

ADAPTED EXERCISE AND PROGRESSIVE MULTIPLE SCLEROSIS

ADAPTED EXERCISE INTERVENTIONS FOR PERSONS WITH PROGRESSIVE
MULTIPLE SCLEROSIS

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A Thesis Submitted to the School of Graduate Studies in Partial Fulfillment of the
Requirements for the Degree Doctor of Philosophy

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PhD Thesis - Lara A. Pilutti; McMaster - Kinesiology

McMaster University DOCTOR OF PHILOSOPHY (2012) Hamilton, Ontario

(Kinesiology)

TITLE: Adapted Exercise Interventions for Persons with Progressive Multiple Sclerosis

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NUMBER OF PAGES: xvi, 201

ABSTRACT

Multiple sclerosis (MS) is an immune-mediated neurodegenerative disease that results in a myriad of physical and mental symptoms. Current disease-modifying therapies do not prevent long-term disability accumulation and are particularly ineffective for patients with a progressive disease onset. Exercise may represent an alternative strategy for managing symptoms and disability accumulation, particularly in progressive MS.

Whereas the benefits of exercise have been established primarily in ambulatory MS patients with a relapsing disease course, few studies have investigated the benefits of exercise for patients with progressive MS with greater impairment. Therefore, the purpose of this dissertation was to determine the short-term, long-term, and maintenance effects of adapted exercise interventions for patients with progressive MS of high disability which was addressed by conducting two adapted exercise interventions.

The first intervention examined the effects of 24 weeks of body weight supported treadmill training (BWSTT) on outcomes of physical and mental functioning, fatigue, quality of life, and brain health. Outcomes were evaluated at baseline, 12, and 24 weeks following the intervention, and again 12 weeks post-intervention. The second intervention evaluated and compared the effects of 12 weeks of total-body recumbent stepper training (TBRST) to BWSTT on outcomes of safety, physical and mental functioning, fatigue, quality of life, and equipment preference.

Safety of BWSTT and TBRST was established. Significant improvements in fatigue and QoL were observed with both training modalities; however, neither

significantly improved physical function. There was some evidence to suggest long-term BWSTT may improve cognitive performance and brain health, and that TBRST was the preferred exercise modality. Furthermore, most beneficial effects of long-term BWSTT tended not to be maintained when exercise was discontinued.

This dissertation established evidence for the potential benefits of BWSTT and TBRST in patients with progressive MS with high disability. BWSTT and TBRST may represent viable alternative strategies for disease management.

ACKNOWLEDGEMENTS

I would first like to acknowledge the support and advice from my supervisor and supervisory committee throughout this process. Audrey, thank you for your patience and guidance throughout my entire PhD. You have always supported me in all of my pursuits and helped guide me down an academic career path. I would also like to thank Dr. Paulseth for providing me with his clinical advice and assistance throughout these projects.

To everyone at the Centre for Health Promotion and Rehabilitation, I have had many great and unique experiences working here and have had the opportunity to meet so many incredible people in this process. The training programs conducted in this dissertation would not have been possible without the assistance and dedication of many student volunteers and staff at the Centre. In particular, I would like to acknowledge Jenn Hohol and Alan Tan for their support throughout these projects. To Susie Ward, for being a great program coordinator and an amazing friend!

Importantly, I would like to thank the people who truly made this research possible: the participants with multiple sclerosis. I would like to thank them and their families for their time and dedication to this research. I feel lucky to have had the opportunity to meet these wonderful people and share their lives with them.

To my fellow graduate students who have gone through this journey with me for all of their advice and friendship over the years. Chelsea, thank you for your support and going on crazy adventures to Ottawa with me!

Finally, I could not have gone through this process without the continual love and encouragement from my family, friends, and Mike. Thank you for keeping me motivated and supporting me no matter what. Mike, thank you for experiencing all of the ups and downs of this process together with me. I look forward to all of the new and exciting challenges and experiences in our future.

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ABBREVIATIONS

3T	Three-Tesla
9HPT	Nine-Hole Peg Test
ADC	Apparent diffusion coefficient
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BBB	Blood-brain barrier
BBS	Berg Balance Scale
BDNF	Brain-derived neurotrophic factor
BI	Barthel Index
BWSTT	Body weight supported treadmill training
CN	Caudate nucleus
CNS	Central nervous system
cMFIS	Cognitive Modified Fatigue Impact Scale subscale
Cr	Creatine
CR-EAE	Chronic-relapsing experimental autoimmune encephalomyelitis
CRP	C-reactive protein
CSF	Cerebrospinal fluid
DTI	Diffusion tensor imaging
EAE	Experimental autoimmune encephalomyelitis
EDSS	Expanded Disability Status Scale
ELISA	Enzyme-linked immunosorbent assay
ES	Effect size
FA	Fractional anisotropy
FAMS	Functional Assessment of Multiple Sclerosis
FIM	Functional Independence Measure
FOV	Field of view
FS	Feeling Scale
FSS	Fatigue Severity Scale

GA	Glatiramer acetate
Gln	Glutamine
Glu	Glutamate
GM	Grey matter
GP	Globus pallidus
GPC	Glycerophosphocholine
¹ H-MRS	Proton magnetic resonance spectroscopy
HLA	Human leukocyte antigen
HR	Heart rate
IFN-B	Interferon-beta
IFN- γ	Interferon-gamma
IL-1 β	Interleukin-1 beta
IL-4	Interleukin-4
IL-6	Interleukin-6
IL-10	Interleukin-10
IL-17	Interleukin-17
Lac	Lactate
MC	Motor cortex
MD	Mean diffusivity
MFIS	Modified Fatigue Impact Scale
MHC	Major histocompatibility complex
mI	myoinositol
MRI	Magnetic resonance spectroscopy
MS	Multiple sclerosis
MSSE	Multiple Sclerosis Self-Efficacy scale
MSFC	Multiple Sclerosis Functional Composite
MSQoL-54	Multiple Sclerosis Quality of Life-54
MSWS-12	Multiple Sclerosis Walking Scale-12
NAA	N-acetylaspartate

NAWM	Normal appearing white matter
NEX	Number of excitations
NGF	Nerve growth factor
PA	Physical activity
PASAT	Paced Auditory Serial Addition Test
pMFIS	Physical Modified Fatigue Impact Scale subscale
PPMS	Primary progressive multiple sclerosis
PRESS	Point RESolved Spectroscopy
PRMS	Progressive relapsing MS
psMFIS	Psychosocial Modified Fatigue Impact Scale subscale
PUT	Putamen
QoL	Quality of life
RCT	Randomized controlled trial
ROI	Region of interest
RPE	Rating of perceived exertion
RRMS	Relapsing remitting multiple sclerosis
SCI	Spinal cord injury
SOD	Superoxide dismutase
SPMS	Secondary progressive multiple sclerosis
T	Thalamus
T25FW	Timed 25-foot walk
TBRST	Total body recumbent stepper training
TE	Echo time
TR	Relaxation time
TNF- α	Tumour necrosis factor-alpha
TUG	Timed Up-and-Go
WM	White matter

CONTRIBUTION TO PAPERS WITH MULTIPLE AUTHORS

Please be advised that the manuscripts included within this dissertation (Chapters 2-6) have been prepared for submission as journal publications with multiple authors. As such, there is some degree of overlap in manuscript content primarily with respect to training intervention details and methodologies. Author contributions for each Chapter are provided below.

Chapter 2

Pilutti LA, Lelli DA, Paulseth JE, Crome M, Jiangs S, Rathbone MP, Hicks AL. Effects of 12 weeks of supported treadmill training on functional ability and quality of life in progressive multiple sclerosis: A pilot study. *Arch Phys Med Rehabil* 2011;92:31-36.

Contribution

LAP, DAL, JEP, SJ, MPR, and ALH were involved in study conception and design. EDSS assessments were conducted by JEP. MSFC, MFIS, and QoL testing were conducted by LAP with assistance from MC. The exercise training protocol was organized and overseen by LAP with the assistance of study coordinator Susie Ward and undergraduate student volunteers. Statistical analyses and manuscript preparation were completed by LAP with editing contributions from the rest of the research team.

Chapter 3

Lara A. Pilutti, Michael D. Noseworthy, John E. Paulseth, Danny A. Lelli, Christopher R. Hansebout, Shucui Jiang, Michel P. Rathbone and Audrey L. Hicks. Long-term effects of supported treadmill walking in persons with progressive multiple sclerosis.

Contribution

LAP, MDN, JEP, DAL, SJ, MPR, and ALH were involved in the study conception and design. EDSS assessments were conducted by JEP. The exercise training protocol was organized and overseen by LAP with the assistance of study coordinator Susie Ward and undergraduate student volunteers. BDNF ELISAs were conducted by CRH and LAP. MSFC, MFIS, and QoL testing were conducted by LAP. Blood samples were drawn by nursing staff of Hamilton Health Sciences at Juravinski Hospital. MRI assessments were conducted by imaging technologists at the Imaging Research Centre at Joseph's Healthcare Hamilton. Statistical analyses and manuscript preparation were completed by LAP and edited by ALH.

Chapter 4

Lara A. Pilutti, Michael D. Noseworthy, John E. Paulseth, Danny A. Lelli, Shucui Jiang, Michel P. Rathbone and Audrey L. Hicks. Exercise reduces brain iron content in progressive multiple sclerosis: Pilot findings using susceptibility-weighted imaging.

Contribution

LAP, MDN, JEP, DAL, SJ, MPR, and ALH were involved in the study conception and design. EDSS assessments were conducted by JEP. The exercise training protocol was organized and overseen by LAP with the assistance of study coordinator Susie Ward and undergraduate student volunteers. MRI assessments were conducted by imaging technologists at the Imaging Research Centre at Joseph's Healthcare Hamilton. Statistical analyses and manuscript preparation were completed by LAP with editing contributions from the rest of the research team.

Chapter 5

Lara A. Pilutti, John E. Paulseth, Danny A. Lelli, Shucui Jiang, Michel P. Rathbone and Audrey L. Hicks. Maintenance of exercise effects in individuals with progressive MS: A 12-week post-treadmill training follow-up.

Contribution

LAP, JEP, DAL, SJ, MPR, and ALH were involved in the study conception and design. EDSS assessments were conducted by JEP. MSFC, MFIS and QoL testing were conducted by LAP. The exercise training protocol was organized and overseen by LAP with the assistance of study coordinator Susie Ward and undergraduate student volunteers. Statistical analyses and manuscript preparation were completed by LAP and edited by ALH.

Chapter 6

Lara A Pilutti, John E Paulseth, Carin Dove, Shucui Jiang, Michel P Rathbone, and Audrey L Hicks. Alternative exercise modalities for persons with multiple sclerosis.

Contribution

LAP, JEP, SJ, MPR, and ALH were involved in the study conception and design. EDSS assessments were conducted by JEP and CD. MSFC, MFIS, MSWS-12, MSSE QoL, and evaluation of exercise equipment were administered by LAP. The exercise training protocol was organized and overseen by LAP with the assistance of undergraduate student volunteers. Statistical analyses and manuscript preparation were completed by LAP with editing contributions from the rest of the research team.

CHAPTER 1

INTRODUCTION

1.0 INTRODUCTION

1.1 MULTIPLE SCLEROSIS

1.1.1 Introduction to Multiple Sclerosis

Multiple sclerosis (MS) is a chronic and debilitating immune-mediated disease characterized by inflammation and neurodegeneration of the central nervous system (CNS).¹ A diagnosis of MS typically occurs between the ages of 15 and 40 years; however, it can be identified in childhood or late adulthood, although this is rare.² The disease occurs more commonly in women than men, and the incidence is generally higher in people of northern European descent.^{2,3} The global distribution of MS tends to follow a latitudinal gradient, such that disease incidence increases with distance travelled away from the equator, although this is not always the case.⁴ Canada, therefore, has one of the highest prevalence of MS worldwide with rates ranging from approximately 55-350 cases of MS per 100,000 people, and approximately 55,000-75,000 people currently living with the disease.^{2,5}

It is believed that MS is an immune-mediated disease, although the exact cause of such immune dysfunction is unclear. Both environmental and genetic contributions have been implicated in disease development. It is suggested that MS develops in individuals with a particular genetic predisposition who are exposed to one or more environmental triggers.^{4,6} The genetic component of MS is complex and may involve many susceptibility genes. Several alleles of the major histocompatibility complex (MHC), particularly HLA-DRB1, as well as some non-MHC alleles have been associated with increased risk of MS.⁶ The familial recurrence rate of MS is approximately 20%, and the

risk of MS is 3 to 5% if a first degree relative is affected, highlighting a non-genetic contribution to disease development.⁴ Several environmental factors have been suggested to be involved in MS development, including viruses, infections, diet, sunlight and vitamin D status, pollutants, and toxins⁴; however, no single environmental factor has been identified as the disease trigger.¹ The contribution of multiple environmental and genetic factors in the development of MS makes it extremely challenging to understand and treat this complex disease.

1.1.2 Pathology of Multiple Sclerosis

The pathological hallmark of MS is the sclerotic plaque, which represents the end stage of multiple underlying processes resulting in tissue damage.⁴ This resulting damage is believed to be initiated by an immune cell infiltration of the CNS, which may include T and B lymphocytes, monocytes, and antigen-presenting cells.^{4,7} The integrity of the blood-brain barrier (BBB) is compromised in persons with MS allowing the infiltrate to permeate the CNS.⁸ Entry of the infiltrate triggers both innate and adaptive immune responses.⁷ The consequent immune-mediated cascade results in tissue injury, the main targets of which are myelin, oligodendrocytes, and neurons.^{9,10}

The early course of MS is characterized by focal inflammatory demyelination which typically progresses to axonal degeneration, although it has been suggested that axonal degeneration may also occur separately from demyelination.⁹ Tissue damage in MS may be mediated through a number of pathways including antibody-dependent cytotoxicity, cytokine-mediated injury, complement-mediated injury, and direct T-cell mediated injury.⁴ The CNS possesses the capacity for self-repair and remyelination of

damaged axons; however, with each successive demyelinating-remyelinating cycle this process becomes less successful and is eventually exhausted.⁴ Demyelination results in slowed and improper neuronal signal conduction resulting in many of the outward clinical symptoms experienced by persons with MS.⁴ Exposure of demyelinated axons to an unfavourable inflammatory environment (i.e., proteases, cytokines, complement, oxidative products, and free radicals) may further lead to axonal degeneration.^{1,9} Insufficient energy supply and glial support to axons may also contribute to neurodegeneration.⁹ It is believed that the loss of neurons and axons is the primary contributor to long-term neurological disability in patients with MS.^{1,9}

1.1.3 Impairments Associated with Multiple Sclerosis: Symptoms and Treatment

The underlying disease processes of MS can result in extensive and significant damage to the brain, spinal cord, and optic nerve. Damage in the CNS results in a myriad of physical and mental symptoms experienced by people with MS. Based on the location and severity of tissue damage, symptoms of MS may include muscle weakness, ataxia, tremor, spasticity, paralysis, imbalance, cognitive impairment, loss of vision, double vision, vertigo, impaired swallowing and speech, sensory deficits, bladder and bowel dysfunction, pain, fatigue, and depression.⁴

The symptomatic experience and impact of MS from a patient perspective is also important for understanding and treating this complex disease. The symptoms experienced most commonly, as reported by a large sample of persons with MS, include fatigue, abnormal sensations, losing balance, muscle spasms, and pain.¹¹ Difficulty walking was reported by 41% of people with MS, 70% of which concluded it was the

most challenging aspect of their MS.¹¹ Further, physical, emotional, social, and economic aspects of life were also impacted by walking difficulties, highlighting the importance of managing ambulatory deficits in persons with MS. The experience of MS has a significant impact on the quality of life (QoL) of patients with the disease, as well as those caring for them.¹¹ Consequently, developing disease-modifying and symptom-management strategies are critical.

Due to the complex disease characteristics and the breadth of symptoms experienced by patients with MS, treatment of the disease has been particularly challenging. There are a number of disease-modifying therapies currently approved for the treatment of MS, with many more currently under investigation.¹² Some common agents used for MS treatment include interferons, glatiramer acetate, natalizumab, mitoxantrone, and fingolimod.¹² Most disease-modifying therapies act through immunomodulatory or immunosuppressant actions; however, more recent efforts have also focused on the development of agents with neuroprotective potential.¹¹ Disease-modifying therapies have proven effective in reducing relapses and slowing early disease progression; however, over time these therapies become ineffective, resulting in long-term disability accumulation.^{12,13} Consequently, exploring alternative disease-management strategies, particularly for patients in the later stage of the disease, will be important to the management of MS.

Although symptom management has been less rigorously investigated than disease-modifying therapies, a number of strategies have been prescribed for patients with MS.¹⁴ A variety of pharmacological, surgical, behavioural, and physical therapy

interventions have been attempted for the treatment of symptoms experienced by patients with MS, although support for treatment efficacy is variable.¹⁴ Symptom-management in MS has proven challenging, which may in part be due to the number of co-occurring symptoms experienced by persons with MS. For example, Motl and colleagues¹⁵ determined symptoms of fatigue, depression, pain, and perceived cognitive deficits co-occurred in persons with MS. An individualized, multi-disciplinary disease management approach is necessary to treat the many and co-occurring symptoms experienced by individuals with MS.¹⁴ Treatment strategies will likely require continual re-evaluation and modification as the disease evolves over time.¹⁴

1.1.4 Multiple Sclerosis Subtypes and Clinical Disease Course

The clinical course of MS has been described as proceeding in four common patterns including: relapsing remitting MS (RRMS); primary progressive MS (PPMS); secondary progressive MS (SPMS); and progressive relapsing MS (PRMS).¹⁶ At onset, typically 80% of cases are diagnosed as RRMS.⁴ The RRMS disease course is characterized by clinical stability with acute, intermitted bouts of neurological dysfunction, or relapses which are believed to be the clinical manifestation of inflammatory demyelinating lesions.^{16,17} The recovery from relapses can be partial or complete, and results in progressive symptom and disability accumulation.⁴ Over time, the majority of RRMS cases develop into a progressive phase with or without relapses, minor remissions, and plateaus which is characterized as SPMS.^{4,16} Approximately 15% of patients present as PPMS from onset which is characterized by a progressive and gradual worsening, with the absence of relapses or disease remission.^{16,17} Patients with a

PRMS course have a similar disease presentation as patients with PPMS although they concurrently experience acute relapses, with or without full recovery.¹⁶ Defining and classifying the clinical course of MS is important in predicting disease manifestation, prognosis, progression, and treatment in both clinical and research settings. Progressive MS will be further explored in subsequent sections.

Disease progression and the consequent accumulation of disability differ according to MS disease course, as well as other clinical and demographic characteristics.^{18,19} Disability benchmarks, based on Expanded Disability Status Scale (EDSS) scores, have been used to characterize the pattern of disability progression in MS.²⁰ The EDSS is the most commonly used measure of neurological impairment and disability in persons with MS and ranges from 0-10, whereby higher scores indicate greater disability.²⁰ EDSS scores of 4.0 (limited walking ability, but able to walk more than 500 meters without aid or rest), 6.0 (ability to walk with unilateral support no more than 100 meters without rest), and 7.0 (ability to walk no more than 10 meters without rest while leaning against a wall or holding onto furniture for support) have been used to characterize disability progression in MS.¹⁸⁻²⁰ Natural history studies have identified median time to reach EDSS scores of 4.0, 6.0, and 7.0, to be 11.4, 23.1, and 33.1 years, respectively, in patients with a RRMS disease course from onset, and 0.0, 7.1, and 13.4 years, respectively, in patients with a progressive disease course from onset.¹⁹ Progression from an EDSS score of 4.0 to 6.0; however, did not differ by disease course. Additional clinical and demographic variables influenced the course of early disease progression including gender, age, symptoms, degree of recovery from the first relapse,

time to a second neurological episode, and number of relapses in the first five years of the disease.¹⁸ Progression from an EDSS score of 4.0 to 6.0 or 7.0 or from an EDSS score of 6.0 to 7.0 was not affected by any clinical or demographic factors.¹⁸ Importantly, these findings suggest that the early course and progression of disability in MS may differ depending on clinical and demographic features; however, long-term disability accumulation proceeds in a similar manner irrespective of other factors.

1.1.5 Progressive Multiple Sclerosis: Natural History and Clinical Features of Progressive Multiple Sclerosis

Patients with progressive MS represent a unique subset of the MS population and differ from patients with a relapsing remitting disease course on a number of epidemiological and etiological factors. A diagnosis of PPMS occurs approximately 10 years later than RRMS, although at a similar time when the transition from RRMS to SPMS occurs.^{18,21} Natural history studies reveal approximately 50-60% of patients initially diagnosed with RRMS transition to SPMS over time.²² Unlike RRMS, PPMS does not demonstrate the classic female predominance, with women and men being equally affected.^{18,21} Patients with PPMS are typically characterized by a progressive spastic paraparesis, slowly developing into quadriparesis.²³ Other, although less common, clinical phenotypes include cerebellar dysfunction, hemiplegia, brainstem syndromes, visual loss, and cognitive decline.²³ Patients with PPMS may also experience more severe symptomatology. For example, patients with PPMS experience fatigue more commonly and more severely than patients with RRMS.^{24,25}

Differences between the clinical course of RRMS and PPMS (i.e., presence of relapses) are reflected by differences in pathological features, suggesting a neurodegenerative rather than inflammatory predominance, although it is unclear as to the mechanisms that may be causing such differences.²¹ Patients with PPMS present with less focal inflammatory lesions, fewer gadolinium-enhancing lesions, more diffuse axonal injury, more cortical demyelination, and greater spinal cord involvement than patients with RRMS.²¹ As the pathological features of progressive MS are less inflammatory in nature, traditional disease-modifying therapies have therefore, had little success in treating this patient population.²⁶ The development of alternative disease-modifying strategies is necessary for the management of patients with progressive MS.

1.2 PHYSICAL ACTIVITY AND MULTIPLE SCLEROSIS

1.2.1 Physical Activity for Persons with Multiple Sclerosis

Participation in physical activity (PA) was originally contraindicated for patients with MS as it was thought that exercise would exacerbate MS symptoms, particularly fatigue.²⁷ It has become established that exercise is safe and well-tolerated by patients with MS. For example, a study examining the effects of an acute bout of combined (i.e.: aerobic, resistance, and stretching) moderate intensity exercise found patients did not report a significant change in fatigue or general physical function immediately post- and 24 hours post-exercise.²⁸ Patients did, however, report a temporary increase in sensory symptoms immediately following exercise; tingling, weakness, blurred vision, and vibration were most frequently reported. Sensory symptoms returned to baseline within a mean time of 18.6 minutes post-exercise. Furthermore, a recent study demonstrated that

increased participation in PA was not associated with a greater number of disease relapses in a large sample of patients with MS (mean EDSS = 3.0).²⁹ In fact, patients stratified as most active actually reported the fewest number of disease relapses. Not only has exercise been found to be safe and well-tolerated by patients with MS, many physical and mental health benefits have also been established.^{30,31} PA participation and the potential relationship with disability progression in persons with MS will be explored in the proceeding section.

1.2.2 Physical Activity Levels in Persons with Multiple Sclerosis

Despite the known benefits of PA, it has been established that people with MS report being less physically active than the non-diseased adult population.³² In a large sample of individuals with MS, fewer than 25% reported participating in moderate or heavy intensity leisure-time PA.³³ PA levels assessed by both self-report and objective measures were also significantly reduced in persons with MS when compared to non-MS controls matched for age, sex, height, and weight.³⁴ Lower levels of self-reported PA have been associated with greater neurological impairment and disability.^{33,35} Disability progression over a 6-month period was further associated with a concurrent reduction in PA behaviour.³⁶ Taken together, these findings suggest PA levels are lower in individuals with MS with greater impairment and the accumulation of disability over time results in less participation in PA.

A proposed relationship between MS, PA, and physiological and functional impairment has been put forward by Motl (Figure 1.1).³⁷ It is suggested that deficits associated with MS, such as muscle weakness and fatigue, result in a reduced ability to

participate in PA. Physical inactivity, in turn, contributes to aerobic and muscular deconditioning. Impairments in cardiorespiratory, metabolic, and muscular fitness have been documented in persons with MS compared to non-MS controls.^{38,39} Physiological deconditioning, in turn, results in mobility limitations which, in a cyclical manner further limits the ability of patients with MS to participate in PA. This process creates a vicious cycle whereby people with MS continue to accrue disability, which further limits their ability to participate in PA. Patients with PPMS in particular, are less physically active than those with RRMS.³² Reduced PA levels in combination with faster disability accumulation may further compound this already debilitating cycle in patients with PPMS.

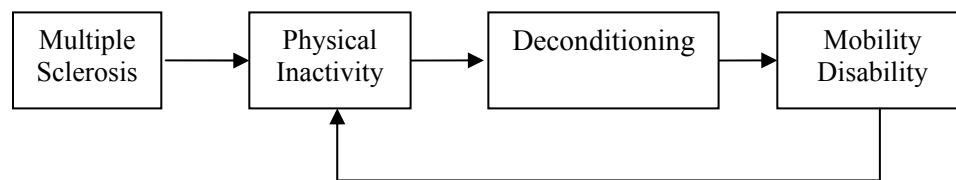


Figure 1.1 Relationship between MS, physical inactivity, deconditioning and mobility disability as described in Motl.³⁷

Reproduced with permission from Wolters Kluwer Health. Motl RW, Irreversible disability and physical activity in multiple sclerosis, *Exercise and Sport Sciences Reviews*, 2010;38(4):186-191.

Reduced participation in PA further places individuals with MS at an increased risk of comorbid health conditions. In a large sample of patients with MS, hypercholesterolemia, hypertension, and arthritis were the most frequently reported comorbid health conditions.⁴⁰ Vascular comorbidities in MS have further been associated

with an increased risk of disability progression.⁴¹ Exercise represents a potential solution to limit the consequences of this vicious cycle (Figure 1.1). Exercise interventions may improve the physical functioning of individuals with MS, which in turn, may maintain and/or improve mobility. Engaging in exercise may further improve fatigue, cognitive function, and QoL, which may also impact PA participation. Consequently, increased functioning may allow individuals with MS to participate in more PA and acquire the resulting health benefits. Although the results are less clear, exercise may also have direct effects on underlying disease processes in persons with MS.

1.3 BENEFITS OF EXERCISE FOR PERSONS WITH MULTIPLE SCLEROSIS

1.3.1 Benefits of Exercise for Physical Fitness and Mobility

Benefits in physical fitness have been observed following both traditional, as well as less traditional exercise interventions in individuals with MS. A number of studies has demonstrated improvements in cardiorespiratory fitness (i.e.: aerobic capacity and power output) in response to exercise interventions.⁴²⁻⁴⁸ Improvements in muscular strength have also been demonstrated following resistance training, as well as other exercise interventions in persons with MS.^{48,49-52} Improvements in leg strength in particular, may be an important benefit of exercise training for persons with MS. Strength of the lower extremities is affected by the disease often earlier and to a greater extent than strength of the upper-extremities.^{53,54} Improvements in other fitness outcomes may include increased flexibility, although the evidence is currently limited.⁵⁵⁻⁵⁸

Mobility outcomes have been among the most commonly examined measures in exercise interventions for individuals with MS. Many studies have demonstrated

improvements in walking speed and walking endurance following aerobic, resistance, and alternative exercise.^{44,49,52,59,60} A meta-analysis of the effects of exercise on walking determined a mean overall effect of .19, suggesting a small effect of exercise on walking ability.⁶¹ The effects of exercise on other mobility outcomes such as agility, balance, and gait have been less studied and are less conclusive. Some studies have demonstrated improvements in agility, assessed by the Timed Up-and-Go (TUG) test, in response to aerobic, resistance, and stability training programs.^{50,55-57,62} Few studies have examined the effect of exercise on balance in persons with MS. Improvements in balance assessed by the Berg Balance Scale (BBS) have been observed following group aquatic and stability training.^{60,63} A loss of balance is one of the most commonly reported symptoms experienced by persons with MS¹¹; further research is therefore needed to determine the potential for exercise to manage balance impairments. The impact of exercise on gait parameters has only been examined in a small number of studies with inconclusive results to date.^{47,64,65}

1.3.2 Benefits of Exercise for Fatigue, Cognitive Function, and Quality of Life

Results are much less conclusive regarding the effects of exercise on fatigue, cognitive function, and QoL outcomes, although several studies provide support for the potential benefits of exercise. Although the evidence is mixed regarding the impact of exercise on fatigue reduction in persons with MS, a number of studies in which fatigue was assessed using the Fatigue Severity Scale (FSS), and the Modified Fatigue Impact Scale (MFIS), have demonstrated a beneficial effect.^{45,63,66-70} To date, two studies have examined the effects of exercise on cognitive performance in persons with MS.^{71,72}

While there has yet to be a significant effect of exercise on cognitive function in persons with MS, the limited number of studies in this area make it premature to draw any conclusions. Several studies have investigated the ability of exercise to improve the QoL of persons with MS, as well as their ability to participate in activities of daily living.

There is some evidence to suggest exercise interventions improve health-related QoL in persons with MS, assessed by a number of health-related QoL scales.^{44,56,62,66,69,72-74}

Accordingly, a small mean effect size of .23 was determined in a meta-analytic review of the impact of exercise on QoL in persons with MS.⁷⁵ The Barthel Index (BI) and the Functional Independence Measure (FIM) are two scales which provide an indication of independence in performing tasks of daily living.^{76,77} Participation in exercise may improve independence in persons with MS assessed using the BI and FIM, although the evidence is limited.^{59,62,73} There is a clear need for an extensive examination of the impact of exercise on mental symptoms of MS, and the consequences for QoL and independence.

1.4 POTENTIAL FOR EXERCISE AS A DISEASE-MODIFYING THERAPY

1.4.1. Traditional Measures of Disability Progression

The measure traditionally used to assess neurological impairment and disability progression in persons with MS is the EDSS. The effect of exercise on EDSS scores has been examined in response to aerobic, resistance, and alternative exercise interventions, with most studies concluding no effect of exercise on EDSS scores.^{42,47-49,59,67,71} A lack of change in EDSS scores in response to exercise training may be due to the limited sensitivity and responsiveness of the scale itself. Alternative measures, such as the

Multiple Sclerosis Functional Composite⁷⁸, have been developed to address the limitations of the EDSS. Few studies, however, have examined the effect of exercise on the MSFC. Romberg and colleagues⁷¹ determined a significant improvement in MSFC scores following combined aerobic and resistance training in a large group of persons with MS. Further evaluation of the effects of exercise on alternative measures of disability progression in MS is warranted.

1.4.2. Evidence from Animal Models of Multiple Sclerosis

Experimental autoimmune encephalomyelitis (EAE) has long been used as the animal model of MS.⁷⁹ Results from a limited number of studies provide support for the role of exercise in influencing the clinical course of MS in the EAE model.^{80,81,82}

Treadmill running (60-120 min) in rats 0-10 days following injection with an EAE-inducing agent resulted in a significant delay in the onset of chronic-relapsing (CR)-EAE (several bouts of disease separated by remission) compared to non-exercising CR-EAE rats.⁸² The duration of the first relapse was also delayed in exercising animals; however, disease severity was comparable between groups. The same research group also examined the effects of 2 days of intense treadmill running (250-300 min/day) in the monophasic EAE model (single bout of disease followed by recovery) immediately following injection.⁸¹ Exercise significantly delayed EAE onset and the day of maximum disease severity, although again there was no effect on overall disease severity.

Additionally, exercise in the form of voluntary wheel running has been shown to attenuate the clinical, dendritic, and synaptic deficits induced by CR-EAE compared to non-exercising control mice.⁸⁰ The authors further suggest the neuroprotective effects of

exercise may be mediated through the release of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), although this was not assessed in this investigation.

1.4.3. Role for Neurotrophic Factors and Cytokines

It has been proposed that neurotrophic factors and cytokines may mediate the effects of exercise on disease processes in MS.^{83,84} Neurotrophic factors are a family of proteins believed to be involved in neuroprotection, neuroregeneration, and neuroplasticity.⁸⁵ BDNF is a particularly activity-dependent neurotrophic factor, making it an excellent candidate for mediating protective effects of exercise in MS.⁸⁶ It has been suggested that a transient dose-response relationship exists between exercise intensity and BDNF production in response to acute aerobic exercise in healthy individuals; however, low-to moderate intensity exercise appears to be sufficient to elicit a BDNF response in populations with chronic disease or disability.⁸⁶ Results are limited and less conclusive regarding the effect of chronic aerobic exercise on resting BDNF concentrations in both healthy and diseased populations.⁸⁶

A limited number of studies have examined the effects of exercise on neurotrophic factors in MS with mixed conclusions. In response to an acute bout of cycling, Gold and colleagues⁸⁷ observed a significant increase in serum BDNF and a trend for an increase in nerve growth factor (NGF) post-exercise. The same group evaluated the impact of chronic cycling in persons with MS and found no change in BDNF or NGF levels at rest or in response to an acute bout of exercise.⁴⁶ Conversely, chronic aerobic exercise was found to reduce BDNF levels in persons with MS and controls following an acute exercise bout, both before and after an 8 week cycling

intervention.⁸⁸ Neurotrophic factor response to acute and chronic exercise clearly requires further investigation in persons with MS.

Cytokines are cell-signalling molecules which play an integral role in cell development, differentiation, and immune regulation.⁸⁹ The inflammatory response in MS can be both harmful and beneficial and it is the balance between these processes that contributes to CNS damage.⁷ Interleukin-6 (IL-6), in particular, may be a candidate cytokine for mediating protective effects of exercise. IL-6 is a myokine (i.e.: a cytokine that is produced and released from skeletal muscle) that increases exponentially in response to acute exercise and has been known to have both pro- and anti-inflammatory effects.⁹⁰ In response to exercise, IL-6 can act in an anti-inflammatory manner by inhibiting the production of pro-inflammatory IL-1 β and TNF- α , and increasing the production of anti-inflammatory cytokines.⁹⁰ The response of IL-6 to an acute bout of exercise has been found to be similar in patients with MS and non-MS controls, both demonstrating significant increases in plasma IL-6.⁹¹ In response to 8 weeks of cycling, patients with MS demonstrated a tendency for reduced resting plasma IL-6; however, resting TNF- α was significantly increased compared to non-MS controls.⁹¹ An 8 week resistance training program tended to reduce resting TNF- α with no effect on resting IL-6 in female patients with RRMS.⁹² Similarly, 8 weeks of cycling did not affect the IL-6 response to acute or chronic aerobic training in persons with MS.⁴⁶

Exercise may play an immunomodulatory role through the regulation of other cytokines known to be involved in neuroinflammation.⁷ A number of pro- and anti-inflammatory cytokines have been modulated in response to acute and chronic exercise

including IFN- γ , IL-17, IL-4, and IL-10.⁹¹⁻⁹⁴ With the small number of studies and variable modalities that have been used to examine the role of exercise on the cytokine profile in MS, it is premature to draw any conclusions as to the exercise response. Further studies are required to establish the relationship between exercise, cytokine regulation, and disease activity in patients with MS, with a particular focus on the potential role of IL-6.

1 4.4. Evidence from Brain Imaging

There is also evidence from brain imaging research that may support a potential role for exercise in promoting structural and functional brain health^{95,96} Cardiorespiratory fitness was found to be positively associated with grey matter (GM) volume and white matter (WM) tract integrity, and this structural integrity further correlated with cognitive processing speed.⁹⁵ A study by the same research group established cardiorespiratory fitness was also related to improved performance on a cognitive task and superior functional recruitment of task-related brain regions.⁹⁶ The prospective role of exercise on brain imaging parameters; however, has yet to be investigated.

1.5 ADAPTED EXERCISE MODALITIES FOR INDIVIDUALS WITH MOBILITY IMPAIRMENTS

To date, the effects of exercise have primarily been investigated in ambulatory patients with MS.³⁰ Individuals with mobility impairment have been restricted from participation in most exercise interventions mainly due to the lack of adapted exercise modalities available. Two adapted exercise strategies that have been implemented in patients with locomotor impairments are body weight supported treadmill training (BWSTT) and total-body recumbent stepper training (TBRST). The methodology and

application of these adapted exercise modalities for persons with MS will further be explored.

1.5.1 Body Weight Supported Treadmill Training

BWSTT is a repetitive task-oriented training modality that allows patients to practice upright walking in a safe environment. Participants are secured in a specialized harness which is connected to an overhead cable system allowing participants to be safely raised and suspended over a treadmill (Figure 1.2). The overhead cable system is attached to weight stacks which offload a portion of the patient's body weight and reduce the effort associated with walking.



Figure 1.2 Body weight supported treadmill training (Woodway-LoCo System, Woodway Inc. USA, Waukesha, WI, USA).

The initial amount of body weight support required to walk on the treadmill is determined on a case-by-case approach and is selected to allow patients to maintain an upright torso and prevent buckling at the knee while standing. Training progression typically proceeds first by increasing treadmill walking speed, followed by reducing the amount of body weight support required to walk on the treadmill. Treadmill walking is facilitated through the aid of two to three therapists, depending on the level of function of the individual. Typically, two trainers are positioned at either lower limb to manually assist in guiding the participant through a proper and symmetrical gait cycle. An additional therapist is positioned behind the patient to assist with weight transfer and stabilization as required.

1.5.1.2 Body Weight Supported Treadmill Training Interventions for Individuals with Multiple Sclerosis

A number of studies have evaluated the potential of BWSTT in patients with chronic mobility impairments. BWSTT has been found to improve mobility, cardiovascular and muscular fitness, and psychosocial health outcomes in persons with stroke and spinal cord injury (SCI).⁹⁷⁻¹⁰² Consequently, BWSTT is an adapted exercise modality that may provide similar beneficial effects for people with MS.

A limited number of interventions have examined the effects of supported treadmill walking for patients with MS. Therapist-assisted overground walking training was compared to BWSTT with robotic assistance in a group of patients with MS of mixed-MS disease course and high disability level (EDSS = 6.0-7.5).¹⁰³ Effect size changes suggest superiority of BWSTT with robotic assistance over overground walking training on outcomes of walking speed and endurance, and knee-extensor strength

following the 3-week intervention (5 sessions/wk, 30min/session). Within group comparisons also demonstrated significant improvements in walking speed and endurance, and knee-extensor strength in the BWSTT group, whereas overground walking training only had significant effects on walking speed. In the same study, a 6-month post-intervention follow-up revealed a return to baseline on all outcomes in both training groups. Lo and Triche¹⁰⁴ similarly evaluated 6 sessions of BWSTT with and without the use of robotic assistance in a mixed-MS subtype patient group with moderate disability (mean EDSS = 4.9). Employing a cross-over study design, no differences were found between the training modalities, and combined effects of both interventions (i.e.: 12 sessions) resulted in significant improvements in function, gait, walking speed, and endurance. The same intervention further resulted in improvements on measures of QoL, perceived fatigue, pain impact, perceived deficits, and life satisfaction.¹⁰⁵ A recent investigation compared the effects of 12 sessions of BWSTT with robotic assistance to a conventional walking training program involving patients with MS (RRMS, PPMS, and SPMS) with high disability level (EDSS = 5.0-7.0).¹⁰⁶ BWSTT with robotic assistance and conventional walking training both significantly improved EDSS scores, FIM scores and balance. BWSTT additionally improved TUG performance, whereas conventional walking training further improved walking speed, walking endurance, and QoL. There was no significant difference between groups in the improvements observed, with the exception of walking speed in favour of conventional walking training over BWSTT. Follow-up evaluation at 3 and 6 months post-exercise revealed most benefits resulting from training were attenuated. Giesser and colleagues¹⁰⁷ were the first to evaluate the

effects of manually-assisted supported treadmill walking in a small group ($n = 4$) of patients with exclusively a SPMS disease course and high disability (EDSS = 7.0-7.5). Improvements were noted in walking speed and endurance, balance, muscle strength, spasticity, and QoL following on average 40 training sessions. BWSTT was also found to be well-tolerated by patients with SPMS of high disability without adverse effects.

Overall, supported treadmill training appears to be superior to conventional overground walking therapy for patients with MS; however, it does not seem to be of importance whether robotic assistance is employed or not. Preliminary results suggest supported treadmill training for patients with MS with severe mobility impairments is safe, well-tolerated, and may have beneficial effects on disability, physical function, MS symptoms, and QoL outcomes. Potential benefits of BWSTT may also not be maintained long-term when exercise is discontinued.

1.5.2. Total Body Recumbent Stepper Training

TBRST is an exercise modality that allows patients to practice stepping from a low-impact seated position (Figure 1.3).



Figure 1.3 Total body recumbent stepper (NuStep™, Ann Arbor, MI, USA).

Using this modality, patients exercise with both upper and lower extremities through the use of coupled arm levers and foot pedals which move in a bilateral reciprocal manner. Graded resistive forces are created using a magnetic eddy current system and can be adjusted through levels 1-10. The smooth stepping motion has been designed to approximate that of natural walking. Similar neuromuscular activation patterns have been shown in recumbent stepping and walking, although TBRST appears to have a much simpler motor activation pattern with different joint kinematics.¹⁰⁸ TBRST has also been found to facilitate recruitment of lower limb muscles through the coupled action of upper limb exercise.¹⁰⁹

The ergonomic design and adjustable features of the NuStep™ make it particularly accessible for patients with mobility impairments. The seat swivels 90 degrees in either direction making it easy for patients in wheelchairs to transfer onto the

equipment. Foot plates are wide with an exterior border and strapping to prevent feet from slipping off the pedals. Arm levers are also retractable and adjust to varying arm lengths. Adapted accessories such as hand straps assist patients with gripping the arm handles when necessary. Leg stabilizers also provide additional unilateral or bilateral leg stability to promote proper leg and foot alignment.

In addition to the accessibility of the NuStep™ trainer, several other features of this piece of equipment make it logistically superior to other adapted training interventions. TBRST is cost-effective, easy to operate and relatively small in size compared to a supported treadmill system. The accessibility of the NuStep™ would allow this piece of equipment to be easily incorporated in home and community exercise settings, which will always be a challenge of BWSTT, regardless of efficacy.

1.5.2.2 Total Body Recumbent Stepper Training Interventions for Individuals with Multiple Sclerosis

Despite the great potential of TBRST as an exercise tool, few studies have empirically evaluated its efficacy in healthy or clinical populations. No studies to date have examined the long-term effects of TBRST exclusively in patients with MS; however, one study compared the acute cardio-respiratory response to maximal exercise testing on four different exercise modalities, including the NuStep™, in 6 women with MS.¹¹⁰ Greater maximal oxygen uptake and higher maximal heart rates were obtained in response to TBRST and combined arm/leg ergometry compared to treadmill walking or leg cycling alone. It is not surprising that the whole-body exercise modalities provided a

greater cardiovascular challenge, and suggests long-term TBRST might provide greater cardiovascular benefits for patients with mobility impairments.

A limited number of investigations have examined the impact of long-term TBRST. Hass and colleagues¹¹¹ determined the effects of 12 weeks of TBRST (3x/week) in sedentary adults. Compared to non-exercising controls, TBRST proved to be effective in improving aerobic capacity, upper and lower body muscular strength and endurance, and body composition, such that lean body mass increased and fat mass and percent body fat were reduced. A group of elderly individuals (mean age 85.5 yrs) in an assisted-living community participated in a 13-week TBRST exercise program.¹¹² Participants who completed > 9 minutes of exercise per week saw improvements in sitting and standing blood pressure, strength, and walking speed. Participants who completed < 9 minutes per week saw no improvements or saw decrements in the same outcomes. A 10-12 week intervention of TBRST in Parkinson's patients also revealed improvements in walking speed and step length; however, no improvements in disease severity were observed.¹¹³ Page and colleagues¹¹⁴ compared the effects of TBRST to a home-based exercise program in 7 patients >1 year post-stroke. Improvements in balance and impairment were seen following the TBRST intervention, which were not exhibited following home-based exercise. Preliminary results suggest beneficial effects of long-term TBRST on cardiovascular, muscular, and functional health outcomes. Further research is needed to determine if the beneficial effects of TBRST can be realized in persons with MS.

1.6 SUMMARY OF BACKGROUND AND DEVELOPMENT OF THESIS QUESTIONS

MS is a debilitating CNS disease that results in the progressive accumulation of disability over time. MS has many physical and mental health consequences that limit the independence and QoL of those living with the disease.¹¹ While successful early on, disease-modifying therapies eventually become ineffective in reducing relapses and slowing disease progression, resulting in long-term disability accumulation.^{13,19} The combination of reduced PA and disease progression in persons with MS may compound mobility impairment over time.³⁷

Exercise represents a potential strategy to manage the many and varied consequences of MS; the benefits of exercise have been established primarily in ambulatory patients with RRMS. The role of exercise as a disease-modifying therapy has received little attention, warranting further research in this area. The effects of exercise have been understudied in patients with more severe disability (i.e.: EDSS \geq 5.0) and patients with progressive MS, both primary and secondary. As patients with PPMS reach disability benchmarks sooner than patients with RRMS, have few options for disease-modifying therapies, and are less active than persons with RRMS, it is imperative to develop and evaluate adapted exercise strategies for this patient population.

Supported treadmill training and recumbent stepper training may be effective adapted therapeutic strategies for patients with progressive MS with severe mobility impairment. Their beneficial effects have been realized in other populations with mobility impairments; however, they have not been extensively evaluated in persons with MS. The purpose of this dissertation was, therefore, to evaluate alternative exercise interventions for patients with progressive MS with severe mobility impairment. Specifically, the

purpose of the first investigation in this dissertation was to determine: (a) the effect of 12 weeks of BWSTT on outcomes of physical and mental functioning, fatigue, and QoL; (b) the effect of 24 weeks of BWSTT on outcomes of physical and mental functioning, fatigue, QoL, BDNF, and brain imaging parameters; and (c) the maintenance of BWSTT-induced changes on outcomes of physical and mental functioning, fatigue, and QoL, by evaluating participants 12 weeks following completion of the 24-week BWSTT intervention in patients with PPMS of high disability ($EDSS \geq 5.0$). It was hypothesized that 12 weeks of BWSTT would be effective in improving fatigue and QoL, but may not be sufficient to significantly improve physical and mental functioning. It was hypothesized that 24 weeks of BWSTT would be a sufficient intervention period for improving physical and mental functioning, fatigue, QoL, neurotrophic factors, and brain imaging parameters. Further, it was hypothesized that benefits resulting from participation in BWSTT would not be maintained at 12-week follow-up.

Whereas BWSTT may be an effective form of therapy for patients with mobility impairments, there are numerous challenges and barriers to this type of intervention. BWSTT is labour-intensive, costly and requires several, highly-trained personnel to operate. Consequently, there is also the need to evaluate accessible and effective exercise interventions that would be applicable for home and community-based settings. Therefore, the purpose of the second investigation detailed in this dissertation was to determine: (a) the safety and tolerability of TBRST in patients with progressive MS of high disability ($EDSS = 6.0-8.0$); (b) whether 12 weeks of TBRST is as effective as BWSTT on outcomes of physical and mental functioning, fatigue, and QoL; and (c)

patient reported evaluation and recommendation of experience with TBRST and BWSTT. It was hypothesized that TBRST would be safe and well-tolerated by patients with progressive MS and would have beneficial effects on outcomes assessed. Due to the task-specific nature of upright treadmill walking, it was thought that BWSTT would produce greater improvements in mobility outcomes, whereas TBRST would be more effective in improving upper body function due to the upper limb training component. It was further hypothesized that participants would not exhibit preference for one exercise modality over the other.

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CHAPTER 2

EFFECTS OF 12 WEEKS OF SUPPORTED TREADMILL TRAINING ON FUNCTIONAL ABILITY AND QUALITY OF LIFE IN PROGRESSIVE MULTIPLE SCLEROSIS: A PILOT STUDY

Published: Archives of Physical Medicine and Rehabilitation 2011;92:31-6.

No reprint permission required. Accepted manuscript version provided.

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The effects of 12 weeks of supported treadmill training on functional ability and quality of life in progressive multiple sclerosis: A pilot study.

Objective: To examine the effects of body-weight supported treadmill training (BWSTT) on functional ability and quality of life in patients with progressive MS of high disability.

Design: Before-after trial.

Setting: Exercise rehabilitation research center.

Participants: Six patients with progressive MS (5 primary progressive, 1 secondary progressive) with high disability (mean EDSS =6.9±1.07). All participants completed the trial.

Intervention: Subjects completed 36 sessions of BWSTT (30 min sessions, 3X/week) over 12 weeks.

Main Outcome Measures: Outcome measures included functional ability assessed by EDSS and Multiple Sclerosis Functional Composite (MSFC). Quality of life and fatigue were assessed by the MS Quality of Life-54 (MSQoL-54) and the Modified Fatigue Impact Scale (MFIS), respectively. All tests were administered at baseline and following 12 weeks of training.

Results: All participants progressively improved training intensity; treadmill walking speed increased (34%, $p<0.001$) and percent body-weight support was reduced (42%, $p<0.001$). A significant improvement in both physical ($p=0.02$) and mental ($p=0.01$) subscales of the MSQoL-54 was found. Fatigue was non-

significantly reduced by 31% ($p=0.22$); however, a large effect size (ES) was noted ($ES= -0.93$). Functional ability remained stable with non-significant improvements in MSFC ($p=0.35$, $ES=0.23$) and EDSS ($p=0.36$, $ES= -0.08$) scores.

Conclusions: Twelve weeks of BWSTT produces beneficial effects on quality of life and potentially reduces fatigue in patients with PPMS of high disability level. Larger trials will be required to confirm these findings and to further evaluate the effects of BWSTT in progressive MS.

Key Words: rehabilitation, exercise, multiple sclerosis, quality of life, fatigue

List of Abbreviations

% BWS percent body-weight support

9-HPT 9-hole peg test

ANOVA analysis of variance

BWSTT body-weight supported treadmill training

cMFIS cognitive modified fatigue impact subscale

EDSS expanded disability status scale

ES effect size

HHS REB Hamilton health sciences research ethics board

km/h kilometres per hour

MFIS modified fatigue impact scale

MSFC multiple sclerosis functional composite

MSQoL-54 multiple sclerosis quality of life -54

PASAT paced auditory serial addition test

pMFIS physical modified fatigue impact subscale

PPMS primary progressive multiple sclerosis

psMFIS psychosocial modified fatigue impact subscale

QoL quality of life

RCT randomized controlled trial

RRMS relapsing remitting multiple sclerosis

SPMS secondary progressive multiple sclerosis

T25-FW timed 25-foot walk

Exercise was originally contraindicated for patients with MS as it was thought that physical activity would exacerbate MS symptoms such as fatigue. Over the last decade, however, it has become accepted that exercise is not only safe and well-tolerated by patients with MS, but it can produce beneficial effects in functional, physical and psychosocial domains ^{1,2-8}.

To date, exercise interventions in the MS population have largely been limited to research with patients with relapsing remitting MS (RRMS) or mixed MS subtype groups ⁹. Insufficient data exist on the effects of exercise specifically in patients with primary progressive MS (PPMS). Furthermore, as most exercise interventions have restricted inclusion criteria to independently mobile subjects, patients with MS with severe disability (EDSS>6.0) have largely been excluded from exercise trials ⁴.

Patients with PPMS present with a specific disease etiology typically characterized by spastic paraparesis, gradually developing into quadriparesis ¹⁰⁻¹². It has been documented that patients with PPMS experience more rapid symptom deterioration than other MS subtypes, reaching critical disability levels of 6 and 8 on the EDSS by a median time of 8 and 18 years, respectively, after disease onset ¹³. Patients with PPMS report being significantly less active than patients with RRMS ¹⁴. Patients with PPMS also experience fatigue more commonly and more severely compared to patients with RRMS ^{15,16}. Unlike other

MS subtypes, there are currently no approved therapies for the treatment of PPMS^{17,18}. Due to the poor prognosis, reduced activity levels and lack of disease-modifying pharmacological options, it is of great importance to develop therapeutic options for patients with PPMS.

A training modality that may address the limitations faced by patients with PPMS is body-weight supported treadmill training (BWSTT). BWSTT is an exercise modality that allows a portion of an individual's body-weight to be counter-balanced by an overhead support system giving an individual the support and safety required to walk upright on a treadmill. BWSTT is a repetitive task-oriented aerobic training modality that can help patients with neurological impairments improve fitness and regain function. BWSTT has been shown to improve functional mobility, cardiovascular and muscular fitness, and psychosocial parameters in people with spinal cord injury¹⁹⁻²¹ and stroke²²⁻²⁴. Limited studies have examined the effects of supported treadmill therapy for patients with MS²⁵⁻²⁷; results suggest BWSTT is safe and well-tolerated and can lead to improvements in functional mobility parameters. However, no studies thus far have looked at the effects of exercise in patients with PPMS specifically. We propose a pilot study to examine the effects of BWSTT in patients with PPMS with severe disability (EDSS of 5.0-8.0) and to guide the implementation of a larger randomized controlled trial (RCT).

METHODS

Participants

This study was approved by the Research Ethics Board of Hamilton Health Sciences (HHS REB). Participants provided informed consent and confidentiality was maintained in accordance with HHS REB guidelines. All potentially eligible participants were provided information about the study from medical staff at the MS Clinic of Hamilton Health Sciences. Interested participants were invited to contact the study coordinator who determined participant eligibility. Prior to enrolment, medical history and screening were completed by a neurologist. Inclusion criteria were clinically definite PPMS as per the diagnostic criteria of Thompson et al. ¹¹, EDSS 5.0-8.0, 18-60 years of age, body weight <200lbs, ability to visit study locations, follow training instructions and tolerate BWSTT. Exclusion criteria were pregnant or planning on becoming pregnant during the study period, current participation in a clinical trial of an experimental or unapproved/unlicensed therapy for PPMS, current use or use within the last 2 months of off-label therapy for PPMS including IFN- β , glatiramer acetate, IV steroids, mitoxantrone, azathioprine, and/or cylophosphamide, acquired disability that could interfere with evaluation of disability due to MS, other serious medical condition that might impair the subject's ability to walk on a treadmill and/or participate in aerobic exercise.

Exercise Intervention

Participants took part in three weekly sessions (30 min/session) of BWSTT for the duration of 12 weeks. All training took place using the Woodway Loco-System^a which consisted of a treadmill with an overhead pulley system connected to a supportive harness. A detailed description of the treadmill set-up has been published elsewhere^{19,28}. The treadmill training strategy promoted proper gait mechanics focusing on weight bearing, weight shifting and body positioning.

During the first training session participants were familiarized with the BWSTT system and tolerability of the training protocol was established. Percent body-weight support was selected based on the minimum amount that would allow subjects to maintain an upright trunk without knee buckling while standing¹⁹. Initial speed was selected based on participant comfort and safety, while allowing for practice of proper walking kinetics. Training progressed by first increasing treadmill speed followed by reducing %BWS, in accordance with individual comfort and tolerance. Initial training commenced with 5-10 min of exercise and progressed to a maximum of two 15 min sessions with one rest period (2-5 min) between sessions.

Outcome Measures and Design

Functional Ability. Disability and neurological impairment were assessed using Kurtzke's Expanded Disability Status Scale (EDSS) and Functional Systems Scale²⁹. The EDSS was performed by a neurologist specializing in MS. Functional ability was assessed with the MS Functional Composite (MSFC;³⁰). The MSFC assesses functional ability using three items: the timed 25-foot walk (T25-FW), the 9-hole peg test (9-HPT) and the Paced Auditory Serial Addition Test (PASAT). Scores on each item were converted to a Z-score and a composite MSFC score was calculated according to standardized instructions³¹. The National MS Society Task Force reference population was used in scoring.

Quality of Life. Health-related quality of life was assessed by the disease-specific MS Quality of Life-54 (MSQoL-54) questionnaire. The MSQoL-54 consists of 54 items divided into 12 multi-item scales, 2 single-item scales, and 2 composite scores (physical and mental health). This measure has shown good reliability and validity within the MS population³².

Fatigue. Fatigue was assessed by the Modified Fatigue Impact Scale (MFIS). The MFIS is a 21-item self-report questionnaire that evaluates fatigue overall, as well as within three subscales: physical (pMFIS); cognitive (cMFIS); and psychosocial (psMFIS), over the previous 4 weeks. Reliability and validity of the MFIS has been established in patients with MS³³⁻³⁵.

Pre-baseline testing of the MSFC was administered in order to minimize practice effects³⁶. All outcomes were assessed at 2 and 4 weeks following pre-baseline to establish stable baseline values. All measures were evaluated again following 12 weeks of BWSTT. The same assessor conducted evaluations at baseline and at 12 weeks at the exercise rehabilitation centre (with exception of the EDSS which was conducted at the neurologists' clinic). Self-report questionnaires were interview administered.

Data Analysis

Descriptive statistics were used to summarize participant characteristics. Treadmill training data (%BWS and speed) were compared by week of training using one-way repeated measures ANOVAs and Tukey's *post hoc* tests. Baseline values were established as an average of the two assessments. We compared baseline values to 12 week values for each outcome measure (EDSS, MSFC, MSQoL-54 and MFIS). A paired t-test was used to analyze normally distributed data and Wilcoxon's test was used to analyze data which did not follow a normal distribution. Statistical analyses were performed using GraphPad PRISM software^b. Statistical significance was set at $p \leq 0.05$. Effect sizes (ES) were calculated and expressed as Cohen's *d*. ESs ≥ 0.2 were considered small, ≥ 0.5 moderate and ≥ 0.8 large.

RESULTS

Participant Characteristics

Six participants were recruited; 4 women and 2 men (Table 1). Five patients had a clinical diagnosis of PPMS, one of secondary progressive (SPMS). In consultation with a neurologist, this patient was accepted in the study due to disease duration, disability level, and lack of relapses. All participants completed baseline and 12 week testing and all completed the training program with an average adherence of $97.7\pm 3.7\%$.

Treadmill Training

Participants began training at an average speed of 1.1 ± 0.10 km/h with an average of $77.9\pm 10.76\%$ BWS required to walk on the treadmill. With training, all participants increased their walking speed and reduced the amount of BWS required to walk on the treadmill (Figure 1). Following 12 weeks of BWSTT, participants significantly increased walking speed to 1.6 ± 0.09 km/h ($p<0.001$) and reduced BWS to $51.7\pm 18.66\%$ ($p<0.001$).

Functional ability

Baseline EDSS was 6.9 ± 1.07 (Table 2). Only one participant demonstrated functional changes that translated into a decrease in EDSS score by 0.5 following 12 weeks of training. MSFC total Z-score improved from -3.0 ± 2.80 at baseline to -2.4 ± 2.59 with a small non-significant ES ($p=0.35$, $ES=0.23$). The greatest improvement in MSFC items was observed in the T25-FW, with participants improving their Z-score from -7.1 ± 7.28 ($n=3$) at baseline to -5.5 ± 6.63 ($n=4$, $p=0.33$, $ES=0.24$). No significant changes were noted in 9-HPT or PASAT scores.

Quality of Life

Following 12 weeks of training, there was a significant increase in physical ($p=0.02$) and mental ($p=0.01$) health composite scores of the MSQoL-54 (Table 3). Significant improvements were also observed in the following subscales: emotional well-being ($p=0.04$), energy ($p=0.01$), and health distress ($p=0.03$). No significant changes were noted in any of the other subscales; however, a large ES was seen for change in health ($p=0.13$, $ES=1.14$) and a moderate ES was observed for pain ($p=0.2$, $ES=0.52$).

Fatigue

A non-significant reduction in MFIS total and subscale scores was noted following treadmill training, with a 31% decrease in MFIS total (Table 2). Large ESs were seen in total MFIS ($p=0.22$, $ES= -0.93$), pMFIS ($p=0.22$, $ES= -0.80$), and cMFIS ($p=0.14$, $ES= -0.78$) scales. A small ES was observed for psMFIS ($p=0.62$, $ES= -0.28$).

DISCUSSION

To the best of our knowledge, this is the first study to examine the effects of BWSTT in patients with PPMS. This study demonstrates that 3 weekly sessions of BWSTT is an effective therapy for increasing QoL and shows promising results for improving fatigue and walking ability in patients with PPMS of high disability. Results of this study provide valuable information to design and implement a future RCT.

Effects of BWSTT on functional ability

A reduction in EDSS was only observed in one of 6 participants after 12 weeks of training with a change in score from 7.5 to 7. It is noteworthy that no deterioration in EDSS was observed in any subjects following BWSTT considering the progressive disease course¹³. While results suggest a minimal change in functional ability, other studies have yielded similar small changes or no change

in EDSS following exercise therapy with patients with MS^{1, 7, 25, 37}. A pilot study of BWSTT in 4 patients with SPMS similarly demonstrated a reduction in EDSS score of 0.5 in one participant following 40 training sessions, although no statistics were reported²⁵. One of the few studies to report a significant improvement in EDSS following exercise found a mean decrease of 1 point following 12 sessions of BWSTT in a group of patients of mixed MS subtype and moderate disability (mean EDSS =4.9)²⁶. It is possible that exercise interventions with patients with MS of higher disability require longer training protocols to observe changes in EDSS.

It is also important to consider that the EDSS is not a particularly sensitive measure for small changes in function and is heavily dependent on lower extremity function, particularly in the middle to upper range³⁸. For these reasons we chose to include the MSFC. Following training, a small non-significant ES of 0.23 was observed for MSFC total. Few studies have reported the effects of exercise on the MSFC. Romberg and colleagues reported a significant ES of 0.16 in patients with mild MS participating in 6 months of combined resistance and aerobic training³⁷. A significant decline in MSFC score was also observed in the control group of patients with MS in this study with a reported ES of -0.18. Although the present study did not include controls, it is possible that a similar group of patients with PPMS may have likewise shown symptom deterioration over the study period.

Patients with MS experience deterioration of lower limb strength earlier and to a greater degree than upper limb impairments emphasizing the importance of lower limb training protocols such as BWSTT to maintain mobility and function³⁹.⁴⁰ The greatest improvement in MSFC components was observed in the T25-FW. All three of the participants who completed the T25-FW at baseline and follow-up improved their walking velocity. One participant was unable to complete the walk at baseline; however, following training was successful in completing the T25-FW. Several studies have found significant improvements in walking ability in patients with MS following aerobic and resistance interventions^{25, 26, 37, 41-43}. A meta-analysis of the effects of exercise on walking in patients with MS described an overall ES of 0.19⁴⁴, slightly smaller than our observed ES of 0.24. Although our results did not yield statistical significance, it has been suggested that an improvement of 20% on the T25-FW is considered to impart a true change in function^{45, 46}. Of the three participants in our study who completed baseline and follow-up testing a mean change of 18% on the T25-FW was observed. A larger participant group and/or a longer training protocol may have yielded significant improvements in mobility.

No change was observed in the 9-HPT or the PASAT components of the MSFC. It was expected that BWSTT would have the greatest effects on lower extremity function due to the specificity of the training program. Other studies have

demonstrated improvements in the 9-HPT following exercise; however, this is likely due to differences in modality, such as resistance training programs which target both upper and lower extremities^{37, 43}. A lack of change in the PASAT score may reflect the minimal cognitive deficits observed in this particular group of patients.

Effects of BWSTT on quality of life

Significant improvements in QoL were observed following BWSTT in both physical and mental health composites and several subscales of the MSQoL-54. In comparison to previous studies, our intervention appears to have improved QoL to a greater extent^{7, 41, 47, 48}. A meta-analysis of exercise interventions in patients with MS found a small significant mean ES of 0.23 for the effects of exercise on QoL⁴⁷. The magnitude of the mean ES was influenced by type of QoL assessment tool and exercise modality; MS-specific measures and aerobic exercise were associated with larger ESs⁴⁷. Improvements in QoL in the present study may be related to the aerobic nature of the training protocol, the supervised training program and social support provided from training personnel and other exercisers.

With respect to MSQoL-54 subscales, significant improvements were noted in emotional well-being, health distress and energy. Large and moderate ESs were

also observed for change in health and pain, respectively. An 8 week aerobic cycling training program in patients with MS produced similarly significant changes in emotional well-being, health distress and energy subscales of the MSQoL-54, although no significant changes were noted in either composite score⁴¹. The significant improvements seen in emotional well-being and health distress may be a function of patients gaining a greater sense of control over their health by participating in a structured training program; however, this concept needs to be further investigated. Significant improvements in energy have also been reported in previous studies^{41, 48} and are reflected by the large ESs observed in the MFIS scores in this study. Several characteristics have been proposed as mediators of the effect of exercise on QoL in MS, such as self-efficacy, physical function, fatigue, mood, coping skills, perceived support and cognitive impairment^{49, 50}. BWSTT may have increased QoL through its effects on the above-mentioned factors and should be considered in future trials.

Effects of BWSTT on fatigue

Fatigue is a major factor affecting patients with MS, particularly those of the progressive subtype^{15, 16}. While BWSTT did not significantly reduce fatigue levels, very large ESs were observed. A 31% reduction was observed in overall fatigue levels (ES= -0.93), 24% in the physical subscale (ES= -0.80), 46% in the cognitive subscale (ES= -0.78), and 14% in the psychosocial subscale (ES=-

0.28). While studies assessing the effects of exercise on fatigue in patients with MS have demonstrated significant reductions^{7, 51}, others have not^{1, 41, 42}; this discrepancy may be related to the choice of evaluation tool. The MFIS assesses fatigue in three dimensions, and may therefore represent a more sensitive tool for fatigue evaluation. It is also interesting to note baseline fatigue values in our study were much higher than those reported in other exercise interventions with patients with MS, likely reflecting the high disability level and distinct PPMS subtype of our subjects^{15, 16}. The etiology of fatigue in MS remains poorly understood, and it is, therefore, difficult to determine the mechanisms by which exercise therapies affect fatigue^{15, 52}. Improvements in fatigue with BWSTT may result from improvements in aerobic fitness and walking ability. Consequently, patients may be able to perform daily tasks more efficiently and at lower relative intensities resulting in energy conservation. Furthermore, exercise may affect psychosocial variables such as mood and depression which have been shown to be closely correlated with fatigue in the MS population^{16, 52, 53}.

Study Limitations

This pilot study was the first exercise therapy trial specifically in the PPMS population and was intended to inform a larger RCT. As a result, several limitations of this study must be mentioned: small sample size, lack of control group, duration of training and long-term follow-up. Evaluation of additional

outcome measures such as gait parameters, muscle strength and spasticity, moderators of QoL and other psychosocial variables will be important to future trial design.

Conclusions

Therapeutic options for patients with PPMS remain limited. BWSTT appears to be an effective therapeutic intervention for increasing QoL and shows promising results for improving fatigue and walking ability in patients with PPMS of high disability level. Future studies should examine the effects of BWSTT in a larger group of patients with PPMS for longer training durations to confirm our initial findings. Furthermore, understanding the mediators of the relationship between exercise and QoL and the underlying mechanisms of fatigue will be beneficial in determining the most effective therapy.

Acknowledgements

We gratefully acknowledge the assistance with treadmill training and data collection provided by coordinator Susie Ward.

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Suppliers

- a. Woodway USA, Inc., W 229 N 591 Foster Ct, Waukesha, WI 53186.
- b. Version 5.01; GraphPad Software, Inc., 2236 Avenida de la Playa, La Jolla, CA 92037.

Table 1: Participant Characteristics.

	Mean (SD)	Range
Age, years	48.2 (9.30)	35-61
Gender (M/W)	2/4	
Disease duration, years	11.5 (6.60)	4-23
Age at onset, years	36.7 (11.45)	28-57
Disease pattern		
PPMS	5	
SPMS	1	
EDSS	6.9 (1.07)	5.5-8.0

NOTE. n=6. Values are means (SD). Abbreviations: EDSS, Expanded Disability Status Scale.

Table 2: Outcome means at baseline and after 12 weeks of treadmill training.

Outcome measure	Baseline	Week 12	Difference	95% CI	Effect Size	p value
EDSS	6.9 (1.07)	6.8 (1.03)	-0.1 (0.02)	-0.25 to 0.08	-0.08	0.36
MSFC	-3.0 (2.80)	-2.4 (2.59)	0.6 (1.43)	-0.55 to 1.74	0.23	0.35
T25-FW	-7.1 (7.28)	-5.5 (6.63)	1.6 (3.56)	-1.27 to 4.42	0.24	0.33
9-HPT	-1.8 (0.98)	-1.7 (0.96)	0.1 (0.37)	-0.19 to 0.41	0.12	0.49
PASAT	-0.1 (0.77)	-0.003 (0.97)	0.1 (0.49)	-0.3 to 0.50	0.12	0.64
MFIS	43.5 (12.26)	30.2 (14.13)	-13.3 (20.96)	-30.11 to 3.44	-0.93	0.22
pmFIS	24.3 (5.8)	18.3 (8.19)	-5.9 (9.27)	-13.33 to 1.50	-0.8	0.22
cMFIS	14.6 (8.92)	7.8 (7.55)	-6.8 (9.46)	-14.32 to 0.82	-0.78	0.14
psMFIS	4.7 (2.58)	4.0 (2.28)	-0.7 (3.08)	-3.13 to 1.80	-0.28	0.62

NOTE. n=6. Values are means (SD). Abbreviations: EDSS, Expanded Disability Status Scale; MSFC, MS Functional Composite; T25-FW, Timed 25-Foot Walk; 9-HPT, 9-Hole Peg Test; PASAT, Paced Auditory Serial Addition Test; MFIS, Modified Fatigue Impact Scale (p=physical, c=cognitive, ps=psychosocial).

Table 3: MSQoL-54 scale scores at baseline and after 12 weeks of training.

Scale	Baseline	Week 12	Difference	95% CI	Effect Size	p value
Physical health	8.8 (11.04)	15.0 (17.32)	6.3 (7.87)	-0.04 to 12.54	0.44	0.1
Role limitations -physical	18.8 (23.39)	25.0 (41.83)	6.3 (25.92)	-14.49 to 26.99	0.19	0.58
Role limitations -emotional	38.9 (49.07)	61.1 (49.07)	22.2 (34.43)	-5.32 to 49.77	0.46	0.17
Pain	67.6 (22.65)	77.5 (14.67)	9.9 (16.43)	-3.28 to 23.02	0.52	0.2
Emotional well-being	69.0 (13.37)	81.3 (11.32)	12.3 (11.20)	3.37 to 21.30	0.91	0.04
Energy	32.0 (19.64)	51.3 (18.32)	19.3 (12.56)	9.28 to 29.39	0.93	0.01
Health Perceptions	41.7 (21.54)	50.8 (19.08)	9.2 (13.29)	-1.47 to 19.80	0.46	0.15
Social function	56.3 (20.70)	64.0 (29.72)	7.1 (15.02)	-4.31 to 19.73	0.31	0.26
Cognitive function	70.4 (28.26)	75.8 (27.64)	5.4 (13.55)	-5.42 to 16.26	0.2	0.37
Health distress	45.8 (15.63)	71.7 (18.35)	25.8 (12.29)	14.40 to 37.27	1.22	0.03
Sexual function	47.5 (36.40)	53.3 (28.64)	5.8 (14.60)	-6.97 to 18.62	0.19	0.42
Sexual satisfaction	27.5 (34.69)	30.0 (32.60)	2.1(14.61)	-10.73 to 14.89	0.08	0.75
Change in health	31.3 (10.46)	62.5 (30.62)	31.3 (29.32)	7.79 to 54.71	1.14	0.13
Overall quality of life	65.3 (9.29)	63.6 (23.65)	-1.7 (21.49)	-18.87 to 15.52	-0.1	0.86
Physical health composite	37.1 (8.87)	48.0 (13.32)	10.9 (7.83)	4.66 to 17.20	0.9	0.02
Mental health composite	58.1 (16.22)	71.1 (18.28)	13.04 (7.01)	7.43 to 18.64	0.74	0.01

NOTE. n=6. Values are means (SD). Abbreviations: MSQoL-54, Multiple Sclerosis Quality of Life-54.

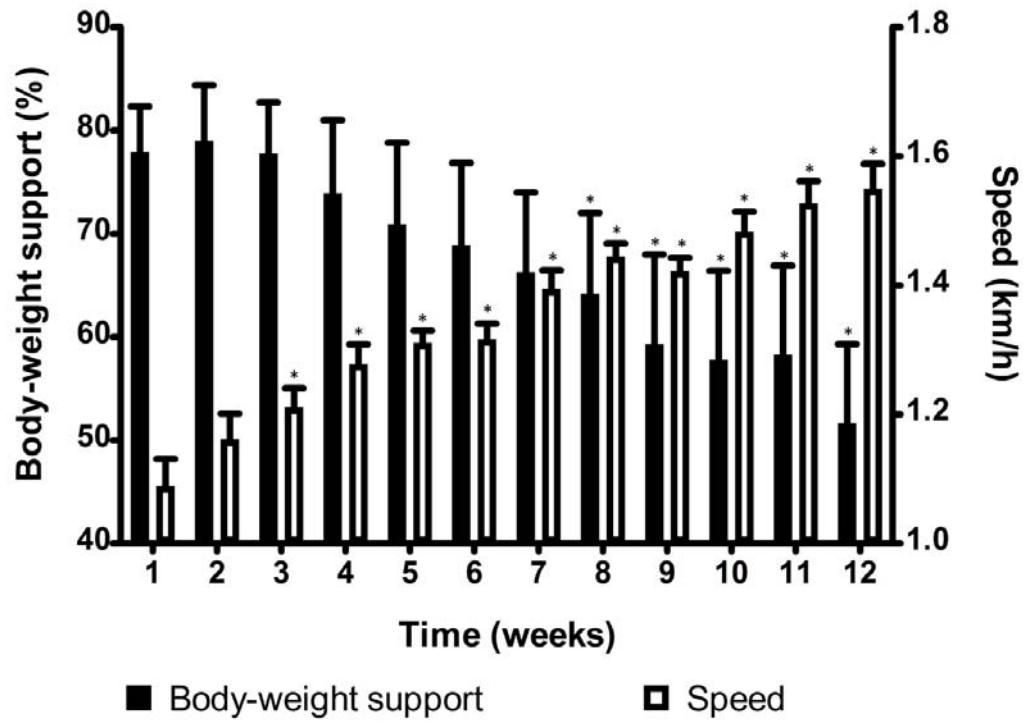
Figure Legends

Fig 1. Percent body-weight support required and treadmill walking speed (kilometres per hour) over 12 weeks of body-weight supported treadmill training.

NOTE. n=6. Values are means \pm SE. *Significantly different from baseline

$P < 0.05$.

Figure 1



CHAPTER 3

LONG-TERM EFFECTS OF SUPPORTED TREADMILL WALKING IN PERSONS WITH PROGRESSIVE MULTIPLE SCLEROSIS

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3.0 LONG-TERM EFFECTS OF SUPPORTED TREADMILL WALKING IN PATIENTS WITH PROGRESSIVE MULTIPLE SCLEROSIS

3.1 Abstract

Background Patients with progressive multiple sclerosis (MS) are faced with a fast rate of disease progression and few options for therapeutic intervention. Consequently, developing alternative therapeutic strategies to maintain function and potentially limit disease progression are imperative. Adapted exercise interventions, such as body weight supported treadmill training (BWSTT), may represent an alternative therapeutic strategy for persons with progressive MS.

Objective This study examined the effects of 24 weeks of BWSTT on outcomes of physical and mental functioning, brain-derived neurotrophic factor (BDNF), and brain imaging parameters in patients with progressive MS with severe mobility impairment.

Methods Six patients with progressive MS (mean Expanded Disability Status Scale [EDSS] = 6.9 ± 1.07) completed 72 sessions of BWSTT. End points were assessed at baseline and following the training intervention. Outcome measures included neurological functioning and disability (EDSS, Multiple Sclerosis Functional Composite [MSFC]), fatigue (Modified Fatigue Impact Scale [MFIS]), quality of life (Multiple Sclerosis Quality of Life-54 scale [MSQoL-54]), serum BDNF, proton magnetic resonance spectroscopy, and diffusion tensor imaging (DTI) metrics.

Results Treadmill walking speed increased ($p < 0.0001$), and percent body-weight support was reduced ($p < 0.0001$) over 72 BWSTT sessions. Small non-significant improvements in EDSS ($p = 0.17$) and MSFC ($p = 0.26$) scores were observed. A significant improvement was observed for MFIS total ($p = 0.02$), as well as physical ($p = 0.02$) and cognitive

($p=0.03$) fatigue subscale scores. There was a significant improvement in MSQoL-54 physical health composite scores ($p=0.02$), and a trend towards an improvement in MSQoL-54 mental health composite scores ($p=0.09$). A non-significant increase was observed in serum BDNF levels ($p=0.57$). Pre-post brain imaging revealed a significant decrease in myoinositol concentrations ($p=0.03$) and a trend for a decrease in glycerophosphocholine concentrations ($p=0.08$) in normal appearing white matter (WM). Further, a significant increase was observed in fractional anisotropy values in the parietal WM ($p=0.03$), and there was a trend for a decrease in mean diffusivity in the parietal WM ($p=0.06$) and the thalamus ($p=0.06$).

Conclusions Long-term supported treadmill walking is beneficial for improving fatigue and aspects of health-related quality of life in patients with progressive MS with severe mobility impairments. Larger interventions are required to determine the effects of BWSTT on BDNF and brain imaging outcomes.

3.2 Introduction

Multiple sclerosis (MS) is a chronic neurodegenerative disease that leads to the progressive accumulation of disability across time (Confavreux et al., 2000). During the early stages, disease-modifying therapies have proven effective in reducing the rate of relapses and slowing disease progression (Katrych et al., 2009; Filipini et al., 2003). Over time, however, disease-modifying agents become less effective in slowing disease progression, ultimately leading to the accumulation of long-term disability (Confavreux et al., 2003). Also, patients with primary progressive MS (PPMS) are faced with a more rapid rate of disease progression than patients with a relapsing remitting MS (RRMS) disease course, resulting in the onset of disability at an earlier age, and severely limiting independence and quality of life (Confavreux et al., 2003; Cottrell et al., 1999).

Consequently, alternative treatment options are needed for the management of patients with MS with more severe mobility impairment, particularly those with a progressive disease course.

Exercise represents a potential tool for managing symptoms and potentially limiting the progression of disability for persons with MS (Dalgas and Stenager 2012; Dalgas et al., 2008). For individuals who have accumulated a significant amount of disability, specifically mobility impairment, participation in physical activity is particularly challenging. An adapted exercise intervention that has been successful in the treatment of patients with mobility impairments is body weight supported treadmill training (BWSTT). BWSTT is an alternative exercise modality that allows individuals with limited mobility to engage in upright treadmill walking through the use of a body weight

counter-balancing system, with or without the assistance of therapists or a robotic orthosis. A limited number of investigations have evaluated the effects of BWSTT in patients with MS with results suggesting improvements in mobility, strength, fatigue, and quality of life (QoL) (Schwartz et al., 2012; Pilutti et al., 2011; Wier et al., 2011; Lo and Triche 2008; Beer et al., 2007; Geisser et al., 2006).

Previous research supports the beneficial effects of BWSTT, and exercise in general, for persons with MS (Dalgas et al., 2008); however, little is known about the effects of exercise on underlying disease processes and long-term disability progression.

Traditional measures of MS progression, such as the Expanded Disability Status Scale (EDSS), have typically been used to determine the effect of exercise on disease progression, with most studies reporting no change in EDSS scores following training (Rasova et al., 2006; Romberg et al., 2005; Petajan et al., 1996). The EDSS, however, has limited responsiveness and does not necessarily reflect underlying disease processes (Hobart et al., 2000). Potential markers of underlying disease activity and measures of disease progression, such as neurotrophic factors and brain imaging parameters, may represent alternative outcomes for exploring the disease-modifying potential of exercise in MS.

Evidence suggests physical activity may exert a protective effect on brain structure and function which to some extent may be mediated by neurotrophic factors (White and Castellano 2008). Neurotrophic factors, such as brain-derived neurotrophic factor (BDNF), are a family of proteins believed to be involved in neuroprotection, neuroregeneration, and neuroplasticity (Ebadi et al., 1997). A limited number of studies

have examined the effects of exercise on neurotrophic factors in MS with mixed conclusions (Castellano and White 2008; Schultz et al., 2004; Gold et al., 2003). In response to an acute exercise bout, Gold and colleagues (2003) observed a significant increase in serum BDNF and a trend for an increase in nerve growth factor (NGF) post-exercise. The response to exercise was the same in persons with MS and non-MS controls; however, persons with MS had higher serum NGF production at baseline. The same group compared the impact of chronic exercise on neurotrophic factor production in persons with MS and non-exercising MS controls and found a non-significant increase in BDNF and a non-significant decrease in NGF levels at rest and in response to an acute bout of exercise compared to controls (Schultz et al., 2004). Conversely, another chronic exercise trial observed a reduction in BDNF in persons with MS and non-MS controls following an acute exercise bout both before and after the cycling intervention (Castellano and White 2008). Although there was a transient, BDNF concentrations did not change by the end of the exercise intervention in persons with MS (Castellano and White 2008).

Magnetic resonance imaging also represents a more sensitive tool for exploring the disease-modifying potential of exercise in MS. To date, no interventions have examined the impact of exercise on brain imaging parameters in persons with MS in a prospective manner; however, two cross-sectional investigations support a potential role for exercise in promoting structural and functional brain health (Prakash et al., 2010; Prakash et al., 2007). One study determined cardiorespiratory fitness was positively associated with grey matter (GM) and white matter (WM) tract integrity, and this structural integrity

further correlated with cognitive processing speed (Prakash et al., 2010). The other study conducted by the same research group suggested improved cardiorespiratory fitness was related to improved performance on a cognitive task and superior functional recruitment of task-related brain regions (Prakash et al., 2007).

No studies to date have examined the long-term effects of BWSTT in patients with MS with severe mobility impairment, making it difficult to determine the effects of BWSTT on disability progression and disease management. In attempt to address several limitations of previous research, the purpose of the present study was to examine the effects of long-term BWSTT on physical and mental functioning, fatigue, quality of life, BDNF and brain imaging parameters in patients with progressive MS with severe mobility impairment ($EDSS \geq 5.0$).

3.3 Methods

3.3.1 Participants

Approval for this study was granted by the Research Ethics Board of Hamilton Health Sciences and St. Joseph's Healthcare Hamilton (Hamilton, Canada). Participants were recruited through contact with medical staff at the MS Clinic of Hamilton Health Sciences. All participants provided written informed consent. Inclusion criteria were clinically definite PPMS as per the diagnostic criteria of Thompson et al. (2000); EDSS 5.0 to 8.0; age 18 to 60 years of age; body weight <90kg; medical clearance from a physician to participate in physical activity; and ability to visit the study locations and tolerate BWSTT. Exclusion criteria were pregnancy or planning on becoming pregnant during the study period; current participation in a clinical trial of an experimental or

unapproved/unlicensed therapy for PPMS; current use or use within the last 2 months of off-label therapy for PPMS including IFN- β , glatiramer acetate, IV steroids, mitoxantrone, azathioprine, and/or cylophosphamide; any disability acquired from trauma or another illness that could interfere with evaluation of disability due to MS; any other serious medical condition that might impair the subject's ability to participate in aerobic exercise; blood disorder; current use of anti-coagulant medication; any condition or circumstance that may prevent the subject from undergoing MRI scanning including: metal in the eye, cardiac pacemaker, artificial cardiac valve, caval filter, stent, aneurysm clip, neurostimulator, shrapnel/bullet, portable catheter, IUD, cochlear implant, tattoo, body piercing, homeopathic/acupuncture balls, implanted metal or devices, prosthetics (limb, eye, joint, ear), claustrophobia, and allergy to contrast agent Gadolinium.

3.3.2 Exercise Intervention

Participants completed three weekly training sessions (30 min/session) of BWSTT over the course of 24 weeks using a Woodway Loco-System (Woodway USA, Inc., Waukesha, WI, USA). A detailed description of the treadmill set-up and training progression has been published elsewhere (Pilutti et al., 2011; Hicks et al., 2005). In brief, participants engaged in upright walking through the use of a supportive harness connected to an overhead pulley system which allowed for a portion of participants' body weight to be counter-balanced. Treadmill walking was assisted by two therapists positioned at both lower limbs and when necessary, a third positioned behind the participant to provide additional support. A familiarization session was conducted prior to

the training program to determine the appropriate initial training settings. Walking speed (km/h), walking duration (min) and percent BWS were recorded at each training session.

3.3.3 Outcome measures

Functional Ability. Functional ability was assessed by the physician-administered EDSS (Kurtzke 1983) and the MS Functional Composite (MSFC) (Fischer et al., 1999a). The MSFC is composed of three items: the timed-25-foot walk (T25FW), the 9-hole peg test (9HPT) and the Paced Auditory Serial Addition Test (PASAT). A Z-score was determined for each individual item and a composite score for the MSFC was generated according to standardized scoring procedures (Fischer et al., 1999b). The MSFC was administered prior to baseline testing in order to minimize known practice effects associated with the various test components (Solari et al., 2005).

Fatigue. The Modified Fatigue Impact Scale (MFIS) was used to assess fatigue (Fisk et al., 1994). The MFIS is a 21-item self-report questionnaire that evaluates fatigue over the past 4 weeks on three subscales: physical (pMFIS); cognitive (cMFIS); and psychosocial (psMFIS), which combine to produce a total fatigue (MFIS) score. The MFIS has shown good reliability and validity (Kos et al., 2005; Fisk et al., 1994).

Quality of Life. Health-related QoL was assessed using the MS Quality of Life-54 (MSQoL-54) questionnaire. The MSQoL-54 is composed of 12 multi-item scales, 2 single-item scales (change in health and sexual satisfaction), and 2 composite scores (physical and mental health). Reliability and validity of the MSQoL-54 has been established (Miller et al., 2005).

BDNF

Blood samples were collected from participants at baseline and following 24 weeks of exercise for determination of serum BDNF. Blood samples were taken from the antecubital vein and collected in 4.0mL heparinised tubes (Vacutainer, Beckton Dickinson, Franklin Lakes, NJ, USA). Samples were centrifuged and serum was stored at -80°C. Serum BDNF was quantified using a commercially available sandwich enzyme-linked immunosorbent assay (ELISA) kit (Quantikine ELISA KIT, R&D Systems, Minneapolis, MN, USA) according to the manufacturer's specifications. Serum samples were analyzed in duplicate. Intra- and inter-assay coefficients of variability were 5% and 9% respectively, provided by the manufacturer. Minimum sensitivity in this ELISA kit was <20pg/mL.

Magnetic Resonance Imaging

MRI scans of the brain were acquired using a 3 Tesla (T) GE Signa HD MRI system with an 8-channel phased array head coil (GE Healthcare, Milwaukee, WI, USA). Brain imaging included proton magnetic resonance spectroscopy (¹H-MRS) and diffusion tensor imaging (DTI) performed at the same testing session. Single-voxel ¹H-MRS measurements were acquired using a PRESS (Point RESolved Spectroscopy) sequence with the following scanning parameters: TE = 35 ms; TR = 2000 ms; field of view (FOV) = 22 cm; 20 mm slice thickness; total number of points = 256; total scan time 9 minutes and 20 seconds. Spectra were measured from voxels placed over an MS lesions and the corresponding contralateral normal appearing white matter (NAWM). At 24 week follow-up, the same voxel of interest was selected and positioned as closely as possible to the baseline voxel location of the MS lesion and contralateral NAWM. LCModel Version

6.2-1 (Provencher et al., 1993) was used to quantify spectral peaks for the following metabolites of interest: creatine (Cr), glutamine (Gln), glutamate (Glu), glycerophosphocholine (GPC), lactate (Lac), myoinositol (mI), and N-acetylaspartate (NAA). Mean absolute concentration for each metabolite in the lesion and NAWM was generated. NAA, mI and GPC were also expressed relative to concentrations of Cr which is assumed to be a relatively stable metabolite (van der Knapp and Pouwels 2005).

A diffusion-weighted echo-planar imaging sequence was applied to collect a series of axial images through the brain using the following parameters: diffusion directions = 25; $b = 1000$ seconds/mm²; TE = minimum; TR = 8000 ms; FOV = 24 cm; number of excitations (NEX) = 2; matrix size = 128 X 128; 3.0 mm slice thickness and zero spacing. Diffusion gradients were applied in x, y, and z orthogonal directions. Image processing was conducted using the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) software library FSL (Analysis Group, FMRIB, Oxford University, UK; Smith et al., 2004). The skull was removed from images using the FSL Brain Extraction Tool and an eddy-current correction was performed. The FSL DTIFIT tool was used to calculate diffusion tensor metrics including fractional anisotropy (FA), and mean diffusivity (MD). Diffusion tensor metrics were determined for two MS lesions and corresponding contralateral NAWM regions of interest (ROI), as well as within normal appearing tissue in five different brain ROIs including frontal, parietal, occipital, and cerebellar WM, and the thalamus. Lesions and NAWM ROIs were selected using T2-weighted images and an MRI brain atlas (Johnson and Becker) in FSL. T2-weighted and diffusion images were linearly registered using FLIRT in FSL in order to compute

average diffusion metrics for each area. An average of multiple lesions, contralateral NAWM regions, and bilateral normal appearing tissue ROIs were generated to obtain a single value for diffusion metrics in each location.

3.3.4 Protocol

Outcomes measures were assessed at baseline and following 24 weeks of exercise. The EDSS was administered by a neurologist specializing in MS and the assessment was conducted at the neurologists' clinic. The MSFC, MFIS and QoL were administered by a member of the research team and were conducted at the Centre for Health Promotion and Rehabilitation (McMaster University, Hamilton, Canada). Questionnaires were interview-administered. Multiple assessments of functional, fatigue and QoL outcomes were conducted to determine stable baseline values (detailed elsewhere; Pilutti et al., 2011). Blood samples were collected by nursing staff of Hamilton Health Sciences at Juravinski Hospital (Hamilton, Canada). MRI data was collected by imaging technologists at the Imaging Research Centre at Joseph's Healthcare Hamilton (Hamilton, Canada).

3.3.5 Statistical Analysis

Descriptive statistics were used to summarize participant characteristics. Treadmill training parameters were analyzed using a one-way repeated measures ANOVA with time as the repeated factor. Paired t-tests and Wilcoxon tests were used to determine the significance of changes in outcome measures from baseline to 24 weeks. Values in the text are presented as mean \pm SD. Significance was set at $p \leq 0.05$.

3.4 Results

3.4.1 Participant Characteristics

A detailed description of participants has been published elsewhere (Pilutti et al., 2011). In brief, 6 participants (2 men; 4 women) with progressive MS (5 PPMS; 1 SPMS) participated in this study. Mean EDSS of study participants was 6.9 ± 1.07 (range = 5.5-8.0). Participants were 48.2 ± 9.30 years (range = 35-61) with a mean disease duration of 11.5 ± 6.60 years (range = 4-24). Program adherence was $94.7 \pm 5.98\%$.

3.4.2 Treadmill Training Parameters

The progression in treadmill training parameters is presented in Figure 1. Over 24 weeks of training, participants significantly increased the speed at which they were able to walk on the treadmill (60% increase; $p < 0.0001$) from 1.1 ± 0.10 km/h at baseline to 1.7 ± 0.19 km/h at 24 weeks. Percent body weight support required to walk on the treadmill decreased significantly over the 24 weeks from $77.9 \pm 10.76\%$ to $38.2 \pm 18.75\%$ (51% decrease; $p < 0.0001$).

3.4.3 Functional Ability

Functional ability outcomes are presented in Table 1. Baseline EDSS was 6.9 ± 1.07 . At follow-up, EDSS score was reduced by 0.5 in two participants and the group mean was 6.8 ± 1.17 ($p = 0.17$). There was a non-significant improvement in overall MSFC Z-score from -3.0 ± 2.80 at baseline to -2.1 ± 2.60 at 24 weeks ($p = 0.26$). Walking speed increased from baseline to follow up with mean Z-score on the T25FW improving from -7.1 ± 7.28 to -5.2 ± 6.70 ($p = 0.33$). Of participants who completed testing at baseline and follow-up, walking velocity increased from 0.54 m/s to 0.67 m/s with a 19.4% improvement in walk times. A non-significant improvement was observed in 9HPT performance, scores improved from -1.8 ± 0.98 at baseline to -1.5 ± 1.07 at 24 weeks ($p = 0.21$). Scores on the

PASAT improved from -0.1 ± 0.77 at baseline to 0.3 ± 0.82 following training which approached significance ($p=0.06$).

3.4.4 Fatigue

Following the training intervention there was a significant reduction in MFIS total ($p=0.02$) from 43.5 ± 12.26 to 30.2 ± 7.33 (Table 1). Physical fatigue (pMFIS) decreased significantly ($p=0.02$) from 24.3 ± 5.8 to 16.0 ± 2.19 , and cognitive fatigue (cMFIS) decreased significantly ($p=0.03$) from 14.6 ± 8.92 to 10.7 ± 6.82 following exercise. A non-significant reduction in psMFIS score ($p=0.34$) was also detected following the intervention.

3.4.5 Quality of Life

QoL parameters at baseline and following 24 weeks of BWSTT are presented in Table 1. Scores on the physical health composite increased significantly from 36.4 ± 8.25 at baseline to 51.4 ± 15.18 following the intervention ($p=0.02$). There was a trend for an improvement in mental health composite scores ($p=0.09$) from 58.1 ± 16.06 at baseline to 73.5 ± 19.12 at follow-up. Non-responder data occurred in subscales of sexual function ($n=4$) and sexual satisfaction ($n=5$).

3.4.6 Brain-derived Neurotrophic Factor

Following exercise there was a non-significant increase in BDNF levels from 3832.3 ± 1056.26 pg/mL to 4664.5 ± 3865.13 pg/mL (21.7% increase; $p=0.57$; Figure 2).

Substantial inter-individual variability was observed in BDNF levels at baseline and follow-up.

3.4.7 Magnetic Resonance Spectroscopy

Metabolite concentrations in lesions and NAWM before and after the intervention are presented in Table 2. There was no significant change in the concentration of any metabolites examined in MS lesions following the exercise intervention. There was a significant decrease in the concentration of ml ($p=0.03$) from 5.7 ± 0.80 to 5.1 ± 0.57 in the contralateral NAWM following exercise. There was also a trend for a reduction in GPC ($p=0.08$) from 1.4 ± 1.03 to 0.8 ± 0.83 in the contralateral NAWM. No change was found in any metabolites when they were expressed relative to concentrations of Cr.

3.4.8 Diffusion Tensor Imaging

Following training, there was no change observed in FA or MD values in the lesion or contralateral NAWM areas. A significant increase in FA values from $0.400 \pm 0.055 \times 10^{-3}$ to $0.417 \pm 0.055 \times 10^{-3}$ ($p=0.03$) was observed in the parietal WM. A trend for a decrease in MD values in the parietal WM ($p=0.06$) and in the thalamus ($p=0.06$) was also observed. Diffusion metrics are presented in Table 3.

3.5 Discussion

This trial represents the first long-term study to evaluate the effects of supported treadmill walking in patients with progressive MS with severe mobility impairments. The use of advanced brain imaging parameters to determine the prospective effects of exercise in persons with MS is also unique. We determined long-term supported treadmill exercise is not only feasible and well-received by participants, it also appears to be beneficial for improving physical and mental fatigue, quality of life, and may potentially improve physical and mental functioning in patients with progressive MS. The increase observed in BDNF levels with exercise did not reach significance. MRI findings report

preliminary changes in some brain biomarkers that may be consistent with improved brain health, although our initial findings require confirmation from future studies.

3.5.1 Effects of BWSTT on Functional Ability

We did not determine a significant change in EDSS scores following 24 weeks of BWSTT; however, we did observe a reduction in EDSS score by 0.5 in 2 of 6 participants. Most exercise interventions in persons with MS have reported no change in EDSS scores following traditional exercise training (Dalgas et al., 2009; Rasova et al., 2006; Romberg et al., 2005; Petajan et al., 1996). Some interventions using BWSTT, however, have similarly observed small improvements in EDSS scores (Schwartz et al., 2012; Lo and Triche 2008; Geisser et al., 2006). In the present study, the decrease in EDSS score from 7.5 to 7.0 in one participant and from 5.5 to 5.0 in the other may have translated into meaningful improvements in community ambulation for these individuals. These findings should be interpreted cautiously in light of the potential for measurement error using the EDSS. The EDSS has demonstrated poor intra-rater reproducibility, precision, and responsiveness (Hobart et al., 2000), highlighting the importance of using other functional scales such as the MSFC.

We observed a non-significant improvement in MSFC scores following 24 weeks of exercise. Romberg and colleagues (2005) similarly reported a small improvement in MSFC scores following a combined aerobic and resistance training program, although the change in that study was statistically significant (Romberg et al., 2005). The most notable changes in function in the present study were observed for walking and cognitive performance. T25FW performance improved by 19.4% ($p=0.33$), which almost reached

the 20% improvement threshold established for a clinically significant change in ambulation (Kaufman et al., 2000). Meta-analytic procedures have also determined the impact of exercise on walking mobility with results revealing a mean effect size (ES) of .19 (Snook and Motl 2009). We observed a small ES of 0.27 (not reported in results) for the effect of BWSTT on T25FW performance, suggesting a slightly stronger effect of our intervention.

The present study observed an improvement in cognitive performance scores which approached significance following training ($p=0.06$). Few studies have examined the relationship between exercise and cognitive performance in persons with MS. Two cross-sectional studies have identified a positive association between cardiorespiratory fitness level and cognitive performance, as well as structural and functional brain integrity in persons with MS (Prakash et al., 2010; Prakash et al., 2007). To the best of our knowledge, only two interventions have examined the effects of exercise on cognitive performance prospectively in persons with MS (Romberg et al., 2005; Oken et al., 2004). Romberg and colleagues (2005) demonstrated a non-significant ($p=0.08$) improvement in PASAT scores following 26 weeks of combined aerobic and resistance training compared to non-exercising controls. Following six months of aerobic exercise or yoga, there was no improvement in cognitive function compared to the control condition; however, the once-weekly training frequency and poor program adherence likely contributed to the lack of change in cognitive outcomes. Improvements in cognitive function with exercise have been observed in other populations who experience cognitive deficits; effects of exercise on cognition in elderly adults, for example, have been studied extensively.

Several meta-analyses provide strong support for the effects of exercise using a variety of modalities for improving cognitive functioning in older adults (Smith et al., 2010; Heyn et al., 2004; Colcombe et al., 2003). As approximately 40-60% of persons with MS experience cognitive deficits (Feinstein 2011), exercise training may represent an alternative therapeutic strategy for managing cognitive impairment in persons with MS. There is a clear need for future research to explore the role of exercise on cognitive functioning in persons with MS.

3.5.2 Effects of BWSTT on Fatigue

We observed a significant reduction in total, physical and cognitive fatigue scores following 24 weeks of BWSTT. The effects of exercise on fatigue outcomes in persons with MS have been somewhat inconsistent. While some interventions have found positive effects of exercise on fatigue reduction (Wier et al., 2011; McCullagh et al., 2008; Rasova et al., 2006), others have not (Rampello et al., 2007; van den Berg 2006; Petajan et al., 1996). Another supported treadmill training intervention in ambulatory individuals with MS experiencing gait impairment determined a significant reduction in MFIS total scores following 12 sessions of BWSTT (Weir et al., 2011). Decreases in fatigue scores assessed by the FSS (Fatigue Severity Scale) in the same study, however, did not reach significance. Discrepancies between studies may be related to the outcome measures used to assess fatigue; MS-specific outcomes, such as the MFIS may be more responsive to changes in fatigue with exercise than general fatigue measures.

Improved physical fatigue scores following training may result from reductions in the energetic cost of movement. It has been demonstrated that persons with MS have higher

metabolic costs of walking compared to non-MS controls, and the metabolic cost of walking has been related to disability level (Motl et al., 2011). Participation in BWSTT may result in improved lower-extremity strength, aerobic conditioning, and gait mechanics which may translate into improved (and more efficient) walking performance. The 19.4% improvement in T25FW performance observed in the present study supports this contention. Improved walking efficiency may also result in greater energy conservation while performing daily tasks and consequently result in less symptomatic fatigue. Future studies should be conducted to determine the effects of BWSTT on outcomes of muscular and aerobic fitness, and spatiotemporal parameters of gait, and the relationship between these factors and fatigue outcomes.

The improvements in cognitive fatigue also noted in this investigation may be related to changes in cognitive function, as reflected by the trend for an improvement in PASAT performance. Improvements in cognitive processes such as memory or processing speed may result in daily cognitive tasks becoming less challenging, requiring less time and energy, and consequently, becoming less mentally fatiguing.

3.5.3 Effects of BWSTT on QoL

We observed a significant improvement in physical health composite scores and a trend for an improvement in mental health composite scores following 24 weeks of BWSTT. Our findings are in line with results from previous exercise interventions which have been successful in improving health-related QoL in persons with MS (Collett et al., 2011; Weir et al., 2011; Rampello et al., 2007; Rasova et al., 2006; Sutherland et al., 2001), as well as a comprehensive meta-analysis which determined a significant mean ES of .23 for

the effects of exercise on QoL in persons with MS (Motl and Gosney 2008). Similarly, Wier and colleagues (2011) reported a significant improvement in physical health composite scores and a non-significant improvement in mental health composite scores following 12 sessions of BWSTT. Other QoL scales administered in that study, including the Pain Effects Scale, the Perceived Deficits Questionnaire, and the Life Satisfaction scale also improved significantly following BWSTT (Wier et al., 2011).

There is ample evidence that QoL is compromised in persons with MS (Benito-Leon et al., 2003). It has been suggested that a cluster of symptoms including fatigue, depression, pain, and perceived cognitive deficits co-occur in persons with MS and these symptoms also have a dose-dependent relationship with QoL (Motl et al., 2010). An indirect association between physical activity and QoL in persons with MS has been proposed, which may be mediated by fatigue, pain, social support, and self-efficacy (Motl and McAuley 2009; Motl and Snook 2008). Taken together, these results suggest that exercise-induced improvements in QoL may be mediated through improvements in a variety of disease-related symptoms and multi-symptom management strategies may be most effective for improving QoL in persons with MS. Exercise may represent a unique and effective tool for improving QoL in persons with MS in that it has the ability to target and improve multiple MS symptoms simultaneously, as seen by improvements in physical and mental functioning, as well as reduced fatigue, observed in the present investigation.

3.5.4 Effects of BWSTT on BDNF

We determined a non-significant increase in resting BDNF levels by almost 22% following 24 weeks of training. Of the few studies evaluating the effects of exercise on BDNF levels in MS, considerable discrepancies exist. Similar to our findings, Schultz and colleagues (2004) reported a non-significant increase in resting BDNF levels following an 8 week cycling program in persons with MS. Castellano and White (2008) found lower resting BDNF levels in persons with MS compared to controls which increased by week 4 of an 8 week cycling program; however, these returned toward baseline levels by week 8. Gold and colleagues (2003) observed an increase in serum BDNF in response to an acute exercise bout both in persons with MS and non-MS controls, suggesting aerobic cycling may increase circulating BDNF levels.

A review of the effects of exercise on peripheral BDNF concentrations suggests a transient dose-response relationship exists between exercise intensity and BDNF production in response to acute aerobic exercise in healthy individuals; however, low-to-moderate intensity exercise appears to be sufficient to elicit a BDNF response in populations with chronic disease or disability (Knaepen et al., 2010). Results are limited and less conclusive regarding the effect of chronic aerobic exercise on resting BDNF concentrations in both healthy and diseased populations (Knaepen et al., 2010). More research on the response of BDNF to BWSTT, and exercise in general, in a large sample of persons with MS and controls is clearly needed.

A number of animal studies have demonstrated exercise-induced expression of BDNF mRNA and protein in various brain areas including the hippocampus, cerebral cortex, cerebellum, and spinal cord (Klinstova et al., 2004; Gomez-Pinilla et al., 2002; Gomez-

Pinilla et al., 2001; Neeper et al., 1996; Neeper et al., 1995). Compared to resting levels, a 2-3 fold increase in BDNF release from the brain has been observed in response to acute exercise in human subjects (Rasmussen et al., 2009). An increase in resting BDNF release from the brain was also observed compared to non-exercising controls following three months of aerobic exercise, although there was no difference in BDNF response during exercise (Seifert et al., 2010). As BDNF is believed to play a key role in neuroprotective and neurorestorative processes in the CNS, the potential exercise-induced release of BDNF may promote neural recovery and plasticity in persons with MS, although the exact mechanisms by which this may occur are unclear (White and Castellano 2008). Exercise provides a non-invasive method to potentially induce repair of the injured CNS in persons with MS, and consequently disease progression, through BDNF-mediated mechanism.

3.5.6 Effects of BWSTT on Brain Imaging Parameters

Recent attention has been drawn to the role of exercise as a disease-modifying strategy for persons with MS, rather than a disease management tool alone (Dalgas and Stenager 2012). Advanced brain imaging techniques, such as ¹H-MRS and DTI, represent highly sensitive and highly specific methods for evaluating pathological changes in MS with disease progression and treatment (Sajja et al., 2009). In patients with PPMS specifically, a greater discrepancy exists between conventional MRI measures and clinical disease manifestation which supports the use of advanced brain imaging metrics to evaluate underlying disease activity and progression in this population (Rocca et al., 2011).

Advanced brain imaging metrics may provide insight into the disease-modifying potential

of exercise in persons with MS. We provide the first study to examine the effects of exercise on advanced brain imaging metrics in persons with MS.

3.5.6.1 Magnetic Resonance Spectroscopy. ¹H-MRS provides a measure of changes in brain metabolites (Sajja et al., 2009). Following the exercise intervention, we did not determine any significant changes in metabolite concentrations in the MS lesions; however, we did find a significant decrease in the concentration of mI in the contralateral NAWM and a trend for a reduction in GPC in the contralateral NAWM. It is generally accepted that normal appearing tissue is, in fact, not normal in patients with MS and that tissue damage may be more diffuse, particularly in patients with PPMS (Rocca et al., 2011; Sajja et al., 2009). Elevated levels of mI and choline have been observed in NAWM regions in patients with MS (Tartaglia et al., 2002; He et al., 2005; Chard et al., 2002). mI is considered to be a glial marker and elevated levels are believed to represent gliosis, astrocytosis, and myelin breakdown (Soares and Law 2009; Castillo et al., 1998). Choline is believed to be a biomarker of cell membrane metabolism which, in MS may reflect inflammation, gliosis, demyelination and remyelination (Soares and Law 2009; Narayana 2005). A reduction in levels of mI and GPC in NAWM may, therefore, suggest underlying processes of repair rather than further tissue damage. We did not, however determine any change in concentrations of NAA, which has generally been accepted as a biomarker of axonal integrity, and is frequently reduced in lesions and NAWM in persons with MS (Sajja, et al., 2009; Rocca et al., 2011). When concentrations of mI and GPC were normalized to Cr the effect of exercise on brain metabolites was not longer significant or trending. It has been suggested that individual and regional variation in

levels of Cr may contribute to instability; absolute metabolite concentrations may provide greater sensitivity and specificity (Li et al., 2003). There are few studies evaluating the effects of long-term interventions on ^1H -MRS outcomes in patients with PPMS. No change in brain metabolite concentrations were observed in lesions, NAWM or GM over a three year period of glatiramer acetate (GA) treatment (Sajja et al., 2008). Metabolite concentrations in the untreated group in that study also remained stable over time. Further evaluation of responsiveness of ^1H -MRS outcomes over time with and without intervention in patients with PPMS is necessary.

3.5.6.2 Diffusion Tensor Imaging. DTI provides an assessment of the diffusion of water molecules in tissue (Filippi et al., 2001). The two main diffusion metrics are mean diffusivity (MD) which reflects the magnitude of molecular diffusion and fractional anisotropy (FA) which reflects the degree of tissue alignment and structural integrity (Rocca et al., 2011; Filippi et al., 2001). The structural integrity and permeability of barriers to diffusion in the CNS can be affected by the pathology of MS, resulting in abnormal water diffusion (Filippi et al., 2001). DTI studies in individuals with MS have reported higher MD values and lower FA values in lesions, NAWM, and GM tissue which correspond to demyelination and axonal loss post-mortem (Rocca et al., 2011; Rovaris et al., 2005). Our study did not determine any changes in diffusion tensor metrics in the lesion or contralateral NAWM areas. We did determine a significant increase in FA values in the parietal WM, and a trend for a decrease in MD values in the parietal WM and in the thalamus. An increase in FA and a decrease in MD would suggest a reduction in diffusivity and greater structural organization within these brain regions which may

ultimately impact disability. A recent study has established a relationship between diffusion metrics and disability progression in patients with PPMS (Mesaros et al., 2011). Average NAWM MD at baseline and change in thalamic FA values over a 15 month time period were predictive of change in EDSS scores at 5 year follow-up in persons with PPMS (based on EDSS score) (Mesaros et al., 2011). Further studies are necessary to determine if improvements in diffusion metrics correspond to improved structural integrity in persons with MS and the impact on disability progression.

A longitudinal study of changes in diffusion metrics in PPMS patients compared to healthy controls, revealed an increase in the apparent diffusion coefficient (ADC) in five bilateral normal-appearing brain regions over 12 months (Schmierer et al., 2004). The increase in ADC over time suggests greater diffusion of water molecules and progressive demyelination and axonal loss in patients with PPMS (Schmierer et al., 2004). The lack of a significant change in most DTI metrics observed in the present study may reflect a reduction in structural brain damage with exercise; however, there was considerable variability in the direction of non-significant changes between brain regions which should be interpreted cautiously. Future studies with non-MS and MS-control conditions are required to determine the role of exercise on diffusion tensor parameters in patients with progressive MS.

3.6 Limitations

The primary limitations of this investigation are the small sample of participants and the lack of a control group. This trial represents the first prospective investigation to examine the effects of BWSTT in patients with MS on brain imaging parameters and neurotrophic

factors, rationalizing the pilot nature of this investigation. Furthermore, the progressive disease course and level of impairment of the sample group suggest participants would deteriorate or maintain the same level of function over time. Although this trial represents the longest supported treadmill training intervention in patients with MS, longer trials and follow-up studies are still required to realize the full potential of BWSTT as a rehabilitation tool. Determining the effect of BWSTT on clinical and mobility outcomes, may require an even longer training protocol in patients with MS with severe mobility impairments. The potential role for seasonality and social support to affect outcomes such as quality of life and fatigue with training should also be acknowledged. Future trials should examine the role of these potentially confounding variables.

3.7 Conclusions

This trial represents the longest supported treadmill training intervention to date in patients with progressive MS with severe mobility impairments. Although encouraging, our findings should be interpreted cautiously considering the pilot nature and limitations of this investigation. Our preliminary findings support a role for BWSTT in improving fatigue and quality of life, and provide preliminary evidence for the potential for BWSTT to impact ambulation, cognition, and brain health. While improvements in ambulation and cognition did not reach statistical significance, such improvements may translate into clinically meaningful changes for patients and those around them. Larger, randomized controlled trials with longer end points are necessary to confirm and extend our preliminary findings. Initial positive findings regarding the impact of BWSTT on

neurotrophic factors and brain imaging parameters also warrant further investigation in a larger sample under controlled conditions.

Acknowledgements

We gratefully acknowledge the dedication and commitment of the subjects and volunteer therapists who participated in this investigation. Financial support for the study was provided by the Multiple Sclerosis Society of Canada pilot grants initiative. LAP was the recipient of a Canada Graduate Scholarship supported by the Canadian Institute of Health Research.

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Figures and Tables

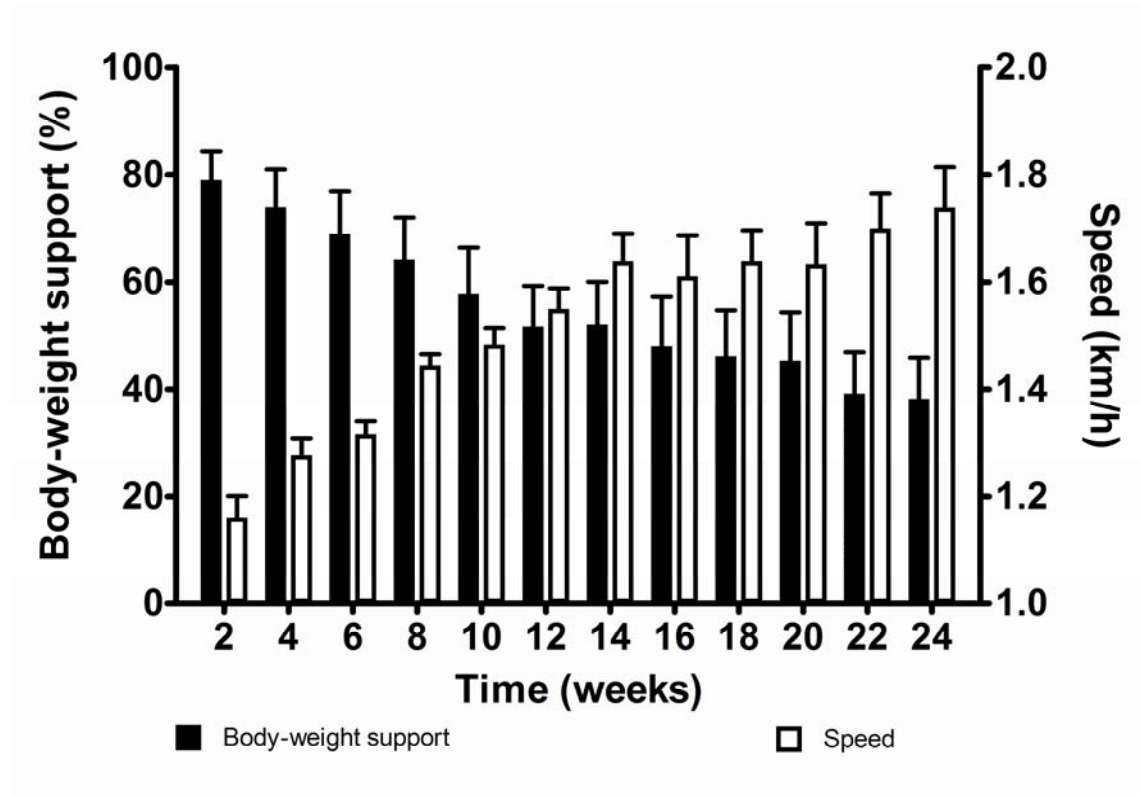


Figure 3.1 Percent body weight support and walking speed (km/h) over 24 weeks of BWSTT. Values are mean \pm SE.

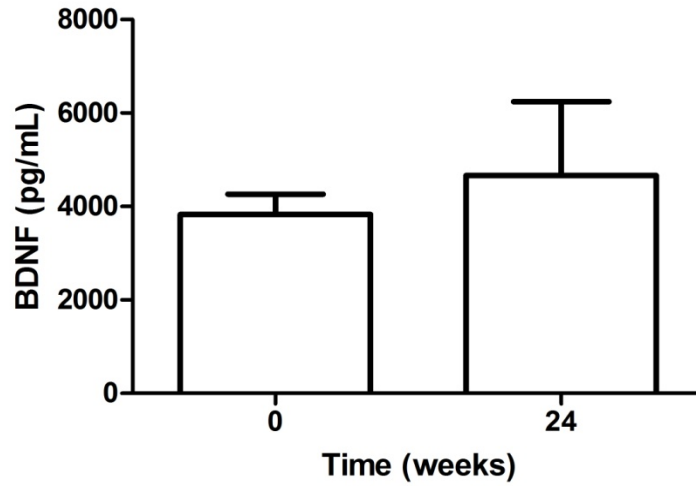


Figure 3.2 Serum brain-derived neurotrophic factor (BDNF; pg/mL) at baseline and after 24 weeks of BWSTT. Values are mean \pm SE.

Table 3.1 Effects of 24 weeks of BWSTT on outcome measures. Values are mean \pm SD.

Measure	Baseline	Week 24	<i>p</i>
EDSS	6.9 (1.07)	6.8 (1.17)	0.17
MSFC	-3.0 (2.80)	-2.1 (2.60)	0.26
T25FW	-7.1 (7.20)	-5.2 (6.70)	0.33
9HPT	-1.8 (0.98)	-1.5 (1.07)	0.21
PASAT	-0.1 (0.77)	0.3 (0.82)	0.06
MFIS	43.5 (12.26)	30.2 (7.33)	0.02
pMFIS	24.3 (5.80)	16.0 (2.19)	0.02
cMFIS	14.6 (8.92)	10.7 (6.83)	0.03
psMFIS	4.7 (2.58)	3.5 (0.84)	0.34
MSQoL physical	36.4 (8.25)	51.4 (15.18)	0.02
MSQoL mental	58.1 (11.04)	73.5 (19.12)	0.09

Note: Expanded Disability Status Scale, EDSS; MS Functional Composite, MSFC; timed twenty-five-foot walk, T25FW; nine-hole peg test, 9HPT; Paced Auditory Serial Addition Test, PASAT; Modified Fatigue Impact Scale, MFIS (p=physical, c=cognitive, ps=psychosocial); MSQoL-54, Multiple Sclerosis Quality of Life-54.

Table 3.2 Metabolite concentrations in lesions and contralateral normal appearing white matter (NAWM) before and after 24 weeks of supported treadmill training. Values are mean \pm SD.

Metabolite	Lesion			NAWM		
	Baseline	Week 24	<i>p</i>	Baseline	Week 24	<i>p</i>
Cr	6.0 (0.79)	6.1 (0.47)	0.71	6.2 (0.86)	6.1 (1.02)	0.84
Gln	3.1 (1.11)	2.1 (0.61)	0.10	2.8 (0.82)	3.6 (2.23)	0.38
Glu	7.7 (1.32)	7.9 (1.39)	0.54	7.9 (0.78)	7.7 (1.92)	0.87
GPC	2.0 (0.47)	1.9 (0.66)	0.50	1.4 (1.03)	0.8 (0.83)	0.08
Lac	0.5 (0.45)	0.8 (0.42)	0.17	0.5 (0.58)	0.4 (0.47)	0.88
mI	5.7 (0.51)	5.8 (0.52)	0.58	5.7 (0.80)	5.1 (0.57)	0.03
NAA	7.9 (1.69)	7.9 (1.16)	0.85	6.6 (1.84)	7.6 (2.61)	0.44
NAA/Cr	1.3 (0.20)	1.1 (0.49)	0.29	1.1 (0.39)	1.2 (0.32)	0.37
mI/Cr	1.0 (0.16)	1.0 (0.12)	0.93	0.9 (0.09)	0.9 (0.21)	0.45
GPC/Cr	0.3 (0.08)	0.3 (0.10)	0.30	0.2 (0.15)	0.1 (0.16)	0.15

Note: creatine, Cr; glutamine, Gln; glutamate, Glu; glycerophosphocholine, GPC; lactate, Lac, myoinositol, mI; and N-acetylaspartate, NAA.

Table 3.3 Fractional anisotropy (FA) and mean diffusivity (MD) of lesions, normal appearing white matter, and ROIs before and after 24 weeks of supported treadmill walking. Values are mean ± SD.

Location	FA		<i>p</i>	MD X 10 ⁻³		<i>p</i>
	Baseline	Week 24		Baseline	Week 24	
Lesion	0.325 (0.053)	0.312 (0.058)	1.00	1.009 (0.124)	1.000 (0.113)	0.76
NAWM	0.438 (0.099)	0.376 (0.065)	0.28	0.806 (0.069)	0.795 (0.043)	0.76
ROIs						
Frontal WM	0.365 (0.060)	0.366 (0.045)	0.97	0.839 (0.042)	0.829 (0.036)	0.74
Parietal WM	0.400 (0.055)	0.417 (0.055)	0.03	0.749 (0.049)	0.704 (0.044)	0.06
Occipital WM	0.298 (0.144)	0.269 (0.110)	0.28	0.819 (0.010)	0.789 (0.094)	0.87
Cerebellar WM	0.476 (0.029)	0.422 (0.063)	0.21	0.625 (0.050)	0.632 (0.040)	0.39
Thalamus	0.395 (0.059)	0.337 (0.077)	0.18	0.747 (0.037)	0.745 (0.011)	0.06

Note: normal appearing white matter, NAWM; regions of interest, ROIs; white matter, WM.

CHAPTER 4

EXERCISE REDUCES BRAIN IRON CONTENT IN PROGRESSIVE MULTIPLE SCLEROSIS: PILOT FINDINGS USING SUSCEPTIBILITY- WEIGHTED IMAGING

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4.0 EXERCISE REDUCES BRAIN IRON CONTENT IN PROGRESSIVE MULTIPLE SCLEROSIS: PILOT FINDINGS USING SUSCEPTIBILITY-WEIGHTED IMAGING

4.1 SUMMARY

Elevated brain iron content has been observed in many neurodegenerative conditions and is currently being debated as an etiological factor in multiple sclerosis (MS). We undertook a pilot trial (6 patients with progressive MS and high disability) to determine the effect of 24 weeks of weight-supported treadmill exercise (3 sessions/week) on regional brain iron content, as measured by magnetic resonance susceptibility weighted imaging (SWI). A significant decrease ($P < 0.05$) in iron content was observed in the caudate nucleus, globus pallidus, putamen, and thalamus following training. Future work should focus on the relationship between exercise and brain iron deposition in MS.

4.2 INTRODUCTION

Excessive accumulation of brain iron has been found to occur in several neurodegenerative conditions including multiple sclerosis (MS).¹ The quantification of brain iron in MS, until recently, has been conducted using T2-weighted MRI techniques or post-mortem staining.^{2,3} The development of susceptibility weighted imaging (SWI), a 3D, high-resolution, fully flow compensated MRI pulse sequence, has allowed for the quantification of regional brain iron with a high degree of sensitivity.⁴ Few studies have employed SWI to quantify brain iron in patients with MS; however, a recent study revealed particularly high iron content in several deep grey matter (GM) structures in patients with relapsing remitting MS (RRMS) compared to healthy controls.⁵ While the exact role of iron in the pathogenesis of MS remains unclear, it has been suggested that iron exerts damaging effects through free radical mediated oxidative stress via Fenton-based chemistry.⁶ Interventions which minimize oxidative damage may, therefore, be protective against neurodegeneration and slow disease progression in MS. Exercise has been found to promote brain health in several neurodegenerative diseases and may play a role in the regulation of oxidative stress.⁷ Determining the underlying effects of exercise on disease pathology in MS has been challenging. However, high-resolution MRI techniques, such as SWI, allow detailed non-invasive assessment of the potential effects of exercise on brain health. Therefore, the purpose of this pilot study was to evaluate the effects of exercise on iron content in deep brain structures of individuals with progressive MS.

4.3 PATIENTS

Participants were recruited through the MS clinic of Hamilton Health Sciences. Inclusion criteria were clinically definite primary progressive MS (PPMS), as per the diagnostic criteria of Thompson et al.⁸; EDSS 5.0 to 8.0; age 18 to 60 years; body weight < 90kg; and ability to visit study locations, follow training instructions, and tolerate body-weight supported treadmill training (BWSTT). Exclusion criteria were pregnancy or plans to become pregnant during the study period; current participation in a clinical trial of an experimental or unapproved/unlicensed therapy for PPMS; current use or use within the last 2 months of off-label therapy for PPMS including interferon- β , glatiramer acetate, steroids, mitoxantrone, azathioprine, and/or cyclophosphamide; inability to undergo MRI, acquired disability that could interfere with evaluation of disability caused by MS; and other serious medical conditions that might impair the subject's ability to participate in the exercise program. This study was approved by the Research Ethics Board of Hamilton Health Sciences and St. Joseph's Healthcare, Hamilton. Written, informed consent was obtained from all participants.

4.4 METHODS

Subjects participated in three weekly sessions (30min/session) of aerobic exercise using BWSTT for the duration of 24 weeks. BWSTT allows participants to walk on a treadmill using a supportive harness connected to an overhead, counterbalancing pulley system. The counterbalancing system allows a portion of the individuals' body-weight to be off-loaded and reduces the energy costs associated with walking. Training took place using

the Woodway-LoCo System (Woodway USA Inc, Waukesha, WI). A description of the treadmill setup and training protocol has been published elsewhere.⁹

Magnetic resonance imaging (MRI) data was acquired before and after a 24 week exercise intervention using a GE 3T Signa HD MRI system and 8 channel phased array head coil (GE Healthcare, Milwaukee, WI). Images were acquired using a three-dimensional, fully flow compensated, spoiled gradient recalled echo sequence (TE/TR=20/30ms; flip angle=15°; 40kHz receiver bandwidth; 512x256 matrix; 24cm FOV; 2mm slice thickness (0 skip); ASSET factor=2, no grad warp, and no Fermi filter). Both phase and magnitude images were reconstructed, and phase images were high-pass-filtered to remove aliasing (Figure 1). Regions of interest (ROIs) were hand-drawn bilaterally on filtered phase images in the following regions of the motor cortex: GM, white matter (WM) and cerebrospinal fluid (CSF); and deep brain areas: caudate nucleus (CN), globus pallidus (GP), putamen (PUT) and thalamus (T), based on anatomical landmarks using an MRI brain atlas.¹⁰ Mean MRI signal phase was calculated from each ROI and related to iron content based on the relationship described by Haacke et al.¹¹ In their approach they determined that 3 Siemens phase units (Φ) corresponds to 1 μg of Fe/g tissue. For our study we determined that 1 μg of Fe/g tissue equates to 4.6 GE MRI phase units. Iron content was determined at baseline and follow-up for each brain region, relative to CSF which is assumed to contain negligible MR-visible iron.¹² ROIs were evaluated as an average of left and right hemispheric values. Paired t-tests were used to determine changes in iron content from baseline to 24 weeks for all brain regions with the exception of CSF which was assumed to have negligible iron. Analyses

were performed using GraphPad PRISM software, version 5.01 (GraphPad Software Inc, La Jolla, CA). Statistical significance was set as $P \leq 0.05$.

4.5 RESULTS

Characteristics of the six subjects (mean age 48.2 ± 9.3 years; mean Expanded Disability Status Scale (EDSS) = 6.9 ± 1.07 ; mean disease duration = 11.5 ± 6.6 years) are presented in Table 1. Five participants were clinically diagnosed as PPMS and one as secondary progressive MS (SPMS). The one patient with SPMS was included in this pilot trial based on disease stability and duration in consultation with our team's neurologist. All participants completed 24 weeks of training. Over the course of the exercise program, treadmill performance outcomes including support required to walk and walking speed improved in all participants. Significant improvements in fatigue and quality of life outcomes were also observed.⁹ Functional improvements were noted in some participants; however, this report focuses on the effects of exercise on regional iron deposition.

Changes in regional iron content following 24 weeks of BWSTT are presented in Table 2. No change in iron content was noted in white ($P=0.36$) or grey matter ($P=0.21$) of the motor cortex. A significant decrease in iron was observed for all deep brain structures assessed: 19.0% decrease in the CN (head; $P=0.01$); 21.0% decrease in the GP ($P=0.003$); 15.9% decrease in the PUT ($P=0.03$); and 11.7% decrease in the T ($P=0.047$).

4.6 DISCUSSION

This is the first study to investigate the effects of exercise on regional brain iron content in patients with progressive MS. Our pilot results reveal a decrease in iron content

following 24 weeks of treadmill exercise in the putamen, globus pallidus, caudate nucleus and thalamus, assessed using MRI. In comparison to findings from a large group of non-diseased older adults (55-89 years),¹¹ our pilot study found similar baseline iron content in the white matter of the motor cortex and the caudate head. Iron content was lower in the grey matter of the motor cortex and the globus pallidus which may be due to subtle differences in ROI selection. In that previous study, the thalamus was not assessed and the putamen was quantified by sub-region making an overall comparison difficult. While regional iron content was determined relative to CSF phase values, we acknowledge the potential for changes in CSF flow as a confounding factor. Further studies are required to establish baseline regional brain iron levels in individuals with MS and other neurodegenerative diseases and in non-diseased populations across the lifespan.

The mechanisms by which iron accumulates in CNS tissue in MS remains incompletely understood. One proposed model suggests a role for the stress response protein heme oxygenase-1 (HO-1) which has been found to be overexpressed in the CNS tissue of patients with MS and other neurodegenerative disorders.¹³ HO-1 degrades heme to biliverdin, free iron and carbon monoxide; production of the latter two molecules promotes intracellular oxidative stress and accumulation of iron within the mitochondrial matrix.¹³ Pro-inflammatory cytokines interleukin-1 β (IL-1 β) and tumor necrosis factor- α (TNF- α) have been shown to upregulate HO-1 mRNA expression and increase nontransferrin-derived iron uptake by mitochondria in cultured neonatal rat astroglia.¹⁴ Exercise may reduce iron storage in CNS tissue by altering cytokine activities, consequently modulating HO-1 expression. Interleukin-6 (IL-6) is a myokine that

increases exponentially in response to acute exercise and has been known to have both pro- and anti-inflammatory effects.¹⁵ In response to exercise, IL-6 acts in an anti-inflammatory manner by inhibiting the production of IL-1 β and TNF- α , and increasing the production of anti-inflammatory cytokines.¹⁵ Regular physical activity has also been associated with attenuated resting levels of pro-inflammatory cytokines, suggesting an anti-inflammatory role for exercise.¹⁶ The acute cytokine response to exercise was found to be similar in patients with RRMS as in non-MS controls, both demonstrating significant increases in plasma IL-6.¹⁷ In response to 8 weeks of cycling exercise patients with MS demonstrated a tendency for reduced resting plasma IL-6; however, TNF- α was significantly increased.¹⁷ The same research group found 8 weeks of resistance training tended to reduce resting TNF- α with no effect on resting IL-6 in female patients with RRMS.¹⁸ Exercise may reduce brain iron accumulation in MS by regulating the inflammatory balance; however, more comprehensive studies are required to establish the relationship between exercise, cytokine regulation and disease activity in patients with MS.

Accumulated brain iron has been suggested to lead to the formation of reactive oxygen species (ROS), which in excess, can lead to widespread tissue damage.⁶ Based on this proposed mechanism, any intervention that reduces brain pro-oxidant or increases brain antioxidant status could therefore be of benefit to patients with MS. An 8 week swimming protocol was found to reduce the production of ROS accompanied by an increase in brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) production in rat brains.¹⁹ A 7.5 week treadmill training protocol was also found to

significantly increase total (i.e. cytosolic + mitochondrial) activity of the antioxidant enzyme superoxide dismutase (SOD) in the brainstem and striatum regions of rat brains.²⁰ Exercise may therefore represent an alternative therapy for reducing oxidative damage and disease progression in MS.

Altered iron metabolism has also been reported in patients with MS which may be a reflection of underlying disease processes. Ferritin, the primary iron storage protein, has been found to be elevated in the serum and CSF of patients with chronic progressive MS compared to patients with RRMS and non-MS controls.^{21,22} It has been suggested that ferritin levels increase in MS in attempt to protect against oxidative damage by binding and storing additional free iron.²¹ Iron transport protein, transferrin, has been found to be lower in the serum of patients with PPMS compared to other MS subgroups; however, no difference was observed in CSF transferrin levels.²³ Exercise may play a role in normalizing iron homeostasis in MS by altering the distribution and storage of iron throughout the body. Schumacher and colleagues²⁴ found moderately trained individuals had significantly lower serum ferritin and higher serum transferrin compared to untrained individuals. Following five weeks of treadmill running non-heme iron was significantly elevated in rat gastrocnemius compared to non-exercised controls.²⁵ Increased iron storage was accompanied by an upregulation of iron uptake proteins divalent metal transporter 1 (iron responsive element) and transferrin receptor 1, and downregulation of iron exporter ferroportin. Skeletal muscle represents a potential source for the redistribution of accumulated brain iron in patients with MS.

Limitations

Our pilot findings should be interpreted in light of several limitations and require further validation under randomized, controlled conditions. The primary limitations of this investigation are the small sample size and the lack of a control condition. This trial was quite exploratory in nature in that it was the first trial to prospectively evaluate the effects of exercise on brain imaging parameters in persons with MS. This trial also used a novel brain imaging technique, SWI, that has had very limited use as an outcome measure in patients with MS. The mechanisms we suggest with respect to the changes in brain iron content with exercise are also very speculative at this point in time and require further investigation.

Conclusions

The results of this pilot study are provocative and warrant further investigation. We have briefly discussed several potential mechanisms by which exercise may reduce accumulated brain iron and oxidative damage to CNS tissue in MS. Exercise may play a role in regulating the inflammatory balance, antioxidant status and iron metabolism in patients with MS, although these mechanisms are not inclusive. SWI represents a novel tool for the quantification of brain iron and has great potential for monitoring disease treatment in patients with MS and other iron-related neurodegenerative conditions.

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4.8 FIGURES AND TABLES

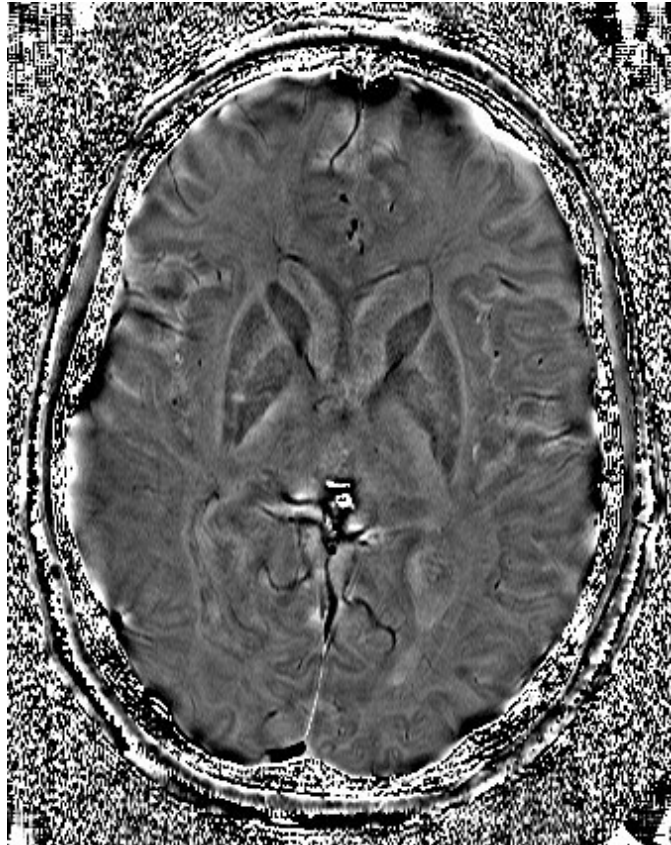


Figure 4.1 SWI filtered phase image of deep grey matter structures in a patient with progressive MS before treadmill training.

Table 4.1 Baseline characteristics of participants.

Subject	Sex	Age (years)	Disease course	EDSS	Disease duration (years)
1	F	35	PPMS	8	7
2	M	42	PPMS	6.5	14
3	M	61	PPMS	5.5	4
4	F	53	SPMS	8	23
5	F	45	PPMS	6	11
6	F	53	PPMS	7.5	10

PPMS = primary progressive multiple sclerosis; SPMS = secondary progressive multiple sclerosis; EDSS = Expanded Disability Status Scale

Table 4.2 Changes in regional iron content following 24 weeks of treadmill training.

		Baseline		24 Weeks		
Location	Phase (M±SD)	Phase difference CSF-ROI	Iron content µg Fe/gm of tissue (M±SD)	Phase (M±SD)	Phase difference CSF-ROI	Iron content µg Fe/gm of tissue (M±SD)
MC						
WM	2061.3 (21.15)	78.5	17.1 (7.83)	2056.2 (16.2)	70.8	15.4 (7.89)
GM	1927.5 (34.10)	212.3	46.1 (11.02)	1925.8 (29.17)	201.2	43.7 (9.23)
CSF	2139.8 (32.68)	0	0	2127.1 (31.75)	0	0
CN						
(head)	1938 (38.94)	201.8	43.9 (9.4)	1963.6 (22.21)	163.4	35.5 (5.18)*
GP	1971.1 (26.64)	168.7	36.7 (10.76)	1993.8 (38.9)	133.3	29 (9.76)*
PUT	1983 (34.01)	156.9	34.1 (10.7)	1995.1 (52.92)	131.9	28.7 (13.63)*
T	2035.2 (8.11)	104.6	22.7 (7.33)	2034.7 (6.85)	92.4	20.1 (7.57)*

Values are means (SD). MC= motor cortex; WM = white matter; GM = grey matter; CSF = cerebrospinal fluid; CN = caudate nucleus; GP = globus pallidus; PUT = putamen; T = thalamus.

CHAPTER 5

MAINTENANCE OF EXERCISE EFFECTS IN INDIVIDUALS WITH PROGRESSIVE MS: A 12 WEEK POST-TREADMILL TRAINING FOLLOW-UP STUDY

Prepared for submission to: Archives of Physical Medicine and Rehabilitation

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5.0 MAINTENANCE OF EXERCISE EFFECTS IN INDIVIDUALS WITH PROGRESSIVE MS: A 12 WEEK POST-TREADMILL TRAINING FOLLOW-UP

5.1 ABSTRACT

Objective: To determine the extent to which exercise training-induced changes in people with progressive MS are maintained when exercise is discontinued for 12 weeks.

Design: Twelve week follow-up after training intervention.

Setting: Exercise rehabilitation research centre.

Participants: Six patients with progressive MS (mean \pm SD Expanded Disability Status Scale, [EDSS] = 6.9 ± 1.07).

Interventions: Patients were assessed 12 weeks after completion of a 24-week supported treadmill walking intervention (30 min, 3X/week). After completing follow-up testing participants were given the opportunity to join a community-based adapted exercise program.

Main Outcome Measures: Functional ability assessed by EDSS and Multiple Sclerosis Functional Composite (MSFC), fatigue assessed by the Modified Fatigue Impact Scale (MFIS), and quality of life (QoL) assessed by the Multiple Sclerosis Quality of Life-54 (MSQoL-54).

Results: Follow-up testing revealed a non-significant tendency towards return to baseline in functional ability, fatigue and physical QoL. Mental QoL, however, improved post-training and at follow-up was significantly increased from baseline ($P < 0.05$). Participants completed the 24-week intervention with a $94.7 \pm 5.98\%$ adherence rate. Five participants chose to join the community-based exercise program, while one participant chose at-home exercise.

Conclusions: Twelve weeks after completion of a supported treadmill walking program in people with progressive MS, improvements in functional ability, fatigue and physical QoL tended to return towards pre-training levels, while effects on mental QoL may be maintained.

Keywords: rehabilitation, exercise maintenance, functional ability, quality of life, fatigue

5.2 INTRODUCTION

The benefits of physical activity for people with multiple sclerosis (MS) have become apparent; however, adults with MS report being less physical active than the non-diseased adult population.^{1,2} Patients with primary progressive MS (PPMS) in particular are even less physically active² and typically experience greater symptom severity^{3,4} than patients with relapsing remitting MS (RRMS). Time to reach disability benchmarks also occurs earlier in patients with PPMS.⁵ The combination of reduced activity and increased disease burden results in physical deconditioning promoting further mobility impairment.⁶ Consequently, developing interventions that increase physical activity and promote long-term maintenance of function in patients with PPMS are crucial.

Creating physical activity interventions for patients with mobility impairments can be challenging, further limiting the opportunity for patients with PPMS to participate in physical activity. One strategy that has been used to deliver physical activity for patients with progressive MS with greater disability burden is body weight supported treadmill training (BWSTT). BWSTT allows people with mobility impairments to walk upright on a treadmill with the support of a harness connected to an overhead, counterbalancing system. BWSTT has been found to be a safe and effective intervention strategy for improving functional and psychosocial parameters in patients with MS.⁷⁻¹⁰ However, if BWSTT is to be used as a rehabilitation tool for people with MS we need to understand not only the effects of using this exercise modality, but also the longevity of any exercise-induced benefits.

We conducted a 24-week intervention to examine the effects of BWSTT in 6 patients with progressive MS (Chapter 3). While supported treadmill training improved functional, fatigue and quality of life (QoL) outcomes, we were unsure as to how long these effects would be maintained. Therefore, this follow-up study provides information on the maintenance of these training-induced changes by evaluating participants 12 weeks following a 24-week BWSTT intervention. This report also discusses exercise adherence during and following the intervention.

5.3 METHODS

5.3.1 Participants

This study was approved by the Research Ethics Board of Hamilton Health Sciences (HHS REB). Participants provided written informed consent and confidentiality was maintained in accordance with HHS REB guidelines. Six participants took part in this study (age 48.2 ± 9.30 ; 4 female, 2 male). Five participants were clinically diagnosed as PPMS, 1 as secondary progressive MS (SPMS; Expanded Disability Status Scale [EDSS] = 6.9 ± 1.07). Participants previously completed a 24-week supported treadmill walking program. In brief, the exercise intervention consisted of three weekly sessions (30 min/session) of therapist-assisted BWSTT using the Woodway Loco-System.^a Treadmill walking was facilitated through an overhead pulley system connected to a supportive harness, off-loading a percentage of the patients' body weight. A detailed description of participant characteristics, criteria and the training protocol are published elsewhere.¹⁰

5.3.2 Design and Outcomes Measures

Twelve weeks following completion of the 24-week treadmill training program participants were re-assessed on the following outcome measures: (i) *Functional Ability*, using Kurtzke's EDSS and Functional Systems Scale¹¹ (performed by a neurologist specializing in MS), and the MS Functional Composite (MSFC)¹²; (ii) *Fatigue*, assessed by the Modified Fatigue Impact Scale (MFIS)¹³; and (iii) *Quality of Life*, as determined by the MS Quality of Life-54 (MSQoL-54) questionnaire.¹⁴ During the 12-week follow-up period participants continued with activities of daily living, but did not participate in any structured exercise program. The same assessors conducted evaluations throughout the study and at 12-week follow-up. A follow-up treadmill trial was also conducted to determine if participants were capable of exercising at the same intensity (speed and %BWS) as when they completed the 24-week exercise intervention. All participants completed the follow-up assessment.

Following completion of the training program and follow-up testing, participants were given the opportunity to return to the same facilities to continue exercising in a structured community-based accessible exercise program. Long-term participation in the structured community program was assessed 12-15 months following completion of the study.

Participants and exercise leaders were asked to provide information on each individual's activity participation such as frequency per week, minutes per session and modality of exercise. Participants who chose not to continue with the structured exercise program were also asked to provide the same information on their level of physical activity, if any.

5.3.3. Data Analysis

This report only presents results pertaining to the effects of training maintenance; effects of the 24-week intervention are detailed elsewhere (Chapter 3). Data were analyzed with a one-way (time) repeated measures analysis of variance (ANOVA). Tukey's *post-hoc* analyses were used to examine differences between time points. Changes occurring between completion of the 24-week training program and post-exercise follow-up, and changes between baseline and post-exercise follow-up are presented. Statistical analyses were performed using GraphPad PRISM software, version 5.01.^b Statistical significance was set at $P \leq 0.05$. Effect sizes (ES) were also calculated and expressed as Cohen's *d*. ESs of 0.2-0.49 were considered small, 0.5-0.79 were considered moderate and ≥ 0.8 were considered large. Data are presented throughout the text as mean \pm SD.

5.4 RESULTS

5.4.1 Summary of the 24-week treadmill training intervention

Results of the 24 week training intervention are reported in Chapter 3. Following 24 weeks of training, a significant increase in treadmill speed (60%, $P < 0.0001$) and a significant decrease in percent body weight support required to walk on the treadmill (51%, $P < 0.0001$) was observed. EDSS was reduced by 0.5 in two of the six participants. Following training, there was a significant decrease in MFIS total, physical (pMFIS) and cognitive (cMFIS) fatigue subscales ($P \leq 0.05$). Significant improvements were seen in the MSQoL-54 physical health composite, as well as several subscales: energy, cognitive function, and sexual function following training ($P \leq 0.05$). Parametric and non-parametric t-tests were used to evaluate the change from baseline to 24-weeks.

5.4.2 Twelve-week post-exercise follow-up

In comparison to training parameters at completion of the intervention (week 24), a significant decrease in treadmill walking speed was observed at 12-week follow-up ($P \leq 0.05$; Figure 1). At follow-up participants also required more body-weight support to walk on the treadmill, although the increase was not significant. Follow-up results are presented in Table 1. No significant change in EDSS was observed from completion of the training program to 12-week follow-up. Of the two participants who's EDSS was reduced by 0.5 at 24 weeks, one maintained this change at follow-up and the others' score increased by 0.5, returning to baseline. No significant change in MSFC total or any subscore was noted from completion of the intervention to follow-up. MSFC total, timed 25-foot walk (T25FW) and nine-hole peg test (9-HPT) demonstrated a return to baseline values at follow-up which was reflected by ES changes. Paced Auditory Serial Addition Test (PASAT) scores also deteriorated from completion of training to follow-up, although scores remained elevated from baseline with a small ES (ES=0.30, baseline to follow-up). A non-significant increase in fatigue was reported from completion of the training program to 12-week follow-up. A large ES was seen in the pMFIS (ES=1.10) and moderate ESs were seen in MFIS total (ES=0.62) and psMFIS (ES=0.50), all indicating a worsening of fatigue symptoms. There was no change in the cMFIS (ES=0.17). Follow-up testing revealed no significant changes in MSQoL-54 scores from completion of the training program. Several MSQoL-54 subscales demonstrated a return towards baseline levels with moderate to large negative ESs indicating poorer QoL including: physical health composite (ES= -0.62), role limitations-physical (ES= -0.83), energy (ES= -0.89) and change in health (ES= -0.72). Conversely, moderate to large

positive ESs, indicating improved QoL at 12-week follow-up, were noted for physical health (ES= 0.60) and role limitations–emotional (ES=0.86) subscales. *Post-hoc* analyses revealed mental health composite and role limitations–emotional subscales were significantly increased from baseline at 12-week follow-up ($P<0.05$). Non-responder data occurred in 2 of the QoL subscales: sexual function ($n=3$) and sexual satisfaction ($n=4$).

5.4.3 Exercise adherence and post-follow-up activity

All six participants completed the 24-week training program with an average adherence of $94.7 \pm 5.98\%$. Adherence was defined as the percentage of available sessions attended. Following completion of the 12-wk follow-up study, 5 of the 6 participants chose to join the community-based exercise program. Twelve to 15 months following completion of the study, all 5 participants continued to attend the program. Participants completed on average 2.0 exercise sessions/week with a mean total of 166 ± 52 minutes of exercise per week. Participants were involved in a combination of activities including: supported treadmill walking; upper and lower body resistance exercises; and aerobic recumbent stepper training. The 1 participant who chose not to continue exercising with the program did so due to travelling distance required to visit the exercise facility. This individual purchased a home treadmill and at 12-15 months following study completion reported on average 120 minutes per week of total walking activity (treadmill and overground), utilizing the home treadmill 5 days/week.

5.5 DISCUSSION

BWSTT appears to be an effective intervention strategy for improving QoL, fatigue and functional ability in people with progressive MS; however, when training is discontinued,

these effects are not necessarily maintained. Although no significant differences were observed between completion of the intervention and 12-week post-exercise follow-up (apart from the decrease in treadmill walking speed), ES changes suggest a tendency for physical health changes to return towards baseline, while mental health improvements appear to be maintained more long-term. The results of this study emphasize the importance of maintaining physical activity and the need for adapted community-based exercise programs for patients with MS.

5.5.1 Post-Exercise Follow-up: Effects on Functional Ability

Few studies have examined the lasting effects of supervised exercise interventions in patients with MS. At follow-up, the improvement in EDSS by 0.5 observed in two participants after 24-weeks of BWSTT was maintained in one individual while the other person's score returned to baseline. The difference in the change in EDSS between the two participants may be related to their functional level. The one individual who maintained the change in EDSS at follow-up was not wheelchair-dependent and therefore may have had the opportunity to perform more overground walking at home or in their community to practice and maintain the improvement in mobility achieved through the exercise training program. The other participant whose score returned to baseline was wheelchair-dependent throughout the program; however, over the 24-week intervention was able to regain use of their walker at home. The 24-week training program may have not have been sufficient for this individual to achieve enough mobility and walking endurance to continue practicing walking outside of a supervised exercise setting. Other studies have demonstrated deterioration in EDSS scores when rehabilitation interventions

are discontinued. An intervention comparing the effects of BWSTT with robotic assistance to conventional walking therapy determined improvements in EDSS scores following 12 sessions of BWSTT were no longer significant 3 months post exercise.¹⁵ Another investigation followed 27 patients with MS who completed 3 weeks of inpatient physical rehabilitation for 12 weeks post-intervention.¹⁶ While no significant improvement in EDSS occurred during the rehabilitation program, the few participants who had improved their EDSS scores during the intervention experienced a gradual return to baseline over the follow-up period. At 12-weeks post intervention there were no longer any improvements in EDSS scores in any of the participants who completed the rehabilitation program. Changes in EDSS scores with training should be interpreted in light of measurement error associated with the EDSS.¹⁷ Thus, differences in scores with training may be attributed to the poor psychometric properties of the scale, rather than true changes in functional status of the participants.

The change in ESs seen in MSFC scores at follow-up also reflects a return towards baseline in functional ability. Mobility and physical function declines have been noted in other training studies with people with MS when exercise program are discontinued. Significant improvements in the 10-meter timed walk and 2-minute walk observed following 4 weeks of treadmill training in ambulatory patients with MS were found to return to baseline at 4 weeks post-training.¹⁸ Similarly, a 3-week comparison of conventional walking training and robot-assisted gait training also found that improvements in walking velocity, walking distance and knee-extensor strength returned to baseline when assessed 6 months post-intervention.⁸ Interestingly, in the present study

PASAT scores at follow-up remained elevated from baseline with a small ES (0.30), suggesting the effects of exercise on cognitive function may be more long-lasting than physical effects.

5.5.2 Post-Exercise Follow-up: Effects on Fatigue and QoL

Although no significant change in fatigue was noted at 12-week follow-up, the total fatigue score and all fatigue subscales were increased, indicating greater fatigue. Whereas the 24-wk training intervention resulted in a significant improvement in fatigue scores from baseline (Chapter 3) there was no longer any significant difference at follow-up. Following a 3-month combined inpatient and home-based exercise program, McCullagh and colleagues¹⁹ reassessed participants 3-months after completing the intervention. Compared to controls, fatigue levels were significantly lower in the exercise group at the end of the intervention and at follow-up; however, fatigue levels did increase in the exercise group over the follow-up period. The improvement in exercise capacity outcomes seen in exercisers compared to controls following the intervention, however, was not maintained at follow-up. In the present study, a large ES (1.10) for the change from completion of the intervention to follow-up was seen in the pMFIS suggesting discontinuing exercise may have a greater impact on physical fatigue outcomes. Detraining, similar to that seen by McCullagh et al¹⁹, combined with poorer mobility (as indicated by the change in T25FW scores) may contribute to less efficient functioning in daily activities and consequently greater physical fatigue. The observation of no change in the cMFIS (ES=0.17) together with the maintenance in PASAT scores at follow-up,

suggests more long-term effects of exercise on mental, rather than physical health outcomes.

Changes seen in MSQoL-54 outcomes at follow-up also unveiled an interesting pattern. In general, physical health QoL subscales deteriorated while mental health QoL subscales were maintained or even improved. At follow-up, many of the QoL subscales and both composite scores remained improved from baseline, with role limitations–emotional and mental health composite scores being significantly improved from baseline. McCullagh and colleagues¹⁹ also reported at 3-month follow-up overall QoL, assessed by the Functional Assessment of Multiple Sclerosis (FAMS) scale, was still significantly improved in the exercise group compared to controls, although subscale results were not provided. The maintenance and/or improvement in mental health QoL outcomes observed in our study may be related to increased self-efficacy achieved through the exercise program. People with MS who are more physically active have been found to have higher MS self-efficacy, and MS self-efficacy has been found to be associated with greater QoL.²⁰ Although self-efficacy was not assessed in this trial, it is possible that by completing the exercise program participants gained a greater overall sense of control over their MS which may have lasted beyond the duration of the exercise intervention. Not all QoL subscales conformed to the aforementioned pattern and future studies are required to further explore this relationship. Further, while most physical health outcomes deteriorated over the follow-up period, returning towards baseline, the physical health QoL subscale improved (ES=0.60). This result is particularly surprising and may be

related to the nature of the questions in this section of the questionnaire and/or their interpretation by this group of participants.

5.5.3 Program Adherence

In comparison with previous exercise studies in patients with MS where adherence rates have been reported, the present study found extremely high compliance rates.^{21,22} Of the few studies investigating treadmill training in MS, adherence rates have not been reported; however, drop-out rates of 14%-16% have been described.^{8, 18, 23} High exercise adherence and a lack of participant drop-out in this study may be related to the structured nature of our training program (as opposed to home-based interventions), the small number of participants, and more interaction of participants with training personnel throughout the program. A high rate of exercise compliance in patients with PPMS with high disability over a 6 month period is particularly encouraging since this group has many barriers to activity participation, such as transportation and health complications.

5.5.4 Post-follow-up Activity Participation

Five of the 6 participants in the intervention chose to continue exercising with the community-based adapted exercise program. In comparison to the training intervention of 3 sessions/wk, the community program is designed for twice-weekly participation. This slightly reduced commitment facilitates transportation and other arrangements necessary for the participants to attend the program and likely contributed to continued participation. Furthermore, participants increased their total exercise time from 90 min/week during the study to 166 min/week with the community program suggesting patients with progressive MS are capable of accumulating greater amounts of physical

activity. Participants also chose to continue with a multi-modality exercise program combining aerobic and resistance training which likely provided participants with more variety and made the program more enjoyable to attend over the long-term.

These results clearly highlight the need for more community-based exercise opportunities for individuals with MS. While long-term community-based programs for people with severe mobility impairments may not be feasible in all settings, effective alternative exercise strategies, such as home-based interventions also require further development. Further studies are required to determine the most effective type of exercise intervention for patients with MS to maintain the functional and psychosocial benefits of physical activity and foster long-lasting exercise participation.

5.5.5 Study Limitations

This pilot trial provides the first preliminary evidence of the degree to which exercise-induced changes associated with BWSTT are maintained in patients with progressive MS. Several limitations, however, should be acknowledged. The small sample size, lack of controls, and limited outcome measures assessed may limit the generalizability of the results, but the positive message with respect to the enduring psychological benefits of exercise participation and the excellent exercise adherence results certainly point to the importance of incorporating exercise interventions in the MS population as a necessary component of their lifelong rehabilitation.

5.6 CONCLUSIONS

Few studies have examined the lasting effects of exercise in patients with MS. While the effects of BWSTT on physical health appear to diminish when exercise is discontinued,

mental health improvements may be maintained more long-term in patients with progressive MS. This trial highlights the importance of continued exercise involvement and the need for accessible community-based or alternative options for people with MS to participate in physical activity.

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5.8 Suppliers

- a. Woodway USA, Inc, W 229 N 591 Foster Ct, Waukesha, WI 53186.
- b. Version 5.01; GraphPad Software, Inc, 2236 Avenida de la Playa, La Jolla, CA 92037.

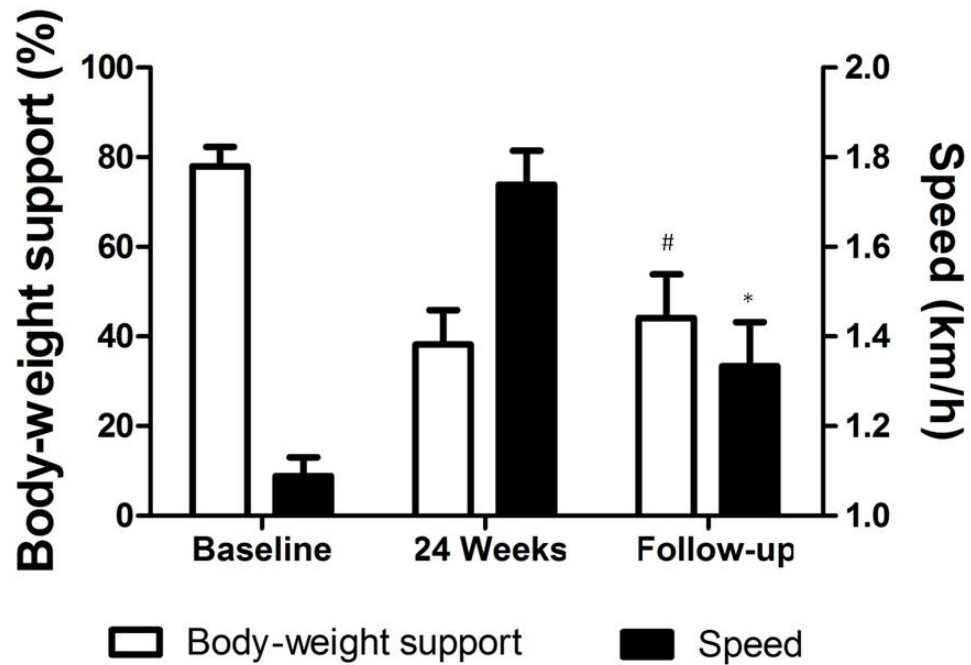


Figure 5.1 Percent body-weight support required and treadmill walking speed (km/h) at baseline, following 24 weeks of body-weight supported treadmill training, and at 12 week follow-up testing. Values are means \pm SE. *Denotes significant difference between 24 weeks and follow-up; [#]denotes significant difference between baseline and follow-up ($P \leq 0.05$).

Table 5.1 Outcome means and effect sizes (ES) at baseline, following 24 weeks of training, and at 12 week follow-up.

Outcome measure	Baseline	24 weeks	Follow-up	ES (Baseline- 24weeks)	ES (24weeks- follow-up)	ES (Baseline- follow-up)
EDSS	6.9 (1.07)	6.8 (1.17)	6.8 (1.21)	-0.16	0.07	-0.08
MSFC	-3.0 (2.80)	-2.1 (2.6)	-2.9 (2.68)	0.32	-0.30	0.03
T25FW	-7.1 (7.28)	-5.2 (6.7)	-7.0 (7.32)	0.27	-0.27	0.005
9-HPT	-1.8 (0.98)	-1.5 (1.07)	-1.8 (0.86)	0.24	-0.33	-0.08
PASAT	-0.1 (0.77)	0.3 (0.82)	0.1 (0.85)	0.53	-0.22	0.30
MFIS	43.5 (12.26)	30.2 (7.33)	36.5 (12.32)	-1.12	0.62	-0.54
pMFIS	24.3 (5.8)	16.0 (2.19)	20.3 (4.27)	-1.40	1.10	-0.74
cMFIS	14.6 (8.92)	10.7 (6.83)	12.0 (9.7)	-0.50	0.17	-0.29
psMFIS	4.7 (2.58)	3.5 (0.84)	4.2 (1.72)	-0.60	0.50	-0.24
MSSoL-54						
physical health	8.8 (11.04)	15.0 (14.4)	28.7 (28.93)	0.50	0.60	0.85
role limitations -physical	18.8 (23.39)	50.0 (47.43)	16.7 (25.82)	0.80	-0.83	-0.09
role limitations -emotional	38.9 (49.07)	66.7 (51.64)	100.0 (0.00)*	0.55	0.86	1.33
pain	67.6 (22.65)	77.5 (22.05)	71.8 (24.18)	0.45	-0.25	0.19
emotional well-being	69 (13.37)	80.7 (13.49)	78.7 (11.5)	0.82	-0.17	0.75
energy	32 (19.64)	56.7 (21.53)	39.3 (13.72)	1.05	-0.89	0.44
health perceptions	41.7 (21.54)	53.3 (28.75)	57.5 (25.64)	0.47	0.16	0.66
social function	56.3 (20.70)	65.3 (26.57)	62.5 (31.07)	0.39	-0.10	0.25
cognitive function	70.4 (28.26)	77.5 (25.45)	75.0 (35.64)	0.27	-0.08	0.15
health distress	45.8 (15.63)	70.0 (13.04)	65.0 (18.44)	1.30	-0.32	1.00
sexual function (n=3)	55.6 (46.84)	63.9 (42.78)	58.3 (46.40)	0.19	-0.14	0.07
sexual satisfaction (n=4)	31.3 (38.86)	31.3 (37.50)	37.5 (47.87)	-0.08	0.16	0.15
change in health	31.3 (10.46)	62.5 (34.46)	41.7 (20.41)	1.07	-0.72	0.64
overall quality of life	65.3 (9.29)	70.3 (22.69)	68.6 (12.17)	0.30	-0.10	0.32
physical health composite	36.1 (8.73)	51.4 (15.18)	44.7 (2.16)	1.07	-0.62	1.13
mental health composite	58.1 (16.22)	73.5 (19.12)	79.5 (5.46)*	0.83	0.44	1.34

NOTE. n=6, unless specified otherwise. Values are means (SD). Abbreviations: EDSS, Expanded Disability Status Scale; MSFC, MS Functional Composite; T25FW, timed twenty-five-foot walk; 9-HPT, nine-hole peg test; PASAT, Paced Auditory Serial Addition Test; MFIS, Modified Fatigue Impact Scale (p=physical, c=cognitive, ps=psychosocial); MSQoL-54, Multiple Sclerosis Quality of Life-54. *Denotes significant difference from baseline to 12-week follow-up ($P \leq 0.05$).

CHAPTER 6

ALTERNATIVE EXERCISE MODALITIES FOR PERSONS WITH PROGRESSIVE MULTIPLE SCLEROSIS

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6.0 ALTERNATIVE EXERCISE MODALITIES FOR PERSONS WITH PROGRESSIVE MULTIPLE SCLEROSIS

6.1 ABSTRACT

Introduction: Body weight supported treadmill training (BWSTT) has been an effective exercise modality for patients with mobility impairments; however, it is difficult to administer outside specialized exercise facilities. Total body recumbent stepper training (TBRST) represents an alternative exercise modality to BWSTT. This study was aimed at determining if TBRST is safe and well-tolerated in patients with progressive multiple sclerosis (MS) of high disability (Expanded Disability Status Scale [EDSS] = 6.0-8.0) and if TBRST is as effective as BWSTT on outcomes of functional ability, fatigue and quality of life (QoL).

Methods: Twelve participants were randomized into two groups: TBRST or BWSTT. Participants completed 3 weekly sessions (30 min) of TBRST or BWSTT (matched for perceived intensity) for 12 weeks. Outcomes included: safety; functional ability (EDSS, MS Functional Composite, 12-item MS Walking Scale); fatigue (Modified Fatigue Impact Scale); self-efficacy (MS Self-Efficacy questionnaire); MS Quality of Life (MSQoL-54 questionnaire); and evaluation of the exercise equipment. Outcomes were evaluated at baseline and following the intervention.

Results: Five participants in each group completed the intervention (TBRST, mean EDSS=7.1 ± 0.89; BWSTT, mean EDSS=7.0 ± 0.35). Safety was confirmed in both groups. TBRST evoked a higher heart rate response than BWSTT, despite similar perceived intensities of effort. Functional outcomes did not change in either intervention. Both interventions reduced fatigue and improved QoL outcomes ($P \leq 0.05$). Patients

reported enjoying both exercise modalities; however, TBRST was reviewed more favourably.

Conclusions: TBRST appears to be a safe exercise modality for patients with progressive MS of high disability level. TBRST and BWSTT were both effective in improving fatigue and QoL outcomes. TBRST should be explored further as an alternative exercise rehabilitation modality for persons with MS.

Keywords: multiple sclerosis, rehabilitation, treadmill walking, mobility, quality of life

6.2 Introduction

Participation in physical activity has been associated with improvements in functional, physiological and psychosocial outcomes in patients with multiple sclerosis (MS) (4). People with MS with severe mobility impairments, however, have limited opportunities to engage in physical activity as most traditional exercise modalities are inaccessible to this group of individuals. An alternative exercise intervention that has been successful for patients with mobility impairments is body weight supported treadmill training (BWSTT). BWSTT allows an individual with reduced mobility to walk on a treadmill with a certain amount of their body weight supported by an overhead pulley system. Studies have found BWSTT to have beneficial effects for patients with stroke and spinal cord injury (14, 20). More recently, supported treadmill walking has been evaluated in patients with MS and has been found to be safe and well-tolerated with preliminary results suggesting improvements in mobility, fatigue, and quality of life (QoL) (1, 11, 18, 29). While BWSTT may be an effective therapeutic strategy for patients with limited mobility, this type of intervention is rarely available in community settings, requires highly trained personnel to operate, and is extremely costly to initiate. Furthermore, improvements gained from BWSTT participation may deteriorate once training is discontinued; therefore, developing feasible long-term training interventions for patients with MS with mobility impairment is extremely important.

An alternative training modality to BWSTT is total body recumbent stepper training (TBRST). TBRST is a recumbent cross trainer which provides patients with mobility impairments the unique opportunity to participate in full-body exercise in a safe and

accessible manner. Using TBRST, patients exercise with both upper and lower extremities through the use of coupled arm levers and foot pedals which move in a bilateral reciprocal fashion.

Despite the great potential of TBRST as an exercise rehabilitation tool, few studies have evaluated the effects of TBRST in healthy or diseased populations. Compared to non-exercising controls, 12 weeks of TBRST proved to be effective in improving aerobic capacity, upper and lower body muscular strength and endurance, and body composition in sedentary healthy adults (13). Walking speed, muscular strength, and blood pressure improved after 13 weeks of TBRST (≥ 9 min/week) in a group of elderly patients in an assisted-living community (16). An improvement in balance and impairment was observed after 8 weeks of TBRST in a preliminary study of patients >1 year post-stroke (28). To the best of our knowledge only one study to date has examined TBRST exclusively in patients with MS, in which the cardio-respiratory response to maximal exercise testing was compared between different exercise modalities (7). Greater maximal oxygen uptake and higher heart rates (HR) were found in response to TBRST and combined arm/leg ergometry compared to treadmill walking or leg cycling alone. No studies to date have examined the long-term effects of TBRST in patients with MS. The development and evaluation of alternative therapeutic strategies for patients with MS with severe mobility impairments has been severely understudied. Preliminary findings suggest beneficial effects of TBRST on cardiovascular, muscular and functional health outcomes; however, results are limited. In attempt to address the limitations of previous research, this trial reports: (i) the safety and tolerability of TBRST in patients with

progressive MS of high disability (Expanded Disability Status Scale [EDSS] 6.0-8.0); (ii) whether TBRST is as effective as BWSTT on outcomes of functional ability, fatigue and QoL; and (iii) patient evaluation and recommendation of TBRST and BWSTT.

6.3 Methods

6.3.1 Participants

This study was approved by the research ethics board of Hamilton Health Sciences.

Participants were recruited through contact with medical staff at the MS Clinic of Hamilton Health Sciences and support staff at the Hamilton Chapter of the MS Society of Canada. All participants provided written informed consent. Inclusion criteria were: clinically definite primary progressive MS (PPMS) as per the diagnostic criteria of Thompson et al (35) OR clinically definite secondary progressive MS (SPMS) as per the diagnostic criteria of McDonald et al (22) for relapsing-remitting MS with slow gradual progression observed over 6 months, not due to deterioration from attacks alone; EDSS 6.0-8.0; age 18-60 years; body weight <90 kg; medical clearance to participate in physical activity; ability to visit study locations, commit to the training program and follow training instructions. Exclusion criteria were: pregnancy or plans to become pregnant during the study period; current use or use within the last 2 months of disease modifying therapies including IFN- β , glatiramer acetate, IV steroids, mitoxantrone, azathioprine, and cylophosphamide; acquired disability that could interfere with the evaluation of disability due to MS; other serious medical conditions that might impair subject's ability to walk on a treadmill and/or participate in aerobic exercise; and previous experience with BWSTT or TBRST.

6.3.2 Randomization

Due to the heterogeneity of the patient population and small sample size, we did not attempt a matched study design, but rather randomized patients who met the study criteria to one of two exercise interventions: TBRST or BWSTT. Randomization was determined by a computer generated group randomization program (GraphPad Software, Inc., La Jolla, CA, USA). Randomization was conducted following baseline assessment.

6.3.3 Exercise Intervention

Each group completed 3 weekly training sessions of BWSTT or TBRST for the duration of 12 weeks. Participants completed a pre-training familiarization session with either BWSTT or TBRST to determine the appropriate training settings. Duration of each training session was gradually increased according to patient ability and comfort level to achieve a maximum of 30 min of exercise.

At each training session participants wore a Polar FS2 HR monitor (Polar Electro Oy, Kempele, Finland) to record resting and exercise HR. To ensure a similar exercise intensity was experienced by both groups, rating of perceived exertion (RPE) was used as an indicator of effort using the Borg CR10 Scale (2). Throughout the training program, patients were instructed to exercise at a perceived exertion of 3-5 which corresponded to a rating of ‘*moderate*’ to ‘*strong*’ on the 10 point scale. Exercise progression in both training groups was based on perceived exertion, comfort, and patient progress.

TBRST

Patients completed the TBRST protocol using the NuStep™ T4 (TRS 4000, NuStep, Inc., Ann Arbor, MI, USA) which is a recumbent cross trainer that allows for upper and lower

body exercise in a seated position. The NuStep™ trainer allows patients to achieve a natural stepping motion against graded loads created by a magnetic resistance system. Arm levers and foot pedals are coupled and move in a bilateral reciprocal manner. Foot straps and leg stabilizers were used for added control and proper leg alignment when necessary. One trainer assisted patients with transferring and equipment set up as required. Workload (resistance), total steps and steps/min were recorded at each training session.

BWSTT

Patients underwent BWSTT using the Woodway Loco-system (Woodway USA, Inc., Wakesha, WI, USA) which consists of a treadmill with an overhead pulley system connected to a supportive harness. BWSTT allows patients with limited mobility to walk upright on a treadmill with a portion of their body weight counter-balanced. A detailed description of the training protocol has been published elsewhere (10, 14). Treadmill training was therapist-assisted with one trainer positioned at either lower limb to promote proper gait mechanics. When necessary, an additional trainer stood behind participants to assist with weight shifting and trunk support. Percent body weight supported, walking velocity (km/hr), and walking distance (km) were recorded at each training session.

6.3.4 Outcome Measures

Safety. Adverse effects including: patient experiences of muscle and joint pain; physical discomfort; excessive fatigue; overheating; chest pain; dizziness/nausea; and any other symptoms during or following training were recorded by a member of the research team.

Functional Ability. Functional ability and neurological impairment was assessed using the EDSS (17), and the Multiple Sclerosis Functional Composite (MSFC) (5). The MSFC assesses lower limb, upper limb, and cognitive function using three scales: the timed-twenty-five foot walk (T25FW), the nine-hole peg test (9HPT) and the Paced Auditory Serial Addition Test (PASAT) respectively. Scores on all three measures were combined to produce a composite Z-score. Pre-baseline administration of the MSFC was conducted to minimize practice effects (34). The impact of MS on walking ability was assessed using the 12-item Multiple Sclerosis Walking Scale (MSWS-12). The MSWS-12 has shown good validity and reliability (15).

Fatigue. Fatigue was assessed using the 21-item Modified Fatigue Impact Scale (MFIS). The MFIS questionnaire assesses overall fatigue (MFIS), as well as physical (pMFIS), cognitive (cMFIS), and psychosocial (psMFIS) fatigue. Reliability and validity of the MFIS has been established (6).

Multiple Sclerosis Self-efficacy. Subjects' ability to manage MS was assessed using the MS Self-Efficacy (MSSE) scale. The MSSE is an 18-item questionnaire which evaluates MS self-efficacy (SE) on two multi-item subscales: function and control. The MSSE scale has shown good consistency and reliability (32).

Quality of Life. QoL was assessed using the MS Quality of Life-54 (MSQoL-54) questionnaire, which is composed of 12 multi-item scales, 2 single-item scales, and 2 composite scores (physical and mental health). The MSQoL-54 has shown good reliability and validity (23).

Participant Evaluation of Exercise Equipment. Participants completed a questionnaire composed of a series of scales evaluating the physical and psychological post-exercise response, enjoyment of equipment, equipment accessibility and safety, perceived benefit to daily functioning, and recommendation and use of the exercise equipment. The questionnaire was based on several established scales including the Feeling Scale (FS) (12), the Exercise Feeling Inventory (8), and the Brief Pain Inventory (3), as well as several additional scales (see Appendices, for complete Participant Evaluation of Exercise Equipment Questionnaire). The Exercise Feeling Inventory was scored on four subscales (revitalization, tranquility, positive engagement, and physical exhaustion) and a mean score for pain was generated. The FS, the Exercise Feeling Inventory and the Brief Pain Inventory have demonstrated good sensitivity and sound psychometric properties (9, 21).

Outcome measures (functional ability, fatigue, SE and QoL) were assessed at baseline and following the 12 week intervention. Participants' evaluation of equipment was assessed during the final week of the intervention, immediately following a training session. Recording of adverse events was ongoing throughout the program. The EDSS was performed by a neurologist. All other outcomes were performed by a member of the research team experienced in administering these measures in patients with MS.

6.3.5 Data Analysis

Participant characteristics were summarized using descriptive statistics. Values are presented in the text as mean \pm SD. Baseline characteristics were compared between groups using independent samples t-tests. Differences between groups in exercise

adherence were determined using independent samples t-tests and Mann Whitney tests. Adverse effects were summarized for each training group. Change in training parameters (i.e., percent body weight support, workload, etc.) over the intervention was analyzed for each training group using a 1-way (time) repeated measures ANOVA. A last observation carried-forward approach was used for analysis of training data where participants did not complete all training sessions. Between group comparisons of outcome measures were analyzed using a 2-way (group x time) repeated measures ANCOVA with age as a covariate. Effect sizes (ES) were used to evaluate the magnitude of change in outcome measure with each exercise intervention. ESs were expressed as Cohen's *d*; ESs of 0.2-0.49 were considered small, 0.5-0.79 were considered moderate, and ≥ 0.8 were considered large. Only moderate-large ESs are discussed in this report. Participant evaluation of exercise equipment data were compared between groups using independent samples t-tests and Mann Whitney tests. ESs were used to compare differences between groups. Statistical significance was set at $P \leq 0.05$.

6.4 Results

6.4.1 Participant Characteristics

Twelve eligible participants were enrolled in this study. Six participants were randomized to the TBRST group (3 men, 3 women; 2 PPMS, 4 SPMS) and six to the BWSTT group (3 men, 3 women; 2 PPMS, 4 SPMS). One participant dropped out of the BWSTT intervention following completion of 17 training sessions. One participant in the TBRST group acquired an injury unrelated to the exercise program following 34 training sessions and was unable to complete the intervention. Five participants in each group completed

follow-up testing. Characteristics of all participants and those completing the intervention are presented in Table 1. Of participants completing the intervention, there were no differences between groups in baseline characteristics with the exception of age. Participants in the TBRST group were significantly older than participants in the BWSTT group ($P=0.002$).

6.4.2 Exercise Intervention

Adherence

Out of a possible 36 training sessions, participants in the TBRST group completed on average 33.2 ± 3.83 sessions with an average adherence of $89.1\% \pm 6.60\%$. Participants in the BWSTT group completed on average 35.6 ± 0.89 out of a possible 36 training sessions, with an average adherence of $89.2\% \pm 10.44\%$. Adherence was defined as the percentage of available sessions attended. There was no significant difference between groups in the number of completed sessions or program adherence. Participants who did not complete all training sessions still completed follow-up testing prior to early termination of the program. Premature study termination in both groups was attributed to personal commitments.

Adverse Effects

Adverse effects in either group occurred rarely and were mild in severity. Adverse effects (physical discomfort, muscle pain, and excessive fatigue) were reported by one of the five participants (on two separate occasions) in the TBRST group. Adverse effects (physical discomfort, minor bruising, joint pain, and excessive fatigue) were reported by four of the five participants (on five separate occasions) in the BWSTT group.

TBRST

Participants significantly increased training workload over the duration of the intervention from level 2.4 ± 1.23 to 4.9 ± 1.44 ($P < 0.0001$; Fig. 1A). There was a non-significant increase in total steps per training session from 1753.1 ± 121.60 to 2043.4 ± 268.52 ($P = 0.13$). Stepping cadence was consistent across the training program and ranged from 62.8 steps/min to 68.2 steps/min (data not shown).

BWSTT

Over the training program participants significantly reduced the amount of body weight support required to walk on the treadmill from $72.2\% \pm 19.56\%$ to $43.1\% \pm 18.13\%$ ($P < 0.0001$; Fig. 1B). Treadmill walking distance increased significantly over the intervention from 0.4 ± 0.21 km to 0.8 ± 0.27 km (< 0.0001). Treadmill walking speed also increased significantly over the 12 weeks from 0.9 ± 0.33 km/hr to 1.6 ± 0.6 km/hr ($P = 0.001$; data not shown).

Exercise Intensity

There was no significant difference in perceived exertion between training groups ($P = 0.63$) or over time ($P = 0.12$; Fig. 2A). Perceived exertion ranged from 3.8 to 4.6 in the TBRST group and from 2.8 to 4.5 in the BWSTT group. Difference in average training HR between the exercise modalities was compared relatively as a percent of age-predicted maximum HR. Average training HR was stable across the training interventions ($P = 0.31$); however, significantly higher training HRs were observed in the TBRST group compared to the BWSTT group ($P = 0.01$; Fig. 2B).

6.4.3 Functional Ability

No significant effect of group, time or the interaction was observed for any functional outcome measures (Table 2). One individual in the TBRST group had a change in EDSS score which increased by 0.5. ESs also reflected a lack of change in EDSS and MSFC scores. A moderate ES (ES= -0.51) was observed for the change in MSWS-12 following TBRST.

6.4.4 Fatigue

There was a significant effect for time on physical (P=0.04) and psychosocial (P=0.01) fatigue subscales; both exercise groups perceived less fatigue following the exercise intervention (Table 2). No significant differences were observed for total or cognitive fatigue scores. In the TBRST group, large and moderate ESs were observed for the change in total (ES= -1.04), physical (ES= -1.05) and cognitive (ES= -0.59) fatigue subscales, respectively. In the BWSTT group, large ESs were noted in total and all fatigue subscales (MFIS, ES= -1.23; pMFIS, ES= -1.58; cMFIS, ES= -0.80; psMFIS, ES= -1.23). While there was a significant reduction in perceived fatigue in both groups, the magnitude of the intervention effect on fatigue reduction was greater in the BWSTT group than in the TBRST.

6.4.5 Self-Efficacy

No significant effect of group, time or the interaction was observed for MSSE function or control (Table 2); however, there was a moderate ES (ES = 0.51) for the mean increase in MSSE control in the BWSTT group.

6.4.6 Quality of Life

Effects of TBRST and BWSTT on QoL outcomes are presented in Table 3. A main effect for time was observed for energy ($P=0.02$), sexual satisfaction ($P=0.01$), and overall QoL ($P=0.02$). A main effect for group was noted for physical health ($P=0.05$). Significant interaction effects were observed for energy ($P=0.03$), and overall QoL ($P=0.04$), indicating there was a larger increase in these scores following TBRST. A significant interaction was also observed for sexual satisfaction ($P=0.05$); sexual satisfaction scores decreased in the BWSTT group, whereas there was no change with TBRST. A trend for an interaction was also observed for physical health scores ($P=0.07$); scores in the TBRST group increased over time, whereas scores in the BWSTT group decreased. In the TBRST group, a large positive ES was observed for energy ($ES=0.95$) and moderate positive ESs were observed for health distress ($ES=0.54$), overall QoL ($ES=0.68$) and the mental health composite scale ($ES=0.51$). Conversely, a moderate negative ES was observed for change in health ($ES= -0.57$). In the BWSTT group, large positive ESs were observed for role limitations – physical ($ES=0.76$), role limitations – emotional ($ES=1.44$), health perceptions ($ES=0.97$), change in health ($ES=0.93$) and the mental health composite ($ES=0.97$). Further, moderate positive ESs were found for social function ($ES=0.58$) and the physical health composite ($ES=0.70$).

6.4.7 Participant Evaluation of Exercise Equipment

No significant differences were found between groups on participant evaluation of exercise equipment (Table 4). Based on ESs, TBRST was more favourably reviewed by participants in comparison to BWSTT. A large ES (0.75) was seen for the difference between groups on the FS: the TBRST group reported feeling better following exercise

than the BWSTT group. Moderate to large ESs were also observed for equipment enjoyment (ES=0.61), accessibility (ES=1.19), safety (ES=0.61), recommendation of equipment purchase by fitness facilities (ES=0.63), and anticipated use of the equipment by participants in a fitness facility (ES=0.75), all in favour of TBRST over BWSTT.

6.5 Discussion

To our knowledge, this is the first trial to evaluate the long-term effects of recumbent stepper training in patients with MS and to compare the effects of TBRST to supported treadmill walking. Findings suggest TBRST is safe and well tolerated by patients with progressive MS with severe mobility impairments, with beneficial effects of exercise on fatigue and QoL outcomes observed in both training groups. Of note, in comparison to BWSTT, patients with progressive MS were able to achieve higher training HRs while engaging in recumbent stepping, despite a similar perception of effort, and evaluated the recumbent stepper more favourably as an exercise modality.

6.5.1 Adherence

Exercise adherence was very good in both training groups (89%) which is likely a reflection of participant enjoyment of both training modalities. While adherence was slightly lower in this intervention than in a previous trial of BWSTT in patients with progressive MS conducted by our research group (98%) (29), program compliance was very good compared with other exercise interventions with patients with MS (27, 30). Missed sessions in both groups were due to poor weather conditions, transportation issues, illnesses, medical appointments, and family commitments. Participants in the

TBRST group completed slightly fewer training sessions overall than did the participants in the BWSTT group. The difference, however, was not significant.

6.5.2 Adverse effects

Overall, both training interventions were well-tolerated with few adverse events reported by either training group. Most adverse events occurred early on in the training program when participants were likely adjusting to the increase in physical activity and the specialized training equipment. On several occasions when adverse events were reported participants were unsure if symptoms were directly related to exercise participation or were due to other health concerns. Adverse events were reported by more participants in the BWSTT group, likely due to the specialized training equipment, particularly the supportive harness, causing minor discomfort and pain.

6.5.3 Response to Exercise

Training parameters in both interventions improved over the duration of the 12 week intervention. There was no difference between groups in perception of exercise intensity; however, the pattern of the change in perceived exertion over 12 weeks was slightly different. Participants in the TBRST group were able to achieve a higher initial RPE which was maintained over the course of the intervention. Participants in the BWSTT group, alternatively, reported a lower initial RPE which increased gradually over the duration of the program. The difference in RPE between training paradigms may have been due to the need to provide a substantial amount of body weight support initially to maintain an upright body position on the treadmill. As body weight support was reduced over the course of the training program, the exercise likely became more challenging.

Familiarization with specialized training equipment may have also taken more time with BWSTT, making it more challenging to reach target exertion levels early on.

A consistently higher average training HR was observed in participants using the recumbent stepper compared with those exercising on the supported treadmill.

Gappmaier and colleagues (7) compared the cardiorespiratory response of 6 women with MS with gait impairment (mean EDSS=4.6) using multiple exercise modalities. Similar to our findings, higher peak HR and peak oxygen consumption were attained with recumbent stepping compared with treadmill exercise. In the present study, recumbent stepping likely provided a greater cardiovascular challenge by engaging a larger muscle mass through the combined use of upper and lower body exercise. A 12-week TBRST intervention was found to significantly improve maximal oxygen consumption assessed by both recumbent stepping and treadmill testing protocols in healthy sedentary adults compared to non-exercising controls (13). Future trials should examine the effect of TBRST and BWSTT on adaptations in cardiorespiratory function to determine if TBRST is superior to BWSTT in patients with MS.

6.5.4 Functional Ability

No change was observed in functional outcome measures in either exercise intervention.

Similarly, a previous study by our research group found no significant change in functional outcomes following 12 weeks of supported treadmill walking in patients with progressive MS of high disability level; however, a small positive ES for the change in the MSFC was noted in the previous trial (29). Previous trials also support the beneficial effects of BWSTT in improving mobility in patients with MS (1, 11, 18). A factor which

may have attributed to the inconsistent result and the lack of improvement in functional outcomes in the current study may have been the slightly lower adherence rate and consequent training inconsistency. The high level of neurological impairment of patients in the current study, compared to previous trials, may have also contributed to a lack of change in functional outcomes.

The most notable change in function was the slight improvement on the MSWS-12 in the TBRST group (moderate ES). The MSWS-12 has been found to be more responsive than other measures of walking ability, such as the EDSS and the T25FW, which may explain the difference observed between functional outcomes (15). Few studies have evaluated the effects of TBRST on functional ability in individuals with mobility impairments. A study of elderly individuals in an assisted-living community found a 15% increase in walking velocity following 13 weeks of recumbent stepper training ≥ 9 minutes per week (16). Improvements in balance and lower extremity motor impairment were also observed following 8 weeks of TBRST in patients >1 year post-stroke (28). We recommend that future trials should examine the effects of longer training interventions and perhaps include additional evaluation tools such as balance and gait kinematics to determine if exercise interventions are effective in improving function in people with progressive MS.

6.5.5 Fatigue

Fatigue is a debilitating symptom which severely affects patients with progressive forms of MS (33). Both exercise interventions proved to be successful in reducing perceived fatigue. Previous studies have also demonstrated improvements in fatigue in patients with MS following participation in exercise interventions in general, and BWSTT specifically

(29, 31, 36). Whereas the effects of TBRST on fatigue have yet to be determined, several studies have found TBRST to improve cardiorespiratory function, as well as muscular strength and endurance in healthy adults and elderly individuals (13, 16). Improvements in physical fitness may reduce the energy costs associated with tasks of daily living resulting in less fatigue in patients with progressive MS.

Perceived fatigue was very high in both exercise groups, which was likely a reflection of the patient population. Higher cognitive and overall fatigue scores were reported by participants in the BWSTT group compared with participants in the TBRST group. The difference in perceived fatigue between training modalities is likely a reflection of the heterogeneity of the patient population and the small sample size of the trial. Although both interventions reduced fatigue, ESs suggests BWSTT may have had a greater effect on fatigue reduction than TBRST.

6.5.6 Self-Efficacy

Recumbent stepper training did not appear to have an effect on SE. A moderate ES for the change in MSSE control over 12 weeks suggests supported treadmill walking improves patients' perceived ability to control MS symptoms better than TBRST.

Patients with MS who report greater physical activity levels have also been found to report higher SE for managing MS (25). Participants in the BWSTT group were able to watch themselves walking upright on the treadmill which may have been a powerful psychological experience as patients were extremely limited in walking or were wheelchair-dependent. The psychological experience of upright walking may have increased participants' self-confidence and fostered a greater sense of control over their

disease. In contrast, patients in the TBRST group remained in a seated position during the activity which may not have impacted SE in the same manner.

6.5.7 Quality of Life

Both exercise interventions were successful in improving some QoL outcomes. Each intervention had a slightly different effect on the various facets of QoL as reflected by changes in QoL subscales. Significant difference between groups was observed for energy, sexual function, and overall QoL scores suggest some superiority of TBRST. However, larger ESs for changes in QoL outcomes were also noted in many QoL subscales in the BWSTT group, suggesting beneficial effects of both training modalities. Results of the current study are in agreement with previous exercise interventions which support the beneficial effects of exercise on QoL in patients with MS (24). BWSTT, in particular, has been associated with significant improvements in QoL outcomes in patients with MS with severe mobility impairment (29, 36). Larger ESs observed in the BWSTT group may also have been mediated by improvements in SE as previously discussed. Motl and colleagues have found physical activity to be related to QoL in patients with MS through an indirect association involving SE (26).

6.5.8 Evaluation of Equipment

There was no significant difference in participant evaluation of the two training modalities. ESs of the differences between groups reflect a generally more favourable review of recumbent stepper training. Similarly, preference for recumbent stepper training over traditional aerobic exercise modalities was also reported by a group of elderly individuals (19). It is likely that participants felt the accessibility and simplicity of

the recumbent stepper, compared with the supported treadmill, made it safer, easier and more enjoyable for them to use.

Limitations

The results of this study are primarily limited by the small sample of participants, the heterogeneity of the sample, and the short duration of the training intervention. However, given the fact that there are so few studies of exercise interventions in people with MS with such high disability levels, the results from this study are extremely promising.

6.6 Conclusions

Findings from this investigation suggest TBRST is a safe exercise alternative to supported treadmill walking for patients with progressive MS with severe disability. Compared with BWSTT, TBRST was found to be a more challenging cardiovascular exercise modality at the same level of perceived intensity. Both exercise interventions were effective in improving fatigue and QoL outcomes. Overall, participants enjoyed using both pieces of equipment; however, participants generally reviewed the experience of TBRST more favourably. This is the first trial to examine the long-term effects of TBRST in patients with MS and further research is warranted to determine its full potential. TBRST represents a viable, cost-effective alternative to BWSTT and, therefore, should be considered as an alternative exercise rehabilitation modality for patients with MS.

Acknowledgements

We gratefully acknowledge the commitment of participants to this training study. We also thank the student volunteers who assisted with the exercise programs.

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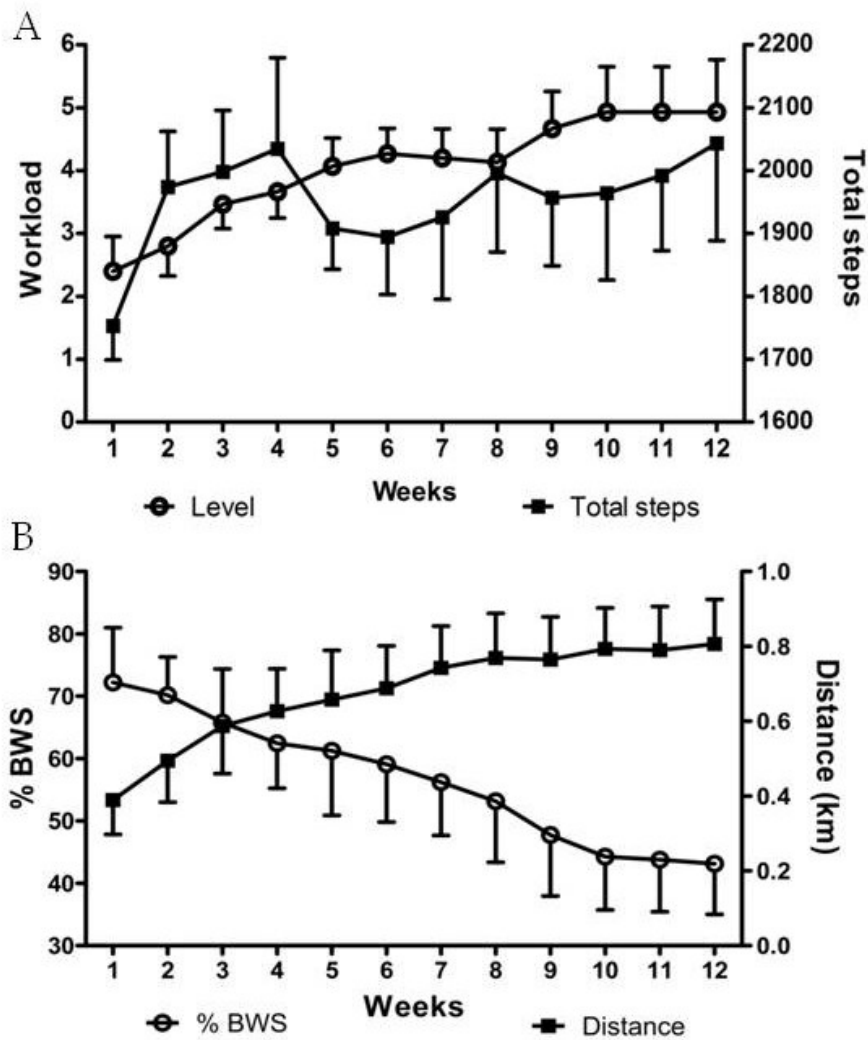


Figure 6.1 Change in training parameters over 12 weeks of A) TBRST; and B) BWSTT. Values are means (SE).

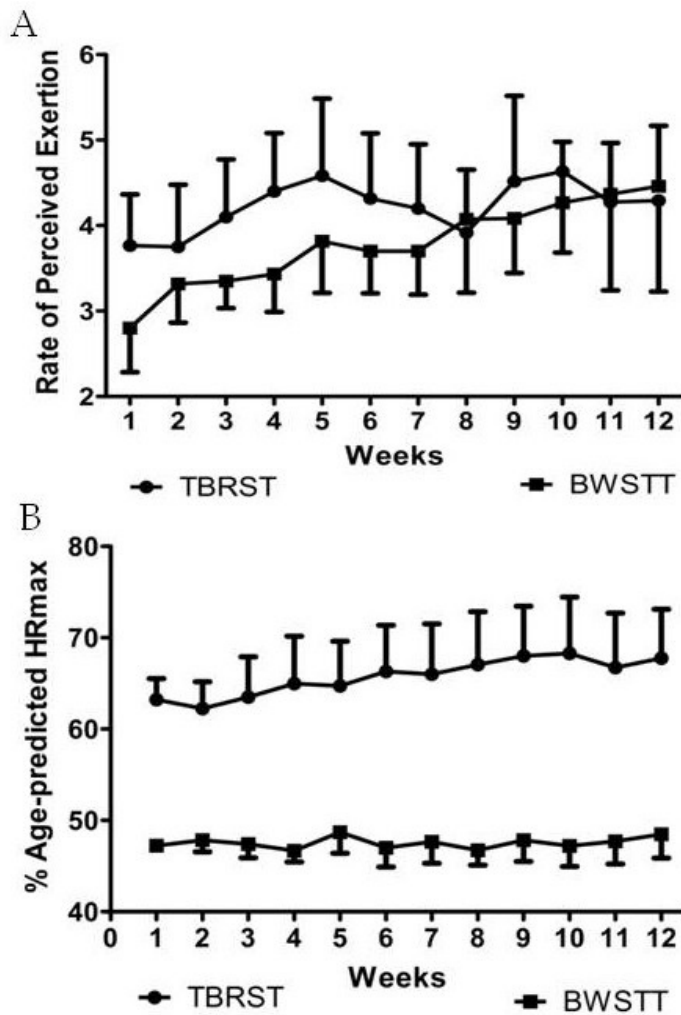


Figure 6.2 Change in A) Rate of perceived exertion; and B) average training heart rate as a percent of age-predicted maximum heart rate over 12 weeks of TBRST and BWSTT. Values are means (SE).

Table 6.1 Participant characteristics.

	All TBRST subjects (n=6)	Subjects completing TBRST (n=5)	All BWSTT subjects (n=6)	Subjects completing BWSTT (n=5)
Age, yrs*	57.2 (4.83)	58.8 (3.03)	49.5 (5.01)	48.2 (4.32)
Disease duration, yrs	17.2 (9.33)	15.2 (8.93)	11.1 (10.93)	12.7 (11.16)
Age at diagnosis, yrs	40 (13.04)	43.6 (10.74)	38.4 (12.34)	35.5 (10.84)
Gender (m/f)	3/3	2/3	3/3	3/2
PPMS/SPMS	2/4	2/3	2/4	2/3
EDSS	7.0 (0.84)	7.1 (0.89)	6.8 (0.82)	7.0 (0.35)

Note: Values are means (SD). TBRST, Total body recumbent stepper training; BWSTT, Body weight supported treadmill training; PPMS, Primary progressive MS; SPMS, Secondary progressive MS; EDSS, Expanded Disability Status Scale.

*Denotes significant differences between subjects completing TBRST and subjects completing BWSTT ($P \leq 0.05$).

Table 6.2 Outcome measures at baseline and after 12 weeks of TBRST and BWSTT.

Outcome	TBRST		BWSTT	
	Baseline	12 weeks	Baseline	12 weeks
EDSS	7.4 (0.75)	7.5 (0.91)	7.0 (0.79)	7.0 (0.79)
MSFC	-2.2 (2.09)	-1.8 (2.20)	-1.0 (2.31)	-0.9 (2.28)
T25FW	-6.9 (7.09)	-6.0 (7.09)	-2.5 (6.28)	-2.5 (6.28)
9HPT	0.02 (0.76)	0.1 (0.82)	-0.03 (1.29)	-0.04 (1.14)
PASAT	0.3 (0.79)	0.4 (0.69)	-0.3 (1.15)	-0.2 (1.02)
MFIS	35.6 (9.21)	25.5 (8.00)	54.2 (9.71)	38.2 (11.18)
pMFIS ^a	22.8 (5.03)	17.0 (4.70)	27.0 (1.66)	18.8 (4.01)
cMFIS	9.2 (6.72)	5.6 (5.42)	22.4 (7.08)	16.3 (7.67)
psMFIS ^a	3.6 (1.47)	2.9 (1.67)	4.8 (1.44)	3.1 (1.47)
MSWS-12	74.0 (6.30)	68.7 (13.81)	74.3 (4.01)	72.5 (5.56)
MSSSE -function	61.3 (19.91)	63.7 (18.33)	62.9 (20.0)	64.8 (17.57)
MSSSE -control	76.1 (14.19)	73.8 (17.89)	67.7 (8.57)	72.9 (12.24)
				ES
				0.00
				0.01
				-0.002
				-0.01
				-0.09
				-1.23
				-1.58
				-0.80
				-1.03
				-0.39
				0.11
				0.51

Note: Values are means (SD). TBRST, Total body recumbent stepper training; BWSTT, Body weight supported treadmill training; ES, effect size; EDSS, Expanded Disability Status Scale; MSFC, Multiple Sclerosis Functional Composite; T25FW, timed 25-foot walk; 9HPT, nine-hole peg test; PASAT, Paced Auditory Serial Addition Test; MSWS-12, 12-item Multiple Sclerosis Walking Scale; MSSSE, Multiple Sclerosis Self-Efficacy scale. ^aDenotes main effect for time (P≤0.05).

Table 6.3 MSQOL-54 outcomes at baseline and after 12 weeks of TBRST and BWSTT.

Outcome	TBRST			BWSTT		
	Baseline	12 weeks	ES	Baseline	12 weeks	ES
Physical health ^b	16.0 (12.20)	18.0 (8.91)	0.20	22.0 (14.19)	18.5 (16.26)	-0.24
Role limitations -physical	32.5 (46.44)	32.5 (33.78)	0.00	27.5 (18.54)	50.0 (36.44)	0.76
Role limitations -emotional	80.0 (44.72)	93.3 (14.91)	0.41	43.3 (30.28)	93.3 (14.91)	1.44
Pain	73.0 (15.14)	78.0 (16.04)	0.33	70.5 (29.63)	77.3 (30.73)	0.24
Emotional well-being	87.6 (4.77)	89.0 (2.83)	0.37	79.6 (15.45)	79.6 (11.35)	0.00
Energy ^{a,c}	48.0 (9.59)	59.2 (11.88)	0.95	42.8 (14.46)	50.0 (20.35)	0.42
Health perceptions	61.0 (18.51)	64.0 (5.76)	0.23	49.0 (14.85)	64.0 (13.30)	0.97
Social function	75.0 (17.43)	75.8 (8.01)	0.07	59.2 (15.70)	68.5 (16.75)	0.58
Cognitive function	88.5 (14.32)	91.0 (10.98)	0.21	64.0 (31.15)	73.5 (11.40)	0.42
Health distress	79.5 (10.22)	84.0 (6.27)	0.54	56.0 (25.65)	61.0 (35.16)	0.17
Sexual function	75.0 (18.15)	70.8 (34.13)	-0.17	70.8 (21.25)	72.5 (26.30)	0.07
Sexual satisfaction ^{a,c}	66.7 (38.19)	66.7 (38.19)	0.00	65.0 (10.46)	62.5 (19.76)	0.00
Change in health	48.0 (17.80)	37.5 (17.68)	-0.57	20.0 (14.25)	47.5 (35.79)	0.93
Overall quality of life ^{a,c}	69.8 (6.93)	75.5 (9.23)	0.68	73.0 (13.39)	76.5 (7.4)	0.34
Physical health composite	52.1 (10.53)	54.8 (5.44)	0.34	47.2 (7.51)	55.3 (14.23)	0.70
Mental health composite	81.6 (13.76)	86.9 (6.03)	0.51	64.1 (15.83)	78.8 (11.51)	0.97

Note: Values are means (SD). TBRST, Total body recumbent stepper training; BWSTT, Body weight supported treadmill training; ES, effect size; MSQOL-54, Multiple Sclerosis Quality of Life-54 Questionnaire. ^aDenotes main effect for time;

^bdenotes main effect for group; ^cdenotes group by time interaction ($P \leq 0.05$).

Table 6.4 Participant evaluation of TBRST and BWSTT.

Outcome	TBRST	BWSTT	P value	ES
Feeling Scale	3.6 (1.14)	1.6 (3.51)	0.26	0.75
Exercise Feeling Inventory				
Revitalization	2.2 (0.69)	2.3 (1.56)	0.87	0.12
Tranquility	3.0 (0.71)	2.7 (1.05)	0.57	0.39
Positive Engagement	3.4 (0.68)	3.1 (0.80)	0.59	0.37
Physical exhaustion	1.5 (0.73)	1.7 (1.63)	0.87	0.11
Pain	2.1 (0.65)	2.1 (1.84)	1.00	<0.001
Enjoyment	6.6 (0.89)	5.8 (1.64)	0.44	0.61
Accessibility	3.2 (2.17)	1.0 (0.00)	0.16	1.19
Safety	6.6 (0.55)	5.8 (1.79)	0.72	0.61
Perceived benefit to improve daily functioning	6.0 (1.22)	5.8 (1.79)	1.00	0.13
Recommendation of purchase by fitness facilities	7.0 (0.00)	6.2 (1.79)	0.23	0.63
Anticipated use of equipment in fitness facility	6.8 (0.45)	5.8 (1.79)	0.44	0.75
Predicted exercise duration without stopping (min)	23.0 (5.70)	23.0 (8.37)	1.00	0.00

Note: Values are means (SD). TBRST, Total body recumbent stepper training; BWSTT, Body weight supported treadmill training; ES, effect size of difference between exercise modalities.

CHAPTER 7
DISCUSSION AND CONCLUSIONS

7.0 DISCUSSION AND CONCLUSIONS

7.1 OVERVIEW OF MAJOR FINDINGS AND CONTRIBUTIONS

The purpose of this dissertation was to evaluate alternative exercise interventions including body weight supported treadmill training (BWSTT) and total body recumbent stepper training (TBRST) for patients with progressive multiple sclerosis (MS), with high disability. This work addresses many limitations of the current literature concerning the effects of exercise for people with MS. One of the novel aspects of this research is the patient population (i.e., progressive MS; high disability, Expanded Disability Status Scale [EDSS] = 5.0-8.0). The evaluation of adapted exercise interventions for people with MS has also received limited attention. This research is the first to evaluate the long-term effects of BWSTT in patients with PPMS and the first to address TBRST in patients with MS in general. Inclusion of markers of disease activity and disease progression are also rarely included in exercise studies with persons with MS. The inclusion of brain imaging parameters as an outcome measure in a prospective exercise intervention in persons with MS further highlights the novelty of this research.

The results of this dissertation add to the current literature by demonstrating the effects of short- and long-term BWSTT and TBRST on outcomes of physical and mental functioning, fatigue, and quality of life (QoL) in persons with progressive MS. Additionally, this dissertation describes the effects of long-term BWSTT on neurotrophic factors and brain imaging parameters, and reports the results of discontinuing long-term BWSTT. An integrated interpretation of the effects of adapted exercise interventions for persons with progressive MS is provided in the preceding section.

7.1.2 Adapted Exercise Interventions for Persons with Progressive MS: An Integrated Model

As a consequence of disease processes and progressive disability accumulation, persons with progressive MS experience deficits in a number of areas including physical function, mental function, fatigue, QoL, and brain health. The studies in this dissertation have included outcome measures which provide an assessment of the effects of adapted exercise within these areas of impairment. Taken together, the results from this dissertation present evidence for the potential of adapted exercise interventions to limit or improve some of the aforementioned deficits in persons with progressive MS. Figure 1 presents a model for summarizing and synthesizing the results of this dissertation which will be further described below.

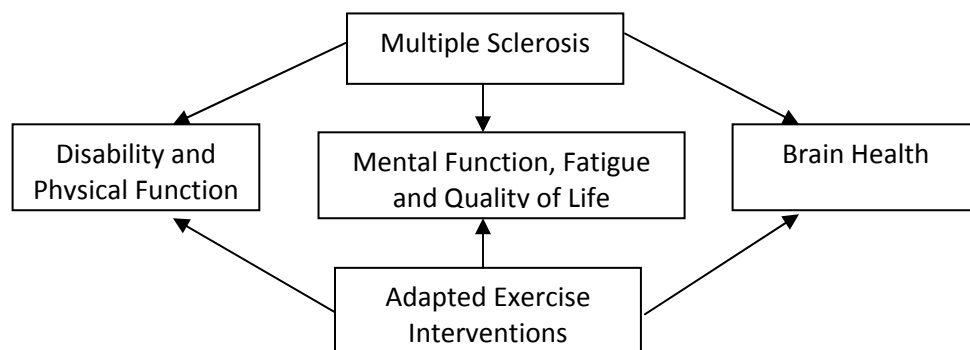


Figure 7.1 Deficits experienced by persons with progressive MS and the potential targets by which adapted exercise interventions may exert beneficial effects.

7.1.2.1 Disability and Physical Function

Disability and physical function in this dissertation were assessed by the EDSS, the Multiple Sclerosis Functional Composite (MSFC), and the Multiple Sclerosis Walking Scale-12 (MSWS-12). Adapted exercise interventions may exert some, although small, beneficial effect on EDSS scores. Following 12 weeks of BWSTT, there was an improvement in 1 of 6 participants in the first intervention; however, there was no effect of BWSTT on EDSS scores in the second comparative intervention. Twenty-four weeks of BWSTT further improved EDSS scores in 2 of 6 participants; however, this improvement was only maintained in 1 participant at 12 week follow-up. Conversely, there was an increase in EDSS score by 0.5 (i.e., worsening disability) in 1 of 5 participants following 12 weeks of TBRST.

Other studies have observed significant improvements in EDSS scores following BWSTT interventions in patients with MS with severe mobility impairment.^{1,2} Gait-specific training involved in BWSTT may be a factor contributing to the ability of BWSTT to improve disability scores, whereas traditional exercise modalities have had less success.³⁻⁷ Baseline EDSS scores in the other two BWSTT interventions were somewhat lower (i.e., less impairment) than those of the patient group in this dissertation, which may explain the difference in responsiveness between studies. Furthermore, our results suggest longer BWSTT interventions may be necessary to result in significant improvements in EDSS scores, particularly in participants with high disability. Importantly, changes in EDSS scores with exercise should be interpreted cautiously in light of the poor psychometric properties of this scale.

Physical function components of the MSFC assessed included the timed 25-foot walk (T25FW) and the 9-hole peg test (9-HPT), which measure lower and upper extremity function, respectively. In the first training intervention, small, non-significant improvements in lower and to a lesser extent upper extremity function were observed following short- and long-term BWSTT, and these improvements were not maintained at follow-up. Although the improvements in lower extremity function were not statistically significant; importantly, they approached clinical significance which may impart meaningful changes for participants. Twelve weeks of BWSTT or TBRST did not, however, improve upper or lower extremity performance in the second intervention. Inconsistent findings between interventions may, in part, be related to the slightly higher level of disability of participants in the second intervention compared to those in the first intervention. Further, less consistent exercise adherence observed in the second intervention may have also contributed to inconsistencies between studies.

The self-reported impact of MS on walking was assessed by the MSWS-12 in the second training intervention. Neither intervention significantly improved MWSW-12 scores; results suggest adapted exercise has a small-to-moderate effect on self-reported walking ability. Taken together, the effects of adapted exercise interventions for persons with progressive MS suggest long-term BWSTT may be beneficial for improving disability and physical functioning, and the improvements are likely not maintained when exercise is discontinued. There is no evidence to suggest TBRST improves disability or physical functioning.

7.1.2.2 Mental Function, Fatigue, and Quality of Life

Mental function, fatigue, and QoL assessment in this dissertation included outcomes of cognitive performance, perceived fatigue, health-related QoL, and self-efficacy. Cognitