Effects of Two High-Frequency Physical Therapy Programs on Balance, Gait, Fatigue, and Quality of Life in People with Multiple Sclerosis

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EFFECTS OF TWO HIGH-FREQUENCY PHYSICAL THERAPY PROGRAMS ON BALANCE, GAIT, FATIGUE, AND QUALITY OF LIFE IN PEOPLE WITH MULTIPLE SCLEROSIS

By

Min Liu

A THESIS

Presented to the Faculty of
the University of Nebraska Graduate College
in Partial Fulfillment of Requirements
for the Degree of Master of Science

Medical Sciences Interdepartmental Area
Graduate Program

Under the Supervision of Professor Ka-Chun Siu and Max J. Kurz

University of Nebraska Medical Center
Omaha, Nebraska

April 2018

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Kathleen G. Volkman, PT, MS.
ACKNOWLEDGEMENT

During my four years of MS/DPT study at UNMC, I would like to thank many people for their various contributions in this journey. First of all, I would like to express my sincere gratitude to my advisor, Dr. Ka-Chun Siu, for all his guidance and assistance over the past four years. Thank you for mentoring all the Chinese students, including me, not only academically, but also personally and socially during our study in Omaha. I greatly acknowledge my committee members, Dr. Max Kurz and Prof. Kathleen Volkman for their dedication, direction, and invaluable suggestions along this project. Special thanks to previous lab member, Dr. Brenda Davies for your countless help and advises for this thesis even after your graduation.

Then, my grateful thanks go to all the patients who participated in this project. Even though I can’t list your names here, I would still like to thank you all for your generous contributions.

In addition, I would like to acknowledge the Chinese Scholarship Council for supporting my study at UNMC. Without this financial aid, I could not pursue my dreams through higher education in United States.

Last, but not least, I am deeply thankful to my family and friends in China, especially my mom (王美云), dad (刘良赛), and sister (刘娟), for their love, support, and sacrifices. Without them, this thesis would never have been written. And most of all for my loving, patient, encouraging, and supportive husband, Nick Dragos, the warmth and fun you have provided for me has made up for the long winter days in Omaha.
ABSTRACT

EFFECTS OF TWO HIGH-FREQUENCY PHYSICAL THERAPY PROGRAMS ON BALANCE, GAIT, FATIGUE, AND QUALITY OF LIFE IN PEOPLE WITH MULTIPLE SCLEROSIS

Min Liu, M.S.

University of Nebraska Medical Center, 2018

Supervisors: Ka-Chun Siu, Ph.D. and Max J. Kurz, Ph.D.

Multiple sclerosis (MS) is an inflammatory disease involving the inflammation and demyelination in both brain and spinal cord. MS typically affects people in early adulthood in the range of 20-40 years old, and most patients with MS experience symptoms on a daily basis, such as walking difficulties, balance impairment, and fatigue, which can be disabling and impact the Quality of Life (QOL).

The main purpose of this investigation is to determine if our novel, adaptive, high-frequency physical therapy protocol, compared with the conventional therapeutic exercise protocol, has the potential to improve participants’ dynamic balance, gait, fatigue, and overall QOL based on clinical measurement scales. After the completion of this investigation, we found that both types of protocols with the same high dosage improved the balance, gait, fatigue, and QOL in people with MS similarly in a clinically relevant manner. Our results provide evidence that a high-frequency physical therapy intervention consisting of twice per day and five days per week sessions may be an important parameter for improving balance, gait, fatigue, and QOL in people with MS.
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<th>Full Form</th>
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<tr>
<td>BC</td>
<td>Brad Corr</td>
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<tr>
<td>BD</td>
<td>Brenda Davies</td>
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<td>CIS</td>
<td>Clinically isolated syndrome</td>
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<td>DGI</td>
<td>Dynamic Gait Index</td>
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<td>EDSS</td>
<td>Kurtzke Expanded Disability Status Score</td>
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<td>MAC</td>
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<td>MS</td>
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<td>MSWS-12</td>
<td>Twelve Item MS Walking Scale</td>
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<td>PPMS</td>
<td>Primary-Progressive multiple sclerosis</td>
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<td>QOL</td>
<td>Quality of Life</td>
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<tr>
<td>RRMS</td>
<td>Relapsing-remitting multiple sclerosis</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>SPMS</td>
<td>Secondary-Progressive multiple sclerosis</td>
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TEC  Therapeutic exercise cohort
UNMC  University of Nebraska Medical Center
Chapter 1 Introduction

Background

Triggered by environmental and genetic factors, multiple sclerosis (MS) is a chronic immune-mediated disease involving inflammation, plaques, and demyelination in the central nervous system.\textsuperscript{1} Clinically, there are four subdivisions of MS, including Relapsing-Remitting MS (RRMS), Secondary-Progressive MS (SPMS), Primary-Progressive MS (PPMS), and Clinically Isolated Syndrome (CIS).\textsuperscript{2} RRMS is characterized by self-limited acute attacks of neurologic dysfunction developing from days to weeks. Then most patients experience a recovery of function over the next few weeks to months. Between attacks, those patients can be clinically stable. The second type, SPMS, begins as RRMS, but its clinical course is characterized by a steady deterioration in function unrelated to acute neurologic attacks. Unlike SPMS, the third one, PPMS starts with a steady increase in disability from the very beginning without acute attacks. The fourth type, CIS, refers to a first episode of MS-related symptoms lasting at least 24 hours caused by inflammatory demyelination in the central nervous system that may or may not continue to develop MS. MS typically affects people in early adulthood in the 20-40 year range and is two to three times more common in women than men.\textsuperscript{3} MS affects approximately 400,000 people in the United States and 2.1 million people worldwide.\textsuperscript{4,5} As a costly chronic disease, the total all-cause health care costs associated with MS including direct and indirect costs ranged from $8,528 to $52,244 per patient per year in the US.\textsuperscript{6} Common symptoms of MS include fatigue, gait difficulties, impaired balance, spasticity, depression, and cognitive impairment.\textsuperscript{7} Most patients with
MS experience symptoms on a daily basis, especially balance impairment, which can be disabling and impact the Quality of Life (QOL). Although pharmacological interventions play an important role in the treatment of these symptoms, a physical rehabilitation approach is also imperative as it may target the dysregulation of the inflammatory balance in MS, but its effectiveness remains elusive.

There is increasing evidence to support that exercise training may yield beneficial effects on the mobility and balance function of individuals with MS. Exercise training for MS includes aerobic exercises, resistance exercises, and other nontraditional exercise training, such as yoga, Tai Chi, and Pilates. Although various exercise training methods were used, there is no universal model of training for individuals with MS. The frequency of exercise training in existing literature ranged from mild to moderate, with most experiments conducted between 30-90 minutes per session, 2-4 times per week. For example, Motl et al. performed a combined training therapy with a maximum of 60 minutes in duration and 3 days per week. Others recommended 20-30 minutes of aerobic exercise more than 3 days per week. Collectively, these investigations showed a small improvement of symptoms in people with MS. It remains to be established what type of training method is optimal, how many times a week a person should train, and how long a training session should last for people with MS.

