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Effect of high intensity interval training on Parkinson's disease

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EFFECT OF HIGH INTENSITY INTERVAL TRAINING ON PARKINSON'S DISEASE

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ABSTRACT

Parkinson's disease (PD) has devastating effects that include both motor and non-motor impairments. Advanced medicine including pharmacotherapy and surgical options have made it possible for individuals that hold this diagnosis to live somewhat normal lives. As treatment options for this disease have been further investigated, exercise has been found to have benefit by preserving function and quality of life for Parkinson's patients.

Although the positive effects of exercise on Parkinson's patients have been explored, the exact type and how much has not been narrowed down. Not one form of exercise can be said to be more efficacious than another for patients with Parkinson's disease. In addition, exercise has not been thoroughly analyzed in the long term for patients with Parkinson's disease.

An exercise modality that recently has gained popularity due to its benefits is high intensity interval training (HIIT). This modality of exercise allows modifiable and accessible training sessions that improve cardiorespiratory fitness. Its benefit has extended to individuals with chronic disease but not robustly in the Parkinson's population.

The proposed study below will consist of a randomized control trial in people with Parkinson's disease comparing a 24-month HIIT program to a control group.

Symptoms will be scored on the movement disorder society's unified Parkinson's disease rating scale (MDS-UPDRS) at baseline, throughout and after treatment and further analyzed to see if there is clinical significance in using this type of exercise in this population. If HIIT proves its efficacy in this study, it allows clinicians more insight on the most appropriate treatment for Parkinson's patients.

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LIST OF ABBREVIATIONS

ACSM.....American College of Sports Medicine

ADLs ..... Activities of Daily Living

AT .....Anaerobic threshold

ATP .....adenosine triphosphate

CDC..... Centers for Disease Control and Prevention

CSP..... Cortical silence period

DBS .....Deep brain stimulation

EMG ..... Electromyography

FOG.....Freezing of gait

HIIT.....High Intensity Interval Training

HRmax .....Age predicted maximal heart rate

HY .....Hoehn and Yahr

LB..... Lewy Body

MDS-UPDRS ..... Movement Disorder Society Unified Parkinson's Disease Rating Scale

MAO-B..... Monoamine oxidase-B

PD..... Parkinson's Disease

PET..... Positron Emission Tomography

PRE ..... Progressive resistance exercise

RBD.....Rapid eye movement sleep behavioral disorder

RCT .....Randomized control trial

SNc..... Substantia nigra pars compacta

UPDRS ....Unified Parkinson's Disease Rating Scale

INTRODUCTION

Background

Parkinson's disease is a neurodegenerative disorder that is most known for the motor impairment it inflicts on the body. Individuals with PD face progressing resting tremor, shuffling gait and bradykinesia that eventually limit activities of daily living (ADLs). Both pharmacologic and nonpharmacologic treatment options have made PD a more tolerable diagnosis. Among the many therapies found to benefit PD patients, exercise has been found to be effective in improving the functionality as well as quality of life. Exercise training programs have become a part of treatment for chronic diseases as they improve exercise tolerance and quality of life. By interrupting deconditioning that usually follows a diagnosis of a chronic disease, these individuals are able to retain their functional capacity and ability to perform ADLs.[1] To PD patients specifically, exercise seems to have neuroprotective effects as well as promote neuroplasticity, contributing to positive outcomes.[2]

Statement of the Problem

The dose and mode of exercise to be most beneficial to PD patients to this day has not been defined. Research has been done on several different modalities of exercise including but not limited to tai chi, Qigong, karate, dance, and other general aerobic and anaerobic exercise regimens. Little investigation has been performed on how high intensity interval training, an accessible and modifiable exercise type, can be beneficial to PD patients. High intensity interval training, a more modern form of exercise, gained

popularity in the 20th century due to its ability to improve individual's maximal aerobic capacity.[1] This type of exercise can be tailored to an individual's needs, which would be favorable to PD patients as some have more prominent manifestations than others.

Hypothesis

The use of HIIT will decrease progression of motor symptoms in patients with Parkinson's disease with greater efficacy than placebo.

