The Therapeutic Effects of Forced Aerobic Exercise in Multiple Sclerosis

Study Protocol

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Research Strategy
Background and Significance

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) affecting 2-3 million people worldwide and an estimated 1 million in the United States. Pathophysiologically, MS is characterized by axonal or neuronal loss, demyelination, and astrocytic gliosis. The neurodegenerative component of MS (axonal and neuronal loss) is thought to be the underlying mechanism associated with clinical disability. The mechanisms associated with axonal loss are primarily due to mitochondrial dysfunction occurring in both the acute and chronic phases of the disease, and decreased myelin trophic support, more commonly found in the chronic disease state. A plethora of disease-modifying pharmacological treatments have been developed primarily targeting neuroinflammation but not neurodegeneration. Therefore, the greatest unmet need is the identification of treatment approaches that incorporate neuroprotection and remyelination to delay, prevent, or reverse disease progression.

While a myriad of disease-modifying pharmacological treatment options have been discovered for the treatment of MS, rehabilitation research has neglected to identify innovative interventions that are disease-modifying or result in meaningful, long-term functional change. Current approaches to MS rehabilitation involve therapies that address deficits at the impairment and functional limitation level of the disability spectrum. Strength training, stretching, and functional mobility training aimed at improving walking ability and balance are foundational approaches commonly used in clinical practice environments. While all of these are considered supportive in nature, none are effective in modifying the long-term prognosis of MS. Numerous systematic reviews and meta-analyses have been conducted to examine the evidence of the effects of exercise training on physical fitness, fatigue, gait, balance, cognition, depressive symptomology, and self-reported quality of life. In general, targeted, task-specific interventions have been found effective in improving the consequences of MS: strength training improves strength, gait training improves gait, balance training improves balance, and so on. From a mechanistic perspective, improvements in these domains are likely induced by a training effect on the peripheral neuromuscular system. However, none of these training approaches target the CNS and studies investigating exercise efficacy in MS have not been designed with the end goal of altering CNS function. Thus, the potential for exercise to aide in neuroprotection, neuroplasticity, and to attenuate neural inflammation has not been tested empirically in persons with MS.

Scientific Premise

Several hypotheses have been proposed explaining the relationship between aerobic exercise (AE) and the global behavioral responses observed related to brain function[1-7]. Aerobic exercise has been shown to increase cerebral blood flow, promote angiogenesis, and is associated with increased levels of dopamine, brain-derived neurotrophic factor (BDNF) and Insulin-like growth factor-1, all of which have been implicated in neuroplasticity and enhanced learning[1, 8-11]. Increased concentrations of endogenous neurotrophins have been implicated as the mechanism for improved cognition, learning, and memory in healthy older adults[2, 3, 6]. Animal studies have shown enhanced motor training and recovery with high-intensity AE, resulting in lasting neuronal changes within the brain[10, 12]. In stroke rehabilitation, it has been posited that increased levels of neurotrophic factors and neurotransmitters are critical in facilitating the neural reorganization that likely underlies motor recovery[4, 9, 10, 13, 14]. Therefore, there is substantial scientific rationale to hypothesize that AE, which results in increased levels of neurotrophic factors and neurotransmitters, could be used to “prime” the CNS to further enhance motor recovery post-stroke.

Klotho, a proposed anti-aging protein, has been identified to have a neuroprotective effect by inhibiting oxidative stress and promoting oligodendrocyte maturation, myelination, and (importantly) remyelination in mouse models.[15-17] In mice, the upregulation of Klotho revealed reverses in age-related deterioration in the physiological functioning of numerous tissues.[18] It is known that Klotho levels decline with age in healthy humans resulting in decreased resistance to oxidative stress.[19] It has been shown that this decline in serum

Klotho levels can be combatted with aerobic exercise. In healthy patients, levels of serum Klotho were shown to increase, both acutely and long term, following high-intensity exercise.[20, 21] Levels of serum Klotho were also higher in highly trained athletes compared to healthy controls.[22] Currently, it is unknown whether patients with MS can have increased serum Klotho levels in response to exercise, and whether this contributes to the positive effects of exercise seen in this population. Furthermore, it is unknown if patients with MS are capable of achieving an exercise intensity high enough to trigger increases in serum Klotho.