Previously we conducted two studies using two types of protocols with high frequency physical therapy and demonstrated that the high frequency of physical therapy protocol may be beneficial to people with MS in regards to mobility, postural balance, and motor control of the ankle plantarflexors. One adaptive physical therapy protocol in our studies was performed at a higher dosage (two times per day, five days per week as
compared to more traditional levels of two to three sessions per week), and progressively challenged the patient’s balance, in hopes of making it more adaptable to unstable situations. Exemplary therapies include forcing patients to use the more impaired limbs and directing the patient’s attention towards focusing on how to adapt their movement patterns. Moreover, the therapeutic dosage in our study (45 minutes per session, twice a day, 5 days a week for a 6-week period) was larger than previous studies\textsuperscript{23,24} (typically 2-4 times per week for 30-60 minutes over a 3-12 week period). We suspected that our high-frequency physical therapy protocol would have clinically relevant improvements in gait, balance, fatigue, and QOL in MS as well, based on different clinical measurements.

**Purpose**

The primary purpose of this investigation is to determine if our novel, adaptive, high-frequency physical therapy protocol, compared with the conventional therapeutic exercise protocol, has the potential to improve participants’ dynamic balance, gait ability, fatigue, and overall QOL based on clinical measurement scales. Specifically, the Dynamic Gait Index (DGI) is used to assess the dynamic walking balance; Twelve-Item MS Walking Scale (MSWS-12) for gait ability; Modified Fatigue Impact Scale (MFIS) for fatigue, and Multiple Sclerosis Impact Scale (MSIS-29) for overall QOL.

**Research Hypothesis**

**Hypothesis 1:**

Compared with the group who completed traditional therapeutic exercise protocol, the group that completed novel motor adaptive therapeutic protocol will have greater improvements in the DGI score after 6 weeks of therapy.
**Hypothesis 2:**

The MSWS-12 score will be improved in the group that completed novel motor adaptive therapeutic protocol than the group who completed traditional therapeutic exercise protocol after 6 weeks of therapy.

**Hypothesis 3:**

The group that completed novel motor adaptive therapeutic protocol will improve fatigue, based on the MFIS score, compared with the group who completed traditional therapeutic exercise protocol after 6 weeks of therapy.

**Hypothesis 4:**

The group that completed novel motor adaptive therapeutic protocol will have a decreased MSIS-29 score than the group who completed traditional therapeutic exercise protocol after 6 weeks of therapy.
Chapter 2 Literature Review

Multiple Sclerosis

Multiple sclerosis (MS) is a chronic autoimmune inflammatory disease in the central nervous system. Several factors have been proposed to explain the pathogenesis of MS, including genetic susceptibility, infectious agents, and other environmental factors. Pathological hallmarks of MS include focal or diffused plagues of demyelination, inflammation, axonal loss, and neurodegeneration in brain and spinal cord. Over time, repeated pathological episodes of disease activity in CNS can lead to a wide range of clinical features of MS, such as weakness, fatigue, gait instability, balance impairments, cognitive deficits, visual and sensory changes. Such symptoms often result in poor Qualify of Life (QOL). The clinical characteristics and disability levels vary significantly among individuals with MS. Kurtzke Expanded Disability Status Scale (EDSS) has been established and gained its international acceptance to measure MS severity, and it is graded as mild (0–3.5), moderate (4–5.5) and severe (6–10).\(^{25}\) The EDSS measures the degree of neurologic impairments within eight functional domains including pyramidal, cerebellar, brain stem, sensory, bladder and bowel, visual, cerebral and other. There is increasing evidence that physical therapy or exercise training may have beneficial effects on people with MS. In this review, we focus on four areas of clinical characteristics to investigate the effects of physical therapy on MS, based on data from previous clinical trials as discussed below.

Balance impairment and effects of physical therapy interventions on balance in MS
One of the primary manifestations in MS patients is the balance impairment. Balance dysfunction can lead to falls, injury, and reduced activity participation.\textsuperscript{26} It is estimated that around 74\% of people with MS have difficulty with the balance and 50\% of MS patients felt balance impairment limited their ability to perform activities of daily living.\textsuperscript{27} A study also suggests that individuals with MS may even experience motor function deterioration during the early stages of the disease with no clinical neurologic signs.\textsuperscript{28} Balance maintenance requires the interaction of visual, vestibular, and proprioception processes to generate coordinated movements that maintain the center of mass within the limits of stability. One study reveals that the delay in postural response is the result of the slowed somatosensory conduction.\textsuperscript{29} People with MS have poor performance in the functional reach test, arm raise test, tandem stance, single-leg stance, and in response to external perturbation.\textsuperscript{30} Specifically for standing posture balance, compared with healthy adults, individuals with MS have decreased ability to maintain position and have more postural sway, which leads to increased risks of falling.\textsuperscript{31,32} And for dynamic balance, people with MS move less far and less quickly towards limits of stability when trying to reach or step.\textsuperscript{28,32,33} MS patients also demonstrate reduced center of pressure displacement during voluntary leaning and reaching.\textsuperscript{33} Moreover, people with MS have less ability to control anticipatory and reactive balance. A few studies indicate that there are trunk control deficits and delayed posture responses to postural displacements and perturbations, as well as reduced ability to control anterior-posterior sway in response to these perturbations in people with MS.\textsuperscript{29,34} Cameron et al. suggests that the primary cause of imbalance in MS is the result of slowed afferent proprioceptive conduction in the spinal cord, unlike the imbalance from cerebellar disorders.\textsuperscript{29}
The Dynamic Gait Index (DGI) is a commonly used tool in rehabilitation settings to assess dynamic balance while adapting gait to changes in task demands, including gait on even surfaces, gait while changing speed, gait while performing head turns, stepping over, or around obstacles, and pivoting during walking and stair climbing. The total score ranges from 0 to 24. A high score indicates better performance on dynamic balance. A score of 19 or less has been shown to be associated with higher risk of falls in MS.35,36 The DGI is a reliable tool to assess balance and gait dysfunction in persons with MS, with inter-rater reliability ranging from .910 to .976, and intra-rater reliability ranging from .760 to .986.35 It also has excellent criterion validity with other balance scales in people with MS, such as Timed Up and Go (TUG), Berg Balance Scale (BBS), and Activities-specific Balance Confidence (ABC).37

There are limited studies determining the therapeutic exercise effects on balance in MS. Several randomized controlled trials (RCT) demonstrated mixed results on balance in people with MS through various training exercises, including combined aerobic and resistance exercise38-40, aquatic training41, and group stability exercise, based on the standard measures, such as TUG, DGI, BBS, and Functional Reach test (FR).42 Specifically, combined resistance and aerobic training were found to have a small, but non-significant effect on balance in people with MS.39,40 Specific balance exercises were also conducted in one RCT. Cattaneo et al.43 demonstrated that specific balance retraining exercises had a significant effect on balance in individuals with MS, based on the BBS, but no significant effect observed on the DGI. Another RCT also suggested that the group exercise program was effective in improving the balance in patients with MS, based on the BBS.44 The intervention consisted of flexibility, range of motion, strengthening for
low extremity, core stabilization, balance and coordination, and functional activities, 60 min per session, 3 times a week for 12 weeks.\textsuperscript{44} Overall, the frequency of the exercise training in the previous studies ranged from mild to moderate, spreading between 3-10 weeks, 3-8 sessions per week, 30-60 min/session, which has been shown to yield significant, but small improvements on balance in patients with MS.\textsuperscript{23} Therefore, the evidence regarding the beneficial effects of physical therapy interventions on balance in MS is still weak and it is based on a limited number of non-RCTs and RCTs.

**Gait dysfunction and relevant physical therapy interventions in people with MS**

Gait abnormalities are common in individuals with MS and associated with increased likelihood of experiencing falls and reduced quality of life. Gait disturbance can be seen in early stages of the disease, even identified in patients with the absence of gait abnormalities on standard clinical examination.\textsuperscript{45} About 85\% of people with MS indicate gait disturbances as their main complaint.\textsuperscript{46} A study reported that approximately 33\% of patients with MS had difficulty walking and required assistance at 10 years from the onset of MS.\textsuperscript{47} While the exact causes of gait abnormalities observed in MS are yet to be identified, it is believed that lower extremity weakness, spasticity, and sensory changes may contribute to the symptoms. People with MS tend to walk slower, have decreased step length and cadence, spend a greater percentage of a gait cycle in double support, and demonstrate less joint motion and more variability in gait parameters during gait than healthy controls.\textsuperscript{46,48,49} A recent study also revealed that individuals with MS showed decreased range of motion at the ankle, knee, and hip associated with increased pelvic tilt and hiking.\textsuperscript{50} Allali et al. suggested gait analysis, such as stride time variability,
represents a clinical potential predictor of falls in people with MS with low disability, and it may be more appropriate than the EDSS in studies focused on fall prevention in MS.\textsuperscript{51}

The 12-item Multiple Sclerosis Walking Scale (MSWS-12) is a MS-specific, patient-based questionnaire to measure the gait ability in individuals with MS in clinical studies and clinical practice. Each item ranges from 1 to 5, generating total scores ranging from 12 to 60, or transformed scores ranging from 0-100, with the higher the sum is, the more severe the degree of ambulatory disability. It is a highly valid and reliable scale in MS.\textsuperscript{52,53} A study reported that MSWS-12 is significantly correlated with spatiotemporal parameters of gait in people with MS, suggesting that it is an easily administered and inexpensive tool for the comprehensive assessment of walking disability in individuals with MS.\textsuperscript{54}

There is emerging evidence that physical therapy interventions can ameliorate gait dysfunction in people with MS. Several studies focused on specific interventions for muscle weakness, spasticity, and reduced gait velocity that contribute to gait abnormalities in MS, including resistance training, aerobic exercise, and body weight-supported treadmill training (BWSTT).\textsuperscript{18,55-58} Resistance training has shown to improve functional mobility based on the 10-meter walk test (10MWT) and 6-minute walk test (6MWT).\textsuperscript{57} Resistance training can also improve gait kinematics, including increased step length, stride length, and foot angle, as well as decreased duration of the double-support phase.\textsuperscript{56}

Aerobic exercise is another type of training program and it has been shown to improve walking speed and endurance in patients with MS.\textsuperscript{58} BWSTT can provide aerobic training for patients with severe MS who are not able to walk independently on a
treadmill, and it is suggested that BWSTT may improve walking speed and endurance in people with severe MS.\textsuperscript{59} Moreover, ankle foot orthoses and functional electrical stimulation have been demonstrated to improve the gait pattern of individuals with MS and to reduce the energy expenditure while walking.\textsuperscript{60,61} The frequency of interventions in most aforementioned studies is mild to moderate, ranging from 2-5 times/week, 20-60 minutes/session for 4-8 weeks.

In summary, there is promising evidence supporting that some types of physical therapy interventions may improve gait/walking abilities in patients with MS. However, it is insufficient to determine optimal dosage and whether patients can tolerate the high-frequency physical therapy intervention.

**Fatigue and related physical therapy interventions in individuals with MS**

Fatigue is also considered to be one of the most common symptoms and disabling features of MS\textsuperscript{62}, with 65-97\% of individuals having significant fatigue\textsuperscript{63} and 15-40\% reporting fatigue as the most disabling symptom.\textsuperscript{64} Fatigue in MS is an abnormal sense of tiredness or lack of energy, out of proportion to the degree of effort or level of energy, which significantly interferes with daily activities. The manifestation of fatigue in MS includes acute fatigue related to specific muscle groups and global, persistent fatigue which adversely affects both mental and physical activity.\textsuperscript{65} Prolonged fatigue associated with localized muscles may lead to weakness, and it should not be confused with weakness. There are two different types of fatigue in MS, including mental (central) fatigue, inability to sustain the central drive to spinal motor neurons, and motor
(peripheral) fatigue, a loss of force-generating capacity within the muscle itself. MS fatigue can also be categorized into primary fatigue and secondary fatigue. Primary fatigue is believed to be directly related to the central nervous system damage specific to MS, such as demyelination, inflammation, and axonal loss. Secondary fatigue may be attributed to pain, depression, stress, anxiety, sleep disorders, medication use, and general deconditioning. The pathophysiology of central fatigue in people with MS is not well understood and probably related to the demyelination, diffuse cerebral axonal injury, brain atrophy, reduced cortical metabolic activity, and inflammation.\textsuperscript{66-68} Two studies have shown that anatomical and metabolic muscle changes may contribute to the symptoms of peripheral fatigue in people with MS, including less Type I (fatigue resistant) fibers, more Type II (fatigable) fibers, decreased fiber size, oxidative capacity impairments, and slowed excitation-contraction responses.\textsuperscript{69,70} Both peripheral and central mechanisms may have some roles in the pathogenesis of fatigue in MS. However, it is believed that central mechanisms play a more important role.\textsuperscript{71} Fatigue may also be related to gait variability in MS. Sehle et al.\textsuperscript{72} suggested that gait variability is significantly correlated with the motor sections of the Fatigue Scale of Motor and Cognition, but not with the cognitive portion of the scale, which indicates that motor fatigue is more related to gait variability than mental fatigue. Kalron\textsuperscript{73} also found that a fatigued group walked slower, took smaller steps, and had a shorter stride length than those in a non-fatigued group. However, two other studies reported that there were minimal associations between fatigue and gait variability during short walks.\textsuperscript{46,74} There is also a relationship between fatigue and balance in MS. A study demonstrated that fatigue was significantly associated with balance as a function of central sensory integration in
people with MS. Collectively, fatigue is one of the common symptoms of MS. Fatigue may be associated with other clinical features, such as gait and balance. It is complex and not fully understood, which warrants further study.