Objectives and specific aims

In conducting this research, the overall goal is to investigate a more modifiable and efficacious exercise therapy for PD patients. If the hypothesis of this study is found to be true, more information will be gathered to choose an appropriate exercise regimen for PD patients that can be accessible from their own home. In addition to accessibility, this form of physiotherapy can be modified to a person's skillset, promoting compliance over the long term. Specifically, this study aims to:

- Determine whether HIIT will bring about a greater decrease in PD motor symptoms compared to a control group
- Based on the findings of the previous objective, be able to make conclusions to where HIIT fits into the existing physiotherapy regimens for individuals with chronic disease

REVIEW OF THE LITERATURE

Overview

Parkinson's disease

James Parkinson first discussed what we now know as Parkinson's disease over 200 years ago in "An essay on the shaking Palsy". He described the condition, then known as shaking palsy or paralysis agitans, as "involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured." His description alluded to the symptoms we use to diagnose Parkinson's Disease today; bradykinesia, resting tremor, rigidity and postural instability.[3]

Even after two centuries the symptoms Parkinson described are still used to clinically assess and diagnose Parkinson's disease today. Since "An essay on the Shaking Palsy" was published, advancements in understanding and defining the disease have taken place, classifying PD as one of many neurodegenerative disorders where these symptoms can also be present.[4] It is known now that bradykinesia, resting tremor, rigidity and postural instability can appear in multiple diagnoses including Progressive supranuclear palsy, Multisystem atrophy, Corticobasal degeneration, Essential tremor, vascular and drug induced parkinsonism. Due to the lack of specificity of these motor symptoms, they are now termed parkinsonism to avoid misdiagnosis.[4] Even though these

cardinal motor symptoms can occur in other disease processes, PD is the leading cause of parkinsonism.[5]

Parkinson's disease is the second most common neurogenerative disease in the world after Alzheimer's disease, affecting about 1 million individuals in the United States or 1% of the population over 60 years old.[5] PD affects 1.6 out of 1000 individuals aged 65, favoring men in a 3:2 ratio. The incidence of PD is low before the age of 50 but greatly increases with age, most notably after 80 years of age.[6] Although evidence for disease preference in specific races or ethnicities is not consistent, prevalence is lower in Africa than in Europe and the Americas.[7]

Depletion of dopaminergic neurons in the substantia nigra pars compacta (SNc) was discovered as a major pathologic feature of PD in the 1950s. Shortly after, positron emission tomography (PET) studies revealed a presynaptic dopaminergic defect in PD by demonstrating impaired [^{18}F]-fluorodopa uptake in striatum in PD patients. The loss of dopaminergic neurons results in disruption of circuits that run through the basal ganglia and, therefore, disturbs subcortical function. This disruption manifests as the motor symptoms we see in PD patients. In the early 1900s, Heinrich Lewy described cytoplasmic inclusion bodies in the remaining dopaminergic neurons of PD patients and coined them Lewy bodies (LB). They are now known as a typical manifestation of PD.[8] An abundant protein in the LBs is α-synuclein and it has been found to be contributory to the pathogenesis of PD. Even though they are common, LBs are not specific to PD and are found in elderly individuals without the disease. [9] Although these are pathological signs of the disease, their etiology remains unclear. [8]

The exact pathogenesis of PD has been investigated for years and still remains indefinite. A multifactorial etiology is most suspected at this point in time with risk factors including aging, environmental and genetic factors, traumatic brain injury, pesticide exposure and reduced physical activity.[9] Over 18 genes have been identified that cause nigrostriatal degeneration and are closely linked to PD. Dysfunction of cellular and molecular mechanisms have also been theorized to contribute to disease progression.[10]

PD has motor and nonmotor manifestations. The motor symptoms, most commonly bradykinesia, tremor, rigidity and postural instability, are often what leads to initial diagnosis. The first motor symptom will occur if dopamine stores go below 60%.[9] Patients usually present to clinicians when they notice a tremor or trouble initiating a movement, but the nonmotor symptoms of PD can precede motor symptoms by 10 or more years.[6] The nonmotor symptoms of PD, though not specific to the disease, can include cognitive dysfunction, hyposmia, GI dysfunction, autonomic dysfunction, sleep disorders and mood disturbances.[9]

Of the motor symptoms, tremor is often the most visible. It often occurs asymmetrically and distally in a limb at first but may move proximally and involve the contralateral side as disease progresses. Tremor in PD is often at rest, not during action, which helps to distinguish it from essential tremor. The clinical manifestations differ between PD patients in which some will have tremor dominant PD while others may have little or no tremor at all.[8]

As disease progresses, the severity of tremor in PD patients may be muted by more pronounced motor symptoms such as bradykinesia and rigidity. Bradykinesia is defined as slowness of initiation of movement and occurs in about 75% of PD patients. PD patients may perceive bradykinesia as weakness when there is no actual motor deficit.[5] It can cause micrographia and decreased amplitude of repetitive movements in PD patients.[9] Patients may experience rigidity as stiffness and vague aching and discomfort.[5] It often causes secondary symptoms including hypomimia, sialorrhea and hypophonia in individuals with PD.[8]

Postural instability is a symptom that manifests later in the course of the disease.[5] It can also cause lateral bending of the trunk as well as flexion of the forearms.[11] Postural instability contributes to gait disturbance, which is another common manifestation of individuals with PD.[6] Gait instability in PD patients is often referred to as "shuffling gait" and is described by small steps, shuffling and reduced arm swing. Freezing of gait (FOG) is a symptom that mixes the cognitive and motor process of PD. It occurs in mentally stressful situations and PD patients feel as if their feet are stuck to the floor.[8]