Advances in magnetic resonance imaging (MRI) techniques now allow for the assessment of structural and functional connectivity, through diffusion tensor imaging (DTI) and resting state functional MRI (rsfMRI).[23] DTI measures can be used to assess tissue integrity, and are thought to reflect the degree of demyelination and axonal loss in pwMS.[24] RsfMRI measures the strength of connection of functional pathways throughout the CNS, and thus changes may reflect neuroplasticity. The transcallosal and posterior cingulum bundle pathways represent motor and cognitive functions, respectively, and changes in structural and functional connectivity within these pathways have been proposed as a metric for longitudinal evaluation of functional decline in pwMS.[23] In mouse models of stroke, voluntary exercise led to enhanced myelin density recovery (measured by DTI) and increased functional connectivity (measured by rsfMRI).[25] However, it is unknown whether exercise promotes changes in structural or functional connectivity in pwMS, or whether these may correlate with positive effects of exercise seen in this population.

Innovation

It is well documented that exercise participation elicits general benefits including improvements in physiological variables such as strength, aerobic capacity, walking; symptoms such as fatigue and pain; and quality of life.[26] As such, exercise recommendations have been created with these primary endpoints in mind, potentially overlooking the ability of exercise to influence CNS function. Substantial evidence exists both in animal and human literature that aerobic exercise (AE) training may facilitate neuroplasticity. As it relates to MS, AE has the potential to enhance neuroplastic markers and attenuate neural inflammation, both critical targets in the restoration of function.[27, 28] However, previous studies investigating exercise efficacy have not prescribed exercise of sufficient intensity to elicit the neurophysiological effects necessary to alter CNS function. Forced exercise is an approach in which the voluntary efforts of the individual are augmented to allow them to exercise at a higher intensity than what they can achieve on their own. It is hypothesized that individuals with MS cannot sustain high rates of voluntary exercise (VE) necessary to trigger the endogenous release of neurotrophic factors which underlie neuroplasticity; therefore, forced exercise (FE) is necessary to overcome physical, behavioral and logistical barriers to improve motor function, QOL and participation in life activities.

Approach

The aim of this project is to conduct a pilot study to investigate the feasibility and initial efficacy of applying FE to individuals with MS to improve motor function, cognitive function, and QOL.

Experimental Overview: A pilot study is proposed in which 20 individuals with MS presenting with an Expanded Disability Status Scale score between 2.0 and 6.5 will be eligible to participate. Participants will be screened using the American College of Sports Medicine Exercise Preparticipation Health Screening algorithm. The potential participant's physician will be notified of the study protocol and their patient's desire to participate. Eligible participants will undergo clinical and biomechanical assessments evaluating lower extremity function, processing speed, memory, and self-reported quality of life at baseline and post-intervention. Following baseline testing, participants will be randomized to undergo FE (n=10) or VE (n=10). Randomization will be stratified based on EDSS level (2.0-4.0 vs. 4.5-6.5) to facilitate comparable levels of disability in both groups. Participants in both groups will attend exercise sessions twice a week for 12 weeks. The FE intervention will consist of forced-rate aerobic exercise on a stationary semi-recumbent bicycle. Target cadence will be 80 revolutions per minute (RPM). Should the participant not tolerate the 80 RPM cadence, a self-selected cadence will be used initially, and increased by 5 RPM each session until the target cadence of 80 RPM is achieved. The VE intervention will be identical to FE, except participants will cycle at a self-selected cadence on a semi-recumbent stationary cycle ergometer without assistance from the motor. Aerobic intensity for both groups will be monitored continuously throughout the exercise using a heart rate chest strap. Target heart rate will be prescribed at 60-80% of the individual's age-predicted maximum. Following a 5-minute