An accurate assessment of fatigue is beneficial to help clinicians and researchers determine the severity of fatigue. The Modified Fatigue Impact Scale (MFIS) is a clinical measurement to evaluate fatigue in MS. The MFIS is based on items derived from interviews with patients with MS regarding how fatigue impacts their lives. It consists of 21 items, with each item scoring between 0 and 4, which gives a self-reported multidimensional measure of fatigue on physical, cognitive, and psychosocial functioning. The MFIS global score range is between 0 and 84, with a higher score indicating more fatigue. Reliability and validity of the MFIS have been established in people with MS and it has been recommended as an outcome measure for use in MS research and clinical practice.

The treatment of fatigue mainly includes pharmacologic and non-pharmacologic therapies. There are a few medications, including Amantadine, Modafinil, and Armodafinil, which may mitigate the fatigue symptom in persons with MS, however, no effective medicine has been found. On the other hand, therapeutic exercise may be an alternative way to reduce fatigue and appears to be more effective in improving fatigue compared to the pharmacological agents. A recent Cochrane systematic review demonstrated that exercise therapy is a promising way to reduce fatigue without harm in patients with MS, based on the results of the 45 RCTs. The frequency in these studies is relatively low to moderate, ranging from 30 to 60 minutes per session, 2 to 5 times per week, with the duration of the interventions ranged from 8 to 12 weeks. A few studies
also explored the effects of high intensity exercises on people with MS.\textsuperscript{57,79-83} A recent exploratory study suggested that high-intensity resistance training is associated with clinical improvements in fatigue in people with relapsing remitting multiple sclerosis, possibly through its positive effects on decreased pro-inflammatory cytokine levels.\textsuperscript{81} This high-intensity intervention was performed twice a week, 60 min per session for 12 weeks, with a 5 min warm-up, three lower body exercises, four upper body exercises, and one whole body exercise in each training.\textsuperscript{81} One RCT also showed that 12 weeks of high-intensity aerobic training combined with resistance training was safe and well tolerated, with improved muscle strength and endurance capacity in MS.\textsuperscript{82} However, another RCT revealed that the standard training including aerobic exercises, lower extremity stretching, upper extremity strength training, and balance exercises, with the addition of high-intensity eccentric muscle training, was not superior to the standard training alone, regarding fatigue, balance, and gait assessments, after the intervention of 45-60 min per session, 3×/week for 12 weeks.\textsuperscript{83} Collectively, some types of exercise training may improve symptomatic fatigue in persons with MS, but the optimal therapeutic paradigm to treat the MS-related fatigue is still yet to be determined.

**Quality of Life (QOL) and related physical therapy interventions in MS**

QOL is an umbrella term that includes social, emotional, physical, economic and cultural dimensions of our lives. There is emerging evidence that QOL is compromised in patients with MS.\textsuperscript{84,85} Several factors, including physical disability status, fatigue, depression, age, sex, and socioeconomic status, have been found to be associated with lower QOL in
people with MS than healthy populations or patients with other chronic diseases.\textsuperscript{86} Statistical results have shown that the unemployment rate is up to 70\% in community-dwelling individuals with MS, and half of them due to the MS consequences.\textsuperscript{87} After the initial diagnosis, at least a third of MS patients experience a significant decline in their standard of living.\textsuperscript{88} Compromised QOL in MS is also associated with the severity of the disease, which has been found to correlate with high economic burden to society.\textsuperscript{89} Therefore, it is imperative for clinicians to find a way to improve QOL in patients with MS.

The Multiple Sclerosis Impact Scale (MSIS-29)\textsuperscript{90} is one of the most common questionnaires to measure QOL in people with MS. It is a twenty-nine item, disease-specific scale to access the impact of MS from the patient’s perspective. It consists of 20 physical items and 9 psychological items that may impact individuals with MS. This is consistent with the definition of health-related QOL incorporating both psychological and physical components.\textsuperscript{91} The MSIS-29 ranges between 29 and 145, with higher scores indicating greater impact or a poor quality of life. It is a valuable outcome measurement, used not only in cross-sectional studies but also in intervention studies to monitor MS progression.\textsuperscript{92} A minimal change of 8 points in the MSIS-29 indicates clinical significance.\textsuperscript{93}

Exercise training is a promising intervention for improving QOL in MS. Fatigue, disability, depression, pain, social support, and self-efficacy act as intermediary roles between physical training and QOL.\textsuperscript{94} There is cumulative evidence supporting that physical exercise is associated with a small improvement in QOL in people MS.\textsuperscript{95} However, the parameters of the exercise training protocols on QOL, such as the type of
exercise training, the length of the intervention, and the amount of the training per week, vary considerably in existing literatures. A study reports that there is a significant effect for aerobic exercise on improving QOL in MS, but not for non-aerobic exercise or aerobic and non-aerobic exercise combined. Exercise training interventions of $< 3$ months and interventions of $\geq 3$ months both are associated with significant improvements in QOL, but shorter duration of interventions are associated with greater effects. This research also suggests that exercise training greater than 90 minutes per week yields greater effects on QOL than that of less than 90 minutes per week. Thus, various exercise training protocols and small treatment effect on QOL underscore the importance of establishing the optimal therapeutic paradigm to improve QOL in MS.

**Summary**

In summary, there is supportive, but not overwhelming evidence for a beneficial effect of physical therapy and exercise training on gait, balance, fatigue, and QOL. The average duration of the existing training protocols was 60 minutes per session (30-90) lasting 9 weeks (range 3–24) with a mean frequency of 3 sessions per week (range 2–6). Existing physical therapy training protocols include resistance exercise, aerobic exercise, combined aerobic and resistance training, and alternative interventions, such as aquatics, yoga, Tai chi, etc. The participants in the majority of existing clinical trials have mild to moderate level of disability based on the EDSS. In spite of the emerging evidence supporting the beneficial effects of physical therapy interventions on gait, balance, fatigue, and QOL in people with MS, the heterogeneity of protocols and participant samples with various levels of severities in previous studies raises questions regarding the optimal components and frequency of training, such as type of exercises, optimal
duration of training, and number of sessions required to elicit significant and clinically relevant improvements. Our previous investigations showed that a high frequency of physical therapy was beneficial to people with MS in regards to walking speed, step length, walking endurance, postural balance, and motor control of the ankle plantarflexors\textsuperscript{21,22}. We suspected that our high-frequency physical therapy protocol would have clinically relevant improvements in gait, balance, fatigue, and QOL in MS as well, based on different clinical measurements.
Introduction

Multiple sclerosis (MS) is an inflammatory disease involving the inflammation and demyelination in both brain and spinal cord.\textsuperscript{1,96} MS typically affects people in early adulthood in the 20-40 year range and is two to three times more common in women than men.\textsuperscript{3} MS affects approximately 400,000 people in the United States and 2.1 million people worldwide.\textsuperscript{4,5} As a costly chronic disease, the total health care costs associated with MS including direct and indirect costs ranged from $8,528 to $52,244 per patient per year in the US.\textsuperscript{6} Common symptoms of MS include fatigue, gait difficulties, impaired balance, spasticity, depression, and cognitive impairment.\textsuperscript{7} Most patients with MS experience symptoms on a daily basis, especially balance impairment, which can be disabling and impact the Quality of Life (QOL).\textsuperscript{8,9} Although pharmacological interventions play an important role in the treatment of these symptoms, physical rehabilitation approach is also imperative as it may target the dysregulation of the inflammatory balance in MS, but its effectiveness remains elusive.\textsuperscript{10}