Although the motor symptoms of PD cause physical struggle, the nonmotor symptoms can create a similar and even more taxing burden. At a later stage in disease progression, 50-80% of PD patients may be affected by PD dementia. Mild cognitive impairment is a risk to 30% of non-demented PD patients.[9] The cognitive impairments seen in PD patients are similar to patients with frontal lobe lesions meaning they can have major issues with executive function such as planning. Other deficits include decreased visuospatial awareness and attention. The pathophysiology that leads to PD dementia and

cognitive deficits is the accumulation of LBs in the cortex of the brain. Cognitive dysfunction is not only a hardship on the individual with disease, worsening their quality of life, but also family and friends.[8]

Sleep disorders are often one of the first nonmotor symptoms of PD patients. Almost all PD patients are affected with some sort of sleep dysfunction. PD patients often suffer from insomnia, excessive daytime sleepiness, and/or rapid eye movement sleep behavioral disorder (RBD), a disorder in which individuals act out vivid and unpleasant dreams with vocalizations and violent movements of extremities.[12] The etiology of sleep dysfunction is multifactorial but it is thought that degeneration of certain sleep pathways are specific to the disease process of PD .[8]

Neuropsychiatric disorders occur in PD patients, most commonly as mood disturbances. Depression occurs in 20-40% of individuals with PD and is associated with poorer emotional status, communication, and ADLs. The cause of depression is multifactorial, arising from PD pathological changes and also from living with a neurodegenerative disease. Research indicates that depression increases mortality in individuals with PD. Anxiety is also common in PD patients in the form of generalized anxiety disorder, panic disorder and situational anxiety related to their motor symptoms. Anti-depressants have resulted in variable and not significant management of anxiety and depression. Current research is being performed that suggests exercise may be a beneficial treatment for mood disorders in individuals with PD.[13] Hallucinations may occur in PD patients, but can also be an adverse event of certain therapeutic PD medications.[5]

PD patients often suffer from dysautonomia. The pathogenesis involves neurodegeneration of the central and peripheral postganglionic autonomic nervous system but is not fully understood. Orthostatic hypotension affects 30-40% of PD patients. Other symptoms of autonomic dysfunction include constipation, urinary incontinence, and hyperhidrosis. In the late stages of disease, PD patients often need daily laxatives due to autonomic dysfunction.[6]

The diagnosis of PD is clinical, being based on a patient's history and physical exam.[5] There have been several scales developed that allow clinicians to define disease progress and severity including the widely used modified Hoehn and Yahr (HY) scale and the unified Parkinson's disease rating scale (UPDRS). The HY scale has been around since 1967 but has since has been modified. It defines disease progression by rating a PD patient's motor and balance dysfunction (Table 1).[14] Its system is based on balance, laterality of the disease and ability to walk independently.[15] The UPDRS scale initially only focused on motor symptoms but now after being updated to the MDS-UPDRS, it includes non-motor issues including sleep, depression, anxiety, dysautonomia and pain, making it a valuable tool for clinicians and in research.[16]

Table 1. Modified Hoehn and Yahr Scale. (Used to rate the progression of disease and degree of disability of PD patients) [17]

"Stage 1.0	Unilateral involvement only
Stage 1.5	Unilateral and axial involvement
Stage 2.0	Bilateral involvement without impairment of balance
Stage 2.5	Mild bilateral disease with recovery on pull test
Stage 3.0	Mild to moderate bilateral disease; some postural instability; physically independent
Stage 4.0	Severe disability; still able to walk or stand unassisted
Stage 5.0	Wheelchair bound or bedridden unless aided"

Many pharmacologic treatment modalities have been explored for PD patients but dopaminergic agents have been found to be most potent.[5] The most effective pharmacologic antiparkinsonism treatment remains to be the dopamine precursor, levodopa, as dopamine deficit is the main pathology of PD. Over 90% of patients with PD have a response to levodopa with the main effect being improvement with motor symptoms and ADLs. Clinicians trial levodopa for three months with a gradual uptitration to at least 1000mg a day or until adverse effects occur before determining the individual does not have an optimal response or a misdiagnosis. Dopamine agonists are considered an alternative first line agent for PD patients due to their lower risk of side effects. Many clinicians use dopamine agonists in conjunction with levodopa in later stages of disease. Dopamine agonists are avoided in patients with dementia because of their possible adverse effect of hallucinations.[5]