warm-up, participants will complete a 35-minute main exercise set with the goal of maintaining their heart rate within the prescribed target zone. A 5-minute cool-down will occur immediately at the end of the 35-minute main exercise set. For the FE group, the cadence during warm up and cool down will be 15-20% less than the target cadence for the main exercise set (80 RPM) during the main exercise set. Water will be provided to the participant ad libitum, but all will be encouraged to drink 16-24 ounces during the exercise session. Cooling vests will be available to participants to avoid overheating as indicated. Rest breaks will be provided as requested, but all participants will be encouraged to progress to an entire 45-minute session without rest breaks.

Recruitment and Sample: Physicians and advance practice clinicians within the Mellen Center who would otherwise prescribe physical therapy to their patients will provide prospective participants with a study brochure. Should they express interest in learning more about the study, the study coordinator will call them to follow up. The study team may use MyChart as a way to contact eligible patients with an IRB approved flyer and/or brochure. Twenty-four patients will be recruited for this pilot feasibility study.

Aim 1: To determine the feasibility of applying FE or VE training to individuals with MS. Primary outcomes to determine feasibility will include measures of exercise compliance (percent of sessions attended, time spent exercising, time spent within target heart rate zone) and the absence of adverse events. The secondary outcomes will include change in levels fatigue and physical activity.
Hypothesis 1: Participants will comply with the FE or VE intervention (exercise frequency, time, and intensity) at ≥90% of the prescribed values and will present with no worsening fatigue or levels of sedentary activity following the FE or VE intervention.
Aim 2: To determine the effects of a 12-week FE or VE intervention on motor function. The primary outcome is change in biomechanical characteristics of gait. Secondary outcomes include changes in walking capacity, balance, manual dexterity test (MDT), and timed up and go (iTUG).
Hypothesis 2: Improvements in gait biomechanics and walking capacity will be observed following the 12-week FE intervention.
Aim 3: To determine the effects of a 12-week FE or VE intervention on non-motor function. The primary outcome measuring QOL is the change in the PROMIS-29 while the Multiple Sclerosis Performance Test (MSPT)[30,31] and two measures of episodic memory (California Verbal Learning Test [CVLT], Brief Visuospatial Memory Test [BVMT]) will serve to measure cognitive function.[29, 30]
Hypothesis 3: Improvements in QOL and cognitive function will be measured following 12-weeks of FE and VE.
Aim 4: To investigate the role of Klotho in promoting neuroprotection following FE or VE in pwMS. For this exploratory aim, our outcomes will include change in serum Klotho expression acutely (pre- to post-exercise) and long-term (from baseline to post-intervention). We will also assess serum levels of neurofilament light (sNfL), a marker of axonal damage and biomarker of disease progression.[31, 32]
Hypothesis 4: The forced exercise group will achieve a higher level of exercise intensity, therefore promoting enhanced Klotho expression acutely (immediately post-exercise) and long-term (from baseline to post-intervention), which we hypothesize will correlate with lower levels of sNfL (i.e. enhanced neuroprotection) and improved motor and non-motor outcomes analyzed in aims 2-3.

Pilot Study Methodology

Screening: Individuals ages 18-75 with MS presenting with an Expanded Disability Status Scale score between 2.0 and 6.5 will be eligible to participate. Participants will be screened using the American College of Sports Medicine (ACMS) Exercise Preparticipation Health Screening algorithm. The potential participant's physician will be notified of the study protocol and their patient's desire to participate.

