TNFα
MBT (+ correlation = improvement as concentration or ratio increases)	On	0.012	0.199	0.031	−0.175	−0.095	−0.127
	Off	0.408[a]	0.122	0.279	−0.036	−0.073	−0.110
UPDRS III (− correlation = improvement as concentration or ratio increases)	On	0.064	0.405	−0.095	−0.244	0.310	0.461[a]
	Off	−0.260	−0.184	−0.239	−0.340	−0.401[a]	−0.479[a]
STS (+ correlation = improvement as concentration or ratio increases)	On	−0.365	0.232	0.402[a]	−0.024	−0.440[a]	−0.349
	Off	0.255	0.123	−0.031	0.355	0.263	0.354
6MWT (+ correlation = improvement as concentration or ratio increases)	On	0.421[a]	0.083	−0.188	−0.175	0.033	0.079
	Off	−0.258	−0.178	−0.394[a]	0.254	0.082	0.242

Abbreviations: BDNF, brain-derived neurotrophic factor; IL, interleukin; MBT, mini-Balance Evaluation Systems Test, MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; 6MWT, 6-minute walk test, STS, sit-to-stand test; TNFα, tumor necrosis factor-α.
[a]Statistically significant at $P < 0.10$.

CONCLUSIONS

The high-intensity multimodal exercise boot camp protocol used in this trial is feasible for people with PD with good compliance and better attainment of CDC aerobic and strength guidelines than UC. Compared with UC, there were no differences in the rate of adverse events. Our results suggest that the intensity may matter as those in the high-intensity arm had more improvements across more domains than UC. Lastly, our results provide preliminary evidence of a possible link between improvement in outcomes and potentially neuroprotective anti-inflammatory conditions.

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