Although levodopa is effective in reducing debilitating symptoms of PD patients, its long-term effects are unfavorable. Many PD patients experience adverse effects being on Levodopa therapy such as dyskinesias, uncontrolled muscle movements, and wearing off phenomenon. Clinicians utilize different combinations of therapy sometimes adding a dopamine agonist or monoamine oxidase b inhibitor to lessen side effects and allow optimal response for the PD individual. PD patients may also experience more peripheral adverse effects such as nausea, vomiting, and hypotension.[5]

Other pharmacologic agents that have been used in therapy are anticholinergic agents, amantadine, and selective monoamine oxidase (MAO-B) inhibitors. These agents

are often used in conjunction with a dopamine agonist or levodopa as they do not achieve symptomatic therapy by themselves.[5]

In refractory diseases, surgical therapy has been proven to be effective in PD patients. Deep brain stimulation (DBS) is used in which implanted electrodes are used in the thalamic region of the brain to reduce motor symptoms, specifically tremor. This type of therapy is only used in patients who have had some response to levodopa, as only 10% of patients with proven PD do not respond to this agent and therefore would be less likely to respond to DBS. DBS is not used in early disease due to other options of therapy, risks and expense.[5]

Nonpharmacologic treatments have been more recently investigated for the treatment of PD. Along with support and education, PD patients are now be counseled on exercise as an adjunct treatment to PD as it is suspected to improve quality of life of PD patients.[9] Clinicians may recommend a combination of stretching, strengthening, and cardiovascular fitness, as it presents little risk and possible benefit to PD individuals.[5]

Exercise

There have been great health benefits associated with exercise including reduction of chronic disease, morbidity and mortality in humans.[18] US Centers for Disease Control and Prevention (CDC) defines physical activity as "any bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above a basal level." Exercise falls under this definition with the added goal of maintaining physical fitness.[19] Exercise is divided into categories of aerobic and anaerobic type. The differences

between the two are attributed to their intensity, type of muscle fibers affected and the time associated with performing each.[20]

Aerobic exercise is defined by the American College of Sports Medicine (ACSM) as "any activity that uses large muscle groups that can be maintained continuously and is rhythmic in nature".[21] The muscles being utilized use aerobic metabolism to provide energy in the form of adenosine triphosphate (ATP) from food stores in our body including amino acids, carbohydrates and fatty acids. Commonly known as endurance exercise, the types of exercise that fall under this category include jogging, cycling, hiking, dancing, swimming, and walking. Everyone has an individual aerobic capacity, which is a product of the cardiorespiratory system to supply oxygen (O_2) and the capacity of skeletal muscles to use oxygen effectively. The measure used to determine aerobic capacity is known as peak oxygen consumption or VO_2. The maximum value of this measure can be equated to an individual's physical condition. Optimal levels of aerobic exercise have been proven to be 1 to 2.4 hours over 2-3 times a week to improve one's health. More than that is not shown to be more beneficial than a sedentary individual.[20]

Anaerobic exercise has been defined by the ACSM as intense physical activity of very short duration.[21] In contrast to aerobic exercise, anaerobic exercise is fueled only by energy sources in contracting muscles and not contributed to inhaled oxygen. ATP is then formed anaerobically through the processes of glycolysis and fermentation, yielding far less than an aerobic process. The anaerobic processes mentioned cause lactic acid to build up in utilized muscles. Types of exercise that fall into the anaerobic category include sprinting, high intensity interval training, power lifting, or anything that involve the fast

twitch muscles. A similar measure to VO_{2max} in anaerobic exercise is called anaerobic threshold (AT). This is known as a transition point in which lactate and metabolic acidosis have a sustained increase.[20]

The World Health Organization has recommended exercise to all age groups of people, expressing the benefits of doing physical activity while limiting sedentary behavior outweigh any potential harms. Research suggests exercise may be beneficial and advised for cardiovascular diseases, diabetes, osteoporosis and dementia.[22] There is ongoing research on the health effects on the brain from exercise and therefore improvement in neurodegenerative diseases such as Huntington's, Parkinson's and Alzheimer's. The mechanisms by which better brain health is achieved include neurogenesis, angiogenesis, synaptic plasticity in the hippocampus and improved metabolism of the central nervous system. In humans without disease, consistent exercise is able to enhance learning, memory, executive function and is able to combat age and disease related mental decline through these mechanisms.[23]

High intensity interval training (HIIT), a type of anaerobic exercise, has been growing more popular due to its accessibility and minimal time burden. HIIT became well known in the early 20th century when Olympians started using the method and having success. The premise of HIIT is that a greater amount of work is performed at a higher intensity during a single exercise session which is achieved by alternating high intensity exercise intervals with low intensity exercise or rest intervals. HIIT is pliable and can be customized to certain athletes. For example, a swimmer can perform HIIT with 6 cycles alternating between a 50-meter sprint and slow 50-meter, whereas a more

sedentary person could perform cycles of 30 second bursts of exercise such as push-ups or squats with a 15 second rest period. This type of training can be done anywhere and tailored to individual needs.[1]