Forced Aerobic Exercise (FE) and Voluntary Aerobic Exercise (VE) Interventions: Individuals will participate in a supervised exercise protocol on a stationary semi-recumbent cycle ergometer, comprised of 45-minute sessions. Target heart rate (HR_{target}) zone for each subject, based on ACSM recommendations, will be determined based on age- and sex-based norms. All participants will be instructed to exercise within their HR_{target} during the 35-minute main exercise set, occurring between a 5-minute warm-up and cool-down phase. Those randomized to the FE group will be administered the high-rate AE protocol based on methodology used

in our previous studies on a custom-engineered cycle that augments cycling cadence.[33-35] Those randomized to the VE group will exercise at their self-selected cadence without assistance from the motor. As in our previous studies, if any patient exhibits signs of cardiac distress or hemodynamic compromise, the session will be stopped immediately, and the on-call physician will be paged to the laboratory. All training will be under the supervision of a physical therapist, exercise physiologist, or medical student certified in Basic Cardiac Life Support.

Data Variables

Exercise Training Variables: Overall time, active exercise time, heart rate, cadence, and power are recorded in a secure, customized REDCap database. The primary training variables of interest for each exercise session are: AE intensity measured as percent heart rate reserve (%HRR) during main 35-minute exercise set, average cadence and work (power) produced by the patient and for the FE participants, by the motor.

Measures of Feasibility (Aim 1): Primary outcomes to determine feasibility will include measures of exercise compliance (percent of sessions attended, time spent exercising, time spent within target heart rate zone) and the absence of adverse events. Secondary outcomes will include change in levels fatigue and physical activity as measured by a body-worn activity monitor.

Effects on Motor Function (Aim 2): The primary outcome is change in biomechanical characteristics of gait, while the secondary outcomes include changes in walking capacity, manual dexterity test (MDT), and timed up and go (iTUG).[36, 37]

Effects on Non-Motor Function (Aim 3)*:* The primary outcome measuring QOL is the change in the PROMIS-29,[38] while the MSPT[36, 37] CVLT, and BVMT will serve as the primary outcomes measuring cognitive function.

Role of Klotho (Aim 4): The primary outcome is the acute and long-term change in serum Klotho levels from baseline to the post-exercise intervention, while the secondary outcome in long-term change in sNfL

Outcomes:

Analysis of Feasibility (Aim 1): Measures of compliance will determine feasibility of individuals with MS to complete the FE intervention. Self-reported fatigue will be measured using the Modified Fatigue Impact Scale. Activity levels will be measured using a Garmin Vivofit 4 body-worn activity monitor. The absence of adverse events will demonstrate safety of FE in MS.

Biomechanical Gait Assessment (Aim 2): The CAREN system is a complete biomechanical assessment system with 10 Vicon cameras, split-belt treadmill with two force plates, and D-flow software. Twenty-five retro-reflective markers will be placed at anatomic landmarks identified for LE assessment.[39] Participants will walk at a self-selected pace for two 2-minute trials. The following biomechanical outcomes will be calculated: 1) spatio-temporal: velocity; cadence, step length, percentage of gait cycle spent in swing and stance phase, single and double limb support time and percentage; 2) Kinematic: hip and knee flexion and extension; ankle dorsi- and plantar-flexion; pelvic obliquity, rotation and tilt. To determine changes in overground walking, gait analysis will also be conducted using the Zeno Instrumented walkway. Participants will walk at a self-selected pace and fast pace for four lengths for each condition along the 15' Zeno Instrumented walkway. The following spatio-temporal outcomes will be calculated: velocity; cadence, step length, percentage of gait cycle spent in swing and stance phase, single and double limb support time and percentage. Lastly, the Timed up and Go will be administered.

Non-Motor Function Data (Aim 3): The PROMIS-29 will be administered to determine self-reported quality of life. The multiple sclerosis performance test (MSPT) and two measures of episodic memory, the California Verbal Learning Test and the Brief Visuospatial Memory Test,[2] will be administered to examine change in cognitive function. All will be administered to determine feasibility with respect to administration approach, sensitivity to detect change over time, and time requirements for a future clinical trial.

Laboratory Assessment (Aim 4): Blood draws will be conducted at 4 different points in time to determine the acute and long-term change in serum Klotho; at baseline, pre- and post-exercise, and at the end of the 12-week exercise intervention, pre- and post-exercise. sNfL will be measured at baseline and at the end of the 12-week intervention.

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