There is increasing evidence to support that exercise training may yield beneficial effects on the balance and mobility function of individuals with MS.\textsuperscript{11-13} Exercise training for MS includes aerobic exercises, resistance exercises, and other nontraditional exercise training, such as yoga, Tai chi, and Pilates.\textsuperscript{13-16} Although various exercise training methods were used, there is no universal model of training targeting specific impairment in individuals with MS, and it is typically driven by personal preferences.\textsuperscript{17} The frequency of exercise training in existing literature ranged from mild to moderate, with
most experiments conducted between 30-90 minutes per session, 2-4 times per week. For example, Motl et al.\textsuperscript{18} performed a combined training therapy incorporating aerobic, resistance, and balance exercises with a maximum of 60 minutes in duration and 3 days per week. Others recommended 20-30 minutes of aerobic exercise more than 3 days per week.\textsuperscript{19} Collectively, these investigations showed a small improvement of symptoms in people with MS.\textsuperscript{11,20} It remains to be established what is the optimal exercise regimen, such as what type of training method is best, how many times a week a person should train, and how long a training session should last for people with MS.

Previously we conducted studies using two types of protocols with high frequency physical therapy and demonstrated that the high frequency of physical therapy protocol may be beneficial to people with MS in regards to mobility, postural balance, and motor control of the ankle plantarflexors.\textsuperscript{21,22} One adaptive physical therapy protocol in our studies was performed at a higher dosage, and constantly challenged the patient’s balance, in hopes of making it more adaptable to unstable situations. Exemplary therapies include forcing patients to use the more impaired limbs and directing the patient’s attention towards focusing on how to adapt their movement patterns. Moreover, the therapeutic dosage in our study (45 minutes per session, twice a day, 5 days a week for a 6-week period) was larger than previous studies\textsuperscript{23,24} (typically 2-4 times per week for 30-60 minutes over a 3-12 week period). We anticipated that our high-frequency physical therapy protocol would have clinically relevant improvements in gait, balance, fatigue, and QOL in MS as well, based on different clinical measurements.
Methods

Participants

Thirty-three participants were recruited from the University of Nebraska Medical Center’s (UNMC) MS clinic with the following inclusion criteria: between 30-70 years old, a Kurtzke Expanded Disability Status Score (EDSS) of 3.0-6.5, a definitive diagnosis of MS, able to walk on a treadmill at a minimum speed of 0.5 miles per hour while holding onto handrails, cognitively competent, and a Mini-Mental State Examination score of >21. The exclusion criteria were: documented MS-related relapse in the previous six months, major MS-specific medication changes in the previous three months, and the presence of another major co-morbidity such as neurological disorders, uncontrolled pain, hypertension, and diabetes. The study was reviewed and approved by the UNMC Institutional Review Board, and all participants provided written consent (clinical trial registration No.: NCT02524483). The participants were pseudo-randomly assigned to either a motor adaptation cohort (MAC) or a therapeutic exercise cohort (TEC) upon enrollment. The pseudo-random assignments were performed such that a participant meeting the inclusion criteria was randomly placed in one of the intervention groups, and a second participant with a similar EDSS was assigned to the other group. All participants were blinded to therapeutic intervention allocations throughout the study.

Interventions
The total intervention period for both cohorts was six weeks. The therapy was performed twice a day for five consecutive days each week. The initial two weeks were conducted under close supervision of a physical therapist (HR, BC, or KV). The remaining four weeks were performed by the patient at their home and were monitored weekly via teleconferences with the therapist. Subjects completed the same activities at home as they did during the initial two weeks and kept a home exercise program log book to track their activity.

**Motor Adaptation Cohort (MAC)**

The motor adaptation session included warm-up, balance training, treadmill and overground walking training. The warm-up lasted 5 minutes, including several repetitions of movements, stretches, and coordination activities for the trunk and limbs.

After the warm-up, the participant proceeded with a 20-minute balance-training program one-on-one with the therapist according to the initial assessment. The balance training program included a sitting/standing balance training, such as sitting on a gym ball or standing in a corner with the feet either on the floor or a piece of foam while keeping eyes closed. The purpose of this training was to challenge and progress the participant’s balance gradually to maintain upright control despite altered visual and somatosensory inputs. For instance, the starting position might be less challenging for the first 5 minutes on the foam with their feet 10 inches apart, then progressing to more challenging positions during next 5-minute periods, and finally returning to a less challenging position for the final 5 minutes. During the training, verbal and tactile cues were provided for upright posture and relaxation of tense body parts, and verbal cues for the increase of sensory awareness (i.e., location of pressure on the soles of feet). The
therapist also observed the participant for the ability to meet the task’s demand (i.e., the number of touches to the wall). The therapist would increase the demands of postural training according to their observations of the participants. In general, no rest periods occurred during the balance sessions. During the balance exercises, the participant was provided with a table or chair in front for temporary support if necessary, and each participant wore a gait belt for balance assistance as needed.

Lastly, the participant completed a 20-minute challenging treadmill and overground walking training. The treadmill training consisted of tasks such as forward, backward, or sideways walking with a harness provided as needed for safety. The use of handrails, the degree of ramp incline, and the treadmill speed were tailored to each participant during the training to provide an appropriate level of intensity. In addition, the therapist provided overground training indoors with varied walking direction, speed, using a less-supportive assistive device than they were accustomed to, and/or increasing dynamic balance activities. The therapist provided verbal and tactile cues, as well as visual feedback by training in front of a mirror to help participants establish a more normal gait pattern. A protocol similar to that described above for the balance task was used to progress each 5-minute locomotor training period. Participants were provided with short rest periods as needed. The intensity of the activities was increased as tolerated based on each participant’s level of performance and fatigue during the previous session.

**Therapeutic Exercise Cohort (TEC)**

Each therapeutic exercise session included 15 minutes of strength and flexibility exercises, 15 minutes of balance exercises, and 15 minutes of treadmill walking performed in a small group setting (3 subjects). The activities selected for the therapeutic
program were similar to those that would be performed in a group exercise program. Subjects were instructed to complete each task at their own pace for 3 minutes with the therapist supervising. Strength exercises consisted of activities such as forward/backward lunges, stepping up/down a step, and squats. Flexibility training was performed both standing up and lying on a mat. Subjects were taught how to stretch the lower extremity muscles, especially any muscle that was specifically problematic to them. Both static and dynamic balance exercises were completed in each session. Static balance exercises included standing on a piece of foam with eyes open and feet wide apart, or standing on one leg as long as possible with support. Dynamic balance exercises included stepping over small obstacles, walking sideways, or walking heel to toe. For treadmill walking, the subjects were encouraged to remove one or both hands from the handrails if possible. The participants were allowed to increase and decrease their speed as needed to accomplish the total time. All subjects reported their rate of perceived exertion based on the Borg scale, and were instructed to attempt to work at a score of 12 or 13, which indicates that the exercise was somewhat hard. Rest was given as needed throughout the entire session.

**Outcome measures & Clinical assessments**

For both MAC and TEC, all measurements were assessed at the baseline, as well as at the end of week 2 and week 6 of the investigation.

**Balance assessment**

The Dynamic Gait Index (DGI) was used to assess dynamic balance while adapting gait to changes in task demands, including gait on even surfaces, gait while changing speed,
gait while performing head turns, stepping over, or around obstacles, and pivoting during walking and stair climbing. The total score ranges from 0 to 24. A high score indicates better performance on dynamic balance. A score of 19 or less has been shown to be associated with higher risk of falls in MS. DGI is a reliable tool to assess balance and gait dysfunction in persons with MS, with inter-rater reliability ranging from .910 to .976, and intra-rater reliability ranging from .760 to .986. In this clinical trial, the scoring was performed by one researcher (ML) after watching the DGI testing videos in two testing sessions 5 days apart. The test-retest reliability was 0.87, which was calculated by a third person (BD).

**Gait assessment**

The 12-item Multiple Sclerosis Walking Scale (MSWS-12) is a self-report questionnaire to measure the gait ability in individuals with MS. Each item ranges from 1 to 5, generating total scores ranging from 12 to 60, or transformed scores ranging from 0-100, with the higher the sum indicating more severe ambulatory disability. It is a valid and reliable scale in MS. A study reported that MSWS-12 is significantly correlated with spatiotemporal parameters of gait in people with MS, suggesting that it is an easily administered and inexpensive tool for the comprehensive assessment of walking disability in individuals with MS.

**Fatigue assessment**

The Modified Fatigue Impact Scale (MFIS) was used to evaluate the patients’ fatigue. The MFIS is based on items derived from interviews with patients with MS regarding how fatigue impacts their lives. It consists of 21 items, with each item scoring between 0
and 4, which gives a self-reported measure of fatigue on physical, cognitive, and psychosocial functioning. The MFIS global score range is between 0 and 84, with a higher score representing more fatigue. Reliability and validity of the MFIS have been established in patient with MS.\textsuperscript{77} It has been recommended as an outcome measure for use in MS research and clinical practice.\textsuperscript{77}

**Quality of Life (QOL)**

The Multiple Sclerosis Impact Scale (MSIS-29)\textsuperscript{90} is a twenty-nine item scale to measure QOL or impact of MS from the patient’s perspective. It consists of 20 physical items and 9 psychological items that impact individuals with MS. The MSIS-29 ranges between 29 and 145, with higher scores indicating greater impact or a poor quality of life. It is a reliable and valid measure of disease impact.\textsuperscript{97} A minimal change of 8 points in the MSIS-29 indicates clinical significance.\textsuperscript{93}

**Statistical analysis**

Descriptive statistics were used to summarize participant characteristics. Initially, independent samples $t$ tests and/or chi-square tests were used to compare the baseline characteristics of the MAC and TEC groups. Then, we conducted a series of mixed-design analysis of variance (ANOVA), which were performed for each outcome measure to assess differences across time (2 and 6 weeks) and between study groups, and for the interaction between time and study group. For the mixed-design ANOVA, the assumptions of sphericity and homogeneity of the variances were tested using Mauchly and Levene tests. The Huynh-Feldt correction was applied if there was a violation of the sphericity assumption. All statistical analyses were performed using IBM SPSS Statistics.
22 statistical software (IBM Corp., Armonk, NY, USA). Data were plotted with
GraphPad PRISM software (GraphPad Software Inc., San Diego, Calif.). Statistical
significance was set at $P \leq 0.05$. Cohen’s $d$ was also used to assess the effect size, which
was interpreted as small ($d=0.2$), medium ($d=0.5$), and large ($d=0.8$), respectively.98

Results

A total of 43 potential subjects with MS were assessed for eligibility (Figure 1). Ten
people were excluded because they did not fit the inclusion criteria. The remaining 32
individuals with relapsing-remitting or secondary progressive MS met the inclusion
criteria and were assigned to either group. In the MAC, two subjects were withdrawn
from the study due to noncompliance to the study procedures. In the TEC, one individual
discontinued due to a non-MS related health condition, and one individual discontinued
due to a fall-related injury that occurred during the training program. At the end of the
intervention period, 15 individuals in the MAC (Mean Age $\pm$ SD: 52.60 $\pm$ 8.72 years, 9
Females; mean EDSS score, 5.43 $\pm$ 0.94) and 13 individuals in the TEC (Mean Age $\pm$
SD: 54.77 $\pm$ 9.27 years, 6 females; mean EDSS $\pm$ SD, 5.26 $\pm$ 0.95) completed the entire
six weeks of their respective programs and were included in the analyses. Table 1
summarizes the characteristics of the subjects between the MAC and TEC at baseline. No
statistically significant between-group differences for any variables, including age, sex,
MS type, MS duration, EDSS, MSWS-12, MFIS, and MSIS-29, were found at baseline,
except DGI ($p=0.04$). At the end of home-based training, participants from both MAC
and TEC had a compliance rate of ≥92%, according to home exercise log book information.

**Figure 1. Flowchart of enrollment procedure**

43 subjects screened for eligibility
EDSS and Mini-Mental State Exam

10 subjects excluded
9 – EDSS < 3.0
1 – unable to walk on treadmill

33 subjects enrolled

15 subjects pseudo-randomly assigned to the Therapeutic Exercise

2 subjects discontinued
- 1 for non-MS related health complication
- 1 for fall-related injury

13 subjects completed the therapy

18 subjects pseudo-randomly assigned to the Motor Adaptation

3 subjects discontinued
- 2 for non-compliance
- 1 for non-MS related health complication

15 subjects completed the therapy
**Table 1 Baseline Characteristics of the Study Participants**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>MAC (n=15)</th>
<th>TEC (n=13)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.60 ± 8.72</td>
<td>54.77 ± 9.27</td>
<td>0.83</td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>46.2%</td>
<td>60%</td>
<td>0.46</td>
</tr>
<tr>
<td>MS type (% RRMS)</td>
<td>69.2%</td>
<td>73.3%</td>
<td>0.81</td>
</tr>
<tr>
<td>MS duration (years)</td>
<td>15.53 ± 6.21</td>
<td>12.23 ± 5.54</td>
<td>0.69</td>
</tr>
<tr>
<td>EDSS</td>
<td>5.43 ± 0.94</td>
<td>5.26 ± 0.95</td>
<td>0.91</td>
</tr>
<tr>
<td>DGI</td>
<td>13.00 ± 3.95</td>
<td>15.85 ± 2.58</td>
<td>0.04*</td>
</tr>
<tr>
<td>MSWS-12</td>
<td>46.53 ± 8.36</td>
<td>41.23 ± 9.40</td>
<td>0.13</td>
</tr>
<tr>
<td>MFIS</td>
<td>71.40 ± 26.59</td>
<td>54.08 ± 42.85</td>
<td>0.20</td>
</tr>
<tr>
<td>MSIS-29</td>
<td>81.13 ± 19.64</td>
<td>71.54 ± 26.98</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Note: values are mean ± SD or percentage. * Indicates significant difference (p < 0.05)

Abbreviations: MAC: motor adaption cohort; TEC: therapeutic exercise cohort; MS: multiple sclerosis. RRMS, relapsing-remitting multiple sclerosis; EDSS: Kurtzke expanded disability status scale; DGI: dynamic gait index; MSWS-12: 12-item multiple sclerosis walking scale; MFIS: modified fatigue impact scale; MSIS-29: multiple sclerosis impact scale.

**Balance measures**

There was a significant pre/post main effect (increase in the composite DGI scores) from baseline to the end of 2-week training (14.42 ± 3.39 vs. 17.53 ± 3.13, respectively) (p < 0.001; Cohen’s d = 0.95), as well as from baseline to the end of 6-week training (14.42 ± 3.39 vs. 18.62 ± 2.77, respectively) (p < 0.001, Cohen’s d = 1.36) (Fig 2, Table 2).

Moreover, there was a statistically significant difference regarding the composite DGI score between 2-week training and 6-week training (17.53 ± 3.13 vs. 18.62 ± 2.77,
respectively) \((p = 0.001, \text{Cohen’s d} = 0.37)\). However, there was no significant interaction between time and group \((p = 0.243)\), indicating both groups improved their dynamic balance similarly (Fig 2).

**Figure 2:** Mean changes in the DGI raw score at 2 and 6 weeks. DGI: Dynamic Gait Index; TEC: Traditional Exercise Cohort; MAC: Motor Adaptation Cohort. * indicates \(p < 0.05\)

**Table 2:** Outcome measures for all participants before and after receiving MAC or TEC (Mean, SD, and 95% CI)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Baseline level, mean (SD)</th>
<th>2-week level, mean (SD)</th>
<th>6-week level, mean (SD)</th>
<th>2-week post-intervention effects (change from the baseline)</th>
<th>6-week post-intervention effects (change from the baseline)</th>
<th>6-week post-intervention effects (change from the 2-week)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean difference (95% CI)</td>
<td>Mean difference (95% CI)</td>
<td>Mean difference (95% CI)</td>
</tr>
<tr>
<td>DGI (range, 0-24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAC</td>
<td>13.00 (3.95)</td>
<td>16.67 (3.24)</td>
<td>18.00 (2.73)</td>
<td>3.10 (&lt;0.001)</td>
<td>4.192 (&lt;0.001)</td>
<td>1.09 (0.001)</td>
</tr>
<tr>
<td>TEC</td>
<td>15.85 (2.57)</td>
<td>18.38 (2.99)</td>
<td>19.23 (2.77)</td>
<td>(1.70, 4.51)</td>
<td>(2.72, 5.67)</td>
<td>(0.40, *)</td>
</tr>
<tr>
<td>Composite result</td>
<td>14.42 (3.39)</td>
<td>17.53 (3.13)</td>
<td>18.62 (2.77)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>MSWS-12 (range, 12-60)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAC</td>
<td>46.53 (8.36)</td>
<td>35.00 (11.83)</td>
<td>32.20 (8.74)</td>
<td>-8.96 (&lt;0.001)</td>
<td>-12.32 (&lt;0.001)</td>
<td>-3.36 (0.097)</td>
</tr>
<tr>
<td>TEC</td>
<td>41.23 (9.40)</td>
<td>34.85 (9.81)</td>
<td>30.92 (7.85)</td>
<td>-4.27 (-)</td>
<td>16.50 (-)</td>
<td>7.17 (-)</td>
</tr>
<tr>
<td>Composite result</td>
<td>43.88 (10.46)</td>
<td>34.92 (10.46)</td>
<td>31.56 (8.37)</td>
<td>-13.65 (-)</td>
<td>16.50 (-)</td>
<td>7.17 (-)</td>
</tr>
<tr>
<td>MFIS (range, 0-84)</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
**Gait measures**

There was a significant pre/post main effect (decrease in the composite MSWS-12 scores) from baseline to the end of 2-week training (43.88 ± 8.87 vs. 34.92 ± 10.46, respectively) \((p < 0.001, \text{Cohen’s} \ d = 0.92)\), as well as from baseline to the end of 6-week training (43.88 ± 8.87 vs. 31.56 ± 8.37, respectively) \((p < 0.001, \text{Cohen’s} \ d = 1.43)\) (Fig 3, Table 2). There was no statistically significant difference in the composite MSWS-12 score between 2-week training and 6-week training (34.92 ± 10.46 vs. 31.56 ± 8.37, respectively) \((p =0.097, \text{Cohen’s} \ d = 0.35)\). And there was no significant interaction between time and group \((p = 0.272)\), suggesting both groups improved their self-reported gait ability similarly (Fig 3).
**Figure 3**: Mean changes in the MSWS-12 raw score at 2 and 6 weeks. MSWS-12: Multiple Sclerosis Walking Scale-12; TEC: Traditional Exercise Cohort; MAC: Motor Adaptation Cohort. * indicates \( p < 0.05 \)

**Fatigue measures**

There was a statistically significant pre/post main effect (decrease in composite MFIS) from baseline to 2-week training (62.74 ± 35.14 vs. 41.57 ± 25.92, respectively) \( (p < 0.001, \text{Cohen’s d} = 0.69) \) and 6-week training (62.74 ± 35.14 vs. 30.26 ± 20.02, respectively) \( (p < 0.001, \text{Cohen’s d} = 1.14) \) (Fig 4, Table 2). And there was a significant difference of the composite MFIS between 2-week training and 6-week training (41.57 ± 25.92 vs. 30.26 ± 20.02, respectively) \( (p = 0.012, \text{Cohen’s d} = 0.49) \). However, there was no significant interaction between time and group \( (p = 0.371) \), indicating both groups improved their fatigue (Fig 4).
Figure 4: Mean changes in the MFIS raw score at 2 and 6 weeks. MFIS: Modified Fatigue Impact Score; TEC: Traditional Exercise Cohort; MAC: Motor Adaptation Cohort. * indicates p < 0.05

QOL measures

There was a significant pre/post main effect (decrease in the composite MSIS-29 scores) from baseline to the end of 2-week training (76.34 ± 23.38 vs. 57.45 ± 15.55, respectively) ($p < 0.001$, Cohen’s d = 0.95), as well as from baseline to the end of 6-week training (76.34 ± 23.38 vs. 55.94 ± 15.78, respectively) ($p < 0.001$, Cohen’s d = 1.02) (Fig 5, Table 2). There was no statistically significant difference regarding the composite MSIS-29 between 2-week training and 6-week training (57.45 ± 15.55 vs. 55.94 ± 15.78, respectively) ($p = 1.000$, Cohen’s d = 0.10). And there was no significant interaction between time and group ($p = 0.835$), suggesting both groups improved their QOL similarly (Fig 5).
Figure 5: Mean changes in the MSIS-29 raw score at 2 and 6 weeks. MSIS-29: Multiple Sclerosis Impact Scale; TEC: Traditional Exercise Cohort; MAC: Motor Adaptation Cohort. * indicates p < 0.05

Discussion

Our pseudorandomized clinical trial showed that both MAC and TEC groups improved the balance, gait, fatigue, and QOL in people with MS in a clinically relevant manner. However, no significant differences were observed between improvements in MAC group as compared to the TEC group. This effect was evident in the assessment tools, including DGI, MSWS-12, MFIS, and MSIS-29. The effect was also consistent with the assessments in our previous study showing the benefits of the high-frequency physical therapy regarding postural balance and mobility in people with MS. Based on the Cohen’s d criteria, our data suggest a large effect size of improvement in balance, gait, and QOL, as well as medium effect size of improvement in fatigue only after 2 weeks of intervention. It also indicates a large effect size of improvement in all outcome measures after 6 weeks of high-frequency physical therapy.
Effects on Dynamic Balance

A statistically significant, but a comparable improvement over time at 2-week and 6-week periods was observed for dynamic balance according to DGI scores in MAC and TEC groups. This is contradictory to our hypothesis that the subjects in the MAC would have greater improvements in the balance than those in the TEC. The minimal detectable change (MDC) for the DGI is between 4.19 and 5.54 in people with MS.\textsuperscript{37} Based on this standard, the composite group at 6 weeks showed a detectable change of DGI score (mean difference: 4.2 points). The minimal clinically important difference (MCID) has not been established for MS patients so far. The trend towards improvement of DGI scores in both groups slowed down after the second week (Fig 1B). We suspect that participants in both groups would have greater improvements in DGI scores if we provided them continuing one-on-one training with the physical therapists. Even though the compliance rate for the both groups was $\geq 92\%$, it may have been difficult for participants to achieve the same effects of the one-on-one training with the therapists after the second week, especially for the subjects in the MAC, as it required them to properly adjust the different levels of exercises themselves.

Effects on Gait

The subjects in the study demonstrated a similar significant decrease of 14.33 (30.80\%) and 10.31 (25.01\%) points (percentage change) in MSWS-12 at 6-week period in MAC and TEC groups respectively. This is evident by our DGI findings, as the DGI is also a clinical tool to assess gait performance in response to changing task demands. Moreover, it is consistent with our previous result that both MAC and TEC group had similar
significant improvements in the walking speed and step length in patients with MS. There is no MCID established for the MSWS-12, but a study reported the minimal detectable change (MDC) for the measure was 22 points. Although it indicates the participants’ perception of the change would not be likely to represent a true change in their gait ability, we suspect that a greater or true improvement would be achieved if our participants would have continued one-on-one training with the physical therapists after the second week.

Effects on Fatigue

Fatigue was significantly diminished in both groups, with a 35.33-point (49.48%) decrease in MAC and a 29.62-point (54.77%) decrease (percentage change) in TEC with regards to the MFIS total score at the 6-week period. To our knowledge, this is the first study to demonstrate that the high-frequency physical therapy protocols are beneficial to improve fatigue in patients with MS. The beneficial effects also exceeded previous reports from various rehabilitation studies: 55 minutes per session, twice weekly, 6-week vestibular program (21.5 points, p<0.001), 30 minutes per session, 3 times weekly, 12-week supported treadmill program (13.3 points, p=0.22), and 40 minutes per session, 3 times weekly, 12-week mixed exercise program (13.0 points, p=0.02). The minimal detectable change (MDC) for the MFIS was found to be 19.23%, while our study showed an improvement of 49.38% and 54.77% in MAC and TEC at 6 weeks respectively, suggesting our high-frequency physical therapy protocols may have resulted in clinically important changes in fatigue as measured by the MFIS. Fatigue is one of the major factors affecting people with MS. Fatigue can worsen MS other MS-related symptoms and lead to increased risk of falls. The cause of fatigue in MS is most likely
multifactorial, including axonal degeneration, demyelination, depression, and physical inactivity.\textsuperscript{104} There is cumulating evidence demonstrating that exercise intervention is safe and it has significant reductions in fatigue in people with MS.\textsuperscript{20,24} Improvements in fatigue from our high-frequency physical therapy protocols may result from improvements in balance, walking ability, and psychosocial variables, such as depression and mood. Consequently, participants may be able to perform daily tasks in a more efficient manner at relatively lower intensities, which results in energy conservation and fatigue improvement.

Effects on QOL

In this study, total MSIS-29 score showed statistically significant improvement for both groups, but no significant interaction effect between group and time. The MCID values have not been established for the MSIS-29, but the MDC has been reported to be 8 points.\textsuperscript{93} The subjects in this study had a mean change of 20.93 (MAC) and 16.85 (TEC) points in the MSIS-29 after 2-weeks of training with therapists, indicating the participants’ perception represent a true improvement of the score. However, there was a minimal improvement of the score during the 4-week home-based training for both groups. It could be due to the lack of motivation and encouragement directly from therapists and other participants at home, even though the compliance rate for the home-based training was relatively high for both groups (≥92%). There has been cumulative evidence to support that physical activity is associated with the improvement of QOL in patients with MS.\textsuperscript{95} Several factors have been proposed to be mediators of the physical activity on QOL in MS, such as physical function, fatigue, mood, and social support.\textsuperscript{94}
Our high-frequency physical therapy protocol may improve QOL in MS through its effects on the previous factors and it remains to be explored in future studies.

This study was designed to test if our motor adaptation therapy protocol would yield better improvements in balance, gait, fatigue, and QOL in people with MS compared with the therapeutic exercise protocol. After 6-week intervention, both groups showed significant improvements in balance, gait, fatigue, and QOL, however, no interaction effects between group and time were found for the aforementioned factors. Since both cohorts completed different training protocols at the same frequency, a high-frequency physical therapy protocol might be an effective and efficient dosage parameter for the rehabilitation of individuals with MS.

Limitations

There are a few limitations in the present study. First, our clinical investigation was based on a relatively small sample size to differentiate the treatment effects between the two groups. However, the large effect size of the improvements in clinical measures suggests that the findings are less likely to be affected by sample size. A larger sample size could improve the generalizability of our findings. Second, there is variability in the level of disability of participants with MS from moderate to severe. We limited the subjects’ EDSS from 3.0 to 6.5. There was no significant difference between two groups with regard to the participants’ mean score of the EDSS at baseline. However, a more homogenous subset of participants according to the severity of disability may have produced different outcomes. And the benefits of high-frequency physical therapy training for patients with more severe disability (EDSS > 6.5) require further
investigation. Third, there is a lack of a controlled group trained at a normal-dosage or less-frequent physical therapy. It would be of help to explore if the high frequency of the physical therapy has a ceiling effect, or if there is a different treatment effect between two different protocols at a typical-dosage level of physical therapy. Finally, we did not perform a follow-up study to determine whether the treatment effect would maintain after the intervention. Subsequent investigations on long-term effectiveness of the high-frequency physical therapy in people with MS would be desirable.

**Conclusions**

Our study shows both motor adaptation exercises and traditional exercises had a significant, but similar treatment effect for primary outcomes after 6-week physical therapy intervention. Our results provide evidence that a high-frequency physical therapy intervention consisting of twice per day and five days per week sessions may be an important parameter for improving balance, gait, fatigue, and QOL in people with MS.