HIIT has been proven to achieve maximal aerobic capacity compared to moderate intensity continuous exercise training in individuals. The mechanism of this is unclear but it is thought to be due to longer time to exhaustion as anaerobic fuel stores are being depleted more slowly. In addition to its benefits in healthy people, it has been studied in individuals with chronic disease showing improvements in cardiovascular disease patients with increased functional capacity, quality of life and increased left ventricular ejection fraction. Ongoing research is being performed to evaluate the effects of HIIT on additional chronic diseases including neurodegenerative ones.[1]

Existing research

There has been much success with the current pharmacologic treatments for the motor symptoms of PD. Levodopa and dopamine agonists have made living with the disease possible. However, even with this success, pharmacologic treatments have significant side effects and do not target the nonmotor symptoms that many PD patients face. Exercise has become recognized as an affordable and accessible adjunct treatment to PD patients worldwide. Over the past 10-15 years, several randomized control trials (RCT) and meta analytic studies have investigated different modalities of exercise and the benefits to PD patients.[2] Fox et al suggests that the principles of exercise that enhance neuroplasticity in PD include maximized synaptic plasticity with intensive exercise, improved structural adaptation with complex activities, and an increase in dopamine

leading to promotion of learning and relearning via rewarding activities. They endorse that dopaminergic neurons respond to exercise as well as inactivity so that when exercise is introduced in an early stage of disease its progression slows.[24] Although the benefits of exercise in PD patients has been shown, the optimal dose and type is still uncertain, making personalized approach more difficult.

Although nonmotor symptoms may precede motor symptoms in PD, motor symptoms are usually what leads to a presentation at a clinician's office as they debilitate a patient's everyday life. Many of the studies performed have therefore investigated exercise and its effect on the classic motor symptoms that occur in PD. Aerobic training has been explored in the PD population with favorable outcomes on motor symptoms.[2] Farashi et al led a meta-analysis study regarding different types of aerobic exercise and tremor in PD patients. Types of exercise that were found to reduce hand tremor included tango dancing, cycling, stretching, karate and hand movements in virtual reality.[25] In addition to decrease in tremor, gait ability, motor coordination and grasp strength were improved in a study done by Palmer et al. In 2006, Burini et al conducted a 6 month long cross over RCT comparing aerobic exercise and a medical Chinese exercise, also known as Qihong. The study included 26 participants in H&Y stage II-III that were randomly assigned to two groups: one that started with aerobic training sessions, progressed to 2 months rest and then Qigong group sessions. The other group had the same interventions in an inverted sequence. The aerobic training consisted of cycle ergometer 3 times a week over 7 weeks for a total of 20 45-minute sessions. Qigong was attended in the same frequency and intensity, but had a focus on breathing, stretching, balance, neck and trunk

exercises. The results revealed scores on two assessment tools to be significantly improved: the 6-minute walking test and the Borg scale. This study was able to exhibit that with an aerobic exercise, PD patients are able to tolerate exercise more adequately, and to benefit in the same way a person without disease benefits from exercise.[26]

To date, several studies have been performed on the impact of resistance and power training on hallmark motor symptoms of PD. These short-term studies reveal improvement in bradykinesia and therefore functionality in PD patients. In 2016, Ni et al conducted a 3-month RCT examining power training (high speed resistance training) and its effect on bradykinesia and upper and lower body strength in PD patients of H&Y I to III. Individuals were found to have significant improvement in bradykinesia scores from the power training intervention.[27] In 2020, Vieira de Moraes Filho et al performed a RCT of 40 participants, to explore progressive resistance training in PD patients and its effects on bradykinesia and motor symptoms, measuring outcomes also using the UPDRS and knee extension strength. The training group in this study followed a 9-week strengthening program using weight machines targeting major muscle groups with sets of leg press, chest press, knee extension, and seated row. Similarly, the short-term training program reduced bradykinesia in PD patients with mild to moderate disease.[28] Limitations of these studies include small sample size as well as short duration of exercise intervention, hindering the ability to detect statistical significance as well as see long term effects, respectively. Corcos et al conducted a two-year RCT in 2013, inquiring about progressive resistance exercise in PD patients. This trial consisted of two groups: the progressive resistance exercise (PRE) group that performed weight training and the modified “fitness

counts" group that performed stretching, balance and strengthening program. After 24 months, the UPDRS-III score decreased more with the PRE group than with the modified fitness counts group, demonstrating a significant reduction in motor signs of PD patients. Although the study only had 51 participants, making sample size a limiting factor, its duration allowed it to show long term benefits of resistance exercise for PD patients. [29]

Anaerobic training such as resistance and power training that utilizes weights has thus shown improvement or a decrease in motor symptoms of PD patients both in the short term and long term. The mechanism of the diminishing of motor symptoms was examined by David et al in a 24-month RCT. The effects that progressive resistance training had on PD patients was discovered to partially restore the triphasic electromyographic (EMG) pattern and improve movement velocity, similar to the effects of DBS and pharmacotherapy for PD. The EMG pattern of PD patients has an abnormal agonist and antagonist muscle activation pattern that is unable to be normalized by medications or DBS. The normalization of EMG waves by exercise allows PD patients to avoid adverse effects of medications.[30]

Though most of the research on exercise and PD has been based on motor symptoms and functionality as outcome measures, there has been a few investigations on the nonmotor symptoms of PD. In 2016, Reynolds et al reviewed the potential therapeutic effect exercise, particularly aerobic and resistance training, can have on mood disturbance, sleep and cognition in PD patients. The basis for their analysis was that these outcomes are greatly improved in healthy adults who undergo this type of exercise training.[13] In addition, aerobic and resistance training is beneficial to Parkinson's

patients in terms of functionality and motor symptoms. Most of the studies that have been performed has mood as a secondary outcome. Canning et al performed a 6-month RCT with 231 adults with PD performing strengthening exercise 3 times a week, finding that a secondary outcome was improved positive affect compared to a control group.[13] Subsequent studies either have participants with few depressive symptoms to begin with or lack a primary outcome measure specific to mood, warranting future studies.

Cognitive dysfunction is another nonmotor symptom that PD patients face. Aerobic and anaerobic exercise have been found to improve cognition in healthy older adults. Specific to PD, aerobic exercise may impact executive function.[13] In a review by Petzinger et al, the possibility of recircuiting in the brains of PD patients by the mechanism of exercise induced neuroplasticity is explored.[31] In a study conducted by Cruise et al, 28 individuals with PD were allocated into either an exercise intervention group (aerobic and anaerobic) or control group for 12 weeks. Using neuropsychological assessments, they were able to gauge what parts of the brain, frontal, frontotemporal or temporal, were being utilized. Although no specific effects on mood were found, exercise had a benefit for cognitive function via improvement of frontal lobe executive function.[32]

Even with the encouraging evidence of the benefits of HIIT, it has not been thoroughly researched in patients with PD. This may be associated with the challenges for PD patients to engage in high intensity exercise.[2] In 2008, Fisher et al performed an 8-week preliminary RCT that compared high intensity, moderate intensity and zero intensity exercise in PD patients using the modality of body weight-supported treadmill training. Their objective was to collect preliminary data on how high intensity exercise

affects motor performance and corticomotor excitability of PD patients. A total of 30 PD individuals of Hoehn and Yahr (H&Y) stages 1 or 2 completed 24 sessions within the 2-month study and were assessed with a self-selected pace walking test, sit to stand test and postintervention UPDRS. The findings supported that there was a small improvement in total and motor UPDRS in all groups. All groups improved their motor tests, but the high intensity group most notably improved their gait and sit to stand test most notably by 4.4% and 4.7% respectively. In the sit to stand test, ground reaction force was noted to be asymmetric in both zero and low intensity groups. In the high intensity exercise group, a 33% increase in symmetry suggested that the exercise intervention promoted a more equal distribution of body weight in the lower legs. Another parameter measured in this study was of corticomotor excitability, to determine whether the central nervous system was affected by the level of intensity of exercise. In the high intensity group, there was lengthening of cortical silent periods (CSP), which is notably shorter in PD patients. Lengthening of the CSP was not consistent in the zero or low intensity groups. As this was a preliminary trial, it failed to note any significance in its findings and statistical analysis included only descriptive analysis using mean and standard deviation. The RCT did however demonstrate PD patient's ability to engage in high intensity exercise, providing framework for future investigations.[33]

With the lack of evidence on high intensity exercise and its effect on PD, in 2018, Schenkman et al continued their research on high intensity treadmill exercise in PD patients through the Study in Parkinson Disease of Exercise (SPARX). It was reconfirmed that high intensity treadmill exercise is feasible for Parkinson's patients, but

needs further investigation to assess its effect on certain motor symptoms of PD. The design study included 128 individuals with PD of H&Y 1 and 2 who participated in a high intensity, moderate intensity or wait list control treadmill program for 6 months. Schenkman et al hypothesized that out of the 4 day a week treadmill regimen, participants would adhere to 3 days a week. The null hypothesis was that either moderate or high exercise intensity would result in at least 3.5 points less change on the UPDRS motor score at the end of the 6-month study. The null hypothesis for the high intensity arm could not be rejected by statistical analysis, but the exercise intervention did slow down worsening on the UPDRS motor score by a clinically meaningful threshold.[34]

Resistance and aerobic training have provided great insight and evidence on how they can be adjunct treatment for PD patients, but high intensity, specifically HIIT, has yet to be significantly investigated in the PD population. The minimal studies that have been performed focus on treadmill exercise, which not everyone may have access to. The pliability of HIIT allows many variations of exercise that may be more accessible and time effective for PD patients. The concern is raised that PD patients may not be able to participate in such vigorous exercise protocols because of the evidence they are more sedentary at baseline.[2] This being said, the flexibility of HIIT makes it possible to construct a low time burden, personalized to an individual's ability, exercise plan.

METHODS

Study design

The proposed study will be a 24-month randomized controlled clinical trial comparing two groups of participants, a control group and HIIT group.

Study population and sampling

The population to be studied in this trial are patients with diagnosed Parkinson's disease specifically early to moderate disease (stages I-III on the modified Hoehn and Yahr scale).[17] Patients will not be included if they have any poorly controlled comorbid medical conditions that hinder someone's ability to reach high intensity exercise such as pulmonary conditions of COPD and asthma, severe dyskinesias from current PD medications, other chronic musculoskeletal injuries, or orthopedic conditions. Exclusion criteria will also include cognitive impairment that will be assessed by the Mini mental status examination, requiring a score of >24. If patients are on previously prescribed PD medications, they should remain on them but instructed not to have any dose adjustments or addition of new agents during the duration of the study. Patients of all demographics (gender, age, ethnicity, etc.) will be included. An appropriate sample size of at least 52 patients, 26 in the placebo group and 26 in the treatment group, will be selected. With this sample size an alpha value of 0.05 and a beta value of 0.2 will be achieved.[35]

The bradykinesia subscale of the UPDRS scale will be used to do a motor examination rating the slowing, amplitude and rhythm of finger taps, hands movement, rapid alternating movements of hands, leg agility and body bradykinesia and hypokinesia.

Each item will be scored 0-4 and be assessed by a trained neurologist who specializes in movement disorders.

Treatment (or intervention)

The intervention performed in this study will be the initiation of a HIIT program three times a week for roughly 20 minutes a session. In the first 6 months, the program will be designed for a sedentary population in a 2:1 rest ratio and then progressed to a more advanced program for the duration of the study. A personal trainer will work with participants at first 3 times a week but by 6 months observation will be tapered down to twice a week. Twelve months into the program, a trainer will observe once a week and then at 18 months participants will be doing the workouts on their own. The sedentary program will consist of a 30-second-high intensity interval of an exercise followed by a 15 second rest period. The exercises included in the regimen are push-ups, squats, butt kicks, tricep dips, side lunges, jumping jacks and sit ups. Patients will perform each of the high intensity exercises for 30 seconds followed by a 15 second rest period in between, making up one cycle. The session will be comprised of 3 cycles with a 1-minute rest between each cycle. If patients do well the first month barring any injuries or complications they will move onto the more advanced exercise therapy which will be structured in a 2:1 work to recovery ratio as well but will consist of 20-second-high intensity bouts of exercise followed by a 10 second rest period. These exercises will be more advanced including squat jacks, push-ups, star jumps, mountain climbers, burpees, high knees and lunges. There will be 4 cycles during this phase of training.[1]

For the control group, they will perform home based exercise with guidance from the National Parkinson Foundation *Fitness Counts* program.[36]

Study variables and measures

The independent variable of this study is the intervention of the HIIT program. The dependent variable to be analyzed will be the bradykinesia scale portion of the UPDRS.

Recruitment

Potential subjects will be referred to this study by movement disorder specialists from Boston Medical Center, Massachusetts General Hospital and Tufts Medical Center. The referred individuals will have an already existing diagnosis of PD that has affected their motor function. After referral, a telephone screen will rule out exclusions related to other chronic conditions. Prior to the trial, potential participants will perform a submaximal graded exercise test to determine if they could exercise safely at intensities of up to 85% of age predicted maximal heart rate (HRmax).[34]

Data collection

Individuals who agree to participate will be asked to take part in several tests to assess their baseline of disease before the clinical trial. Participants will complete an initial MDS-UPDRS prior to the study, and every 6 months until the end of the study. Over 24 months participants in the intervention group will follow their assigned exercise regimen and advance as tolerated. The training program will be done at participants' homes as no use of exercise equipment will be needed. Each participant will wear a heart rate monitor that will measure their HRmax and duration of exercise. This data will be to ensure each

participant is hitting a HRmax of at least 85% so that the exercise is considered high intensity as well as keeping track of their exercise sessions.

Data analysis

Data will be grouped based on participant's age and Hoehn and Yahr scale. Mean and standard deviation will be calculated for both the control and treatment groups. T tests will be used to compare the results of the MDS-UPDRS scores between the control group to the treatment group. Any variation within the groups will be analyzed by ANOVA. Patients that drop out or are unable to continue in the study will be reported in writing as a total number in the experimental and control group.

Timeline and resources

The study proposed could reasonably start in January 2023. This tentative start date would allow sufficient time to get approval from the IRB, recruit participants and acquire the necessary resources. The only prior test needed from participants is the graded exercise test which can be done a few weeks before data collection starts.

Human resources needed to run the study include one primary investigator for general management and oversight. An exercise trainer with experience with PD patients for each of the participants in the treatment group will also need to be recruited. At least three clinicians will be needed to assess severity of PD in participants prior to the start of the study. In addition, one statistician will be needed to assist and verify data analysis.

The study will be conducted over a time span of 24 months. Participants will return to Boston medical Center every 6 months to assess continuing members and gather MDS-UPDRS scores. As data will be collected and analyzed throughout the study, post-

experimental analysis will take no longer than 6 months post completion date. The only materials needed will be a personal heart rate monitor for each participant. No exercise equipment will be necessary as the proposed training plan focus on body weight exercises.

Institutional Review Board

An application for full board approval of the Institutional Review Board of Boston University Medical center prior to patient recruitment will be submitted due to the use of human subjects and the risk of harm during exercise.[37]

CONCLUSION

Discussion

One of the strengths of the study is the ability to perform workouts at home with no equipment. Subjects will be in the comfort of their own home or backyard, not having to worry about getting to and from a certain place. This training allows individuals to learn how to work out in an accessible and affordable way that will continue to be so even after the experiment ends. The design of having the training program at home allows patients to incorporate it into their daily life and therefore may lead to overall better compliance. Another strength is having exercise trainers coming to the individual's home for training sessions. This allows opportunity for patients to learn the correct way to execute each exercise to prevent future injury as well as accountability to do the workout sessions. As the study goes on and the exercise trainers are tapered, it allows PD patients to become independent in their exercise, preparing them for continuation after the study is complete.

While there are many strengths to this study there also comes limitations. The lack of camaraderie that some people thrive on in group workout settings will be lacking in this specific experiment due to the training sessions taking place at home. It may feel isolating to some patients only having a personal exercise trainer with them during their sessions. Another limitation is our control group as it would be unethical to stop them from exercising for a 24-month trial. In addition, measuring our results with solely the MDS-UPRDS will be limiting. This parameter focuses on motor and some non-motor components of PD but lacks the ability to assess functional changes (gait or falls),

physiologic fitness or disease modifying effects such as neuroplastic or neuroprotective changes.

A goal of this study is to allow the results to be generalized to all of the PD population. Boston Medical Center as a recruitment site works in favor of generalizability due to its diverse patient population as a safety net hospital. In addition, HIIT exercise can be performed by anyone with its focus on body weight exercises and lack of equipment.

Summary

Based on the literature review, exercise has benefits to the PD population, but its full mechanism is not fully understood. Functionality, improvement and slowing of symptoms and even non-motor symptoms of PD have been demonstrated to show improvement with physical activity. The existing literature in multiple case studies shows little clinically significant evidence and a lack of exact type or duration of physiotherapy that allows these benefits for PD patients. Often the modalities of exercise investigated require equipment and other resources that are not available to a majority of the population.

High intensity interval exercise has been advancing since its adoption by Olympic athletes with beneficial results. Since then it has been the subject of several investigations in patients with chronic diseases, showing benefit in cardiorespiratory fitness as well as slowing of disease progression. HIIT programs are able to be accessed by everyone and can be modified to a person's certain fitness level and strengths. This makes it an ideal form of activity for a chronic neurodegenerative disease such as Parkinson's disease.

If the hypothesis is confirmed, HIIT is an affordable and attainable adjunct to add to the treatment plans for PD patients. In improving the progressive motor symptoms of PD, it allows patients to keep their independence and maintain their own safety. Establishing its benefit on motor symptoms will open the door to future studies utilizing HIIT programs in the PD population to see its effect on the actual disease and its other manifestations.

Clinical and/or public health significance

Chronic diseases in our country continue to gain prevalence as the life expectancy gets higher, meaning more people are living with PD each year. The disease burden has greatly decreased with modern medicine allowing PD patients to live more independently and with less debilitating factors that come with the diagnosis of PD. With a longer life expectancy, however, PD patients face other problems including side effects from medications and other non-motor symptoms of the disease. Exercise is the newest addition to treatment recommendations that some providers have been utilizing but the clinical benefits have not been solidified.

Patients diagnosed with Parkinson's disease may suffer side effects with commonly used medications. The medication that initially was supposed to alleviate the motor impairment PD poses can cause a whole new issue. Patients can go backwards after treatment to a more dependent version of themselves. The benefits of exercise, particularly HIIT, may improve motor symptoms so that less of PD medication is needed. By further exploring this form of exercise, treatment recommendations for PD patients

can be fine-tuned to meet the populations needs and target specific manifestations of this disease.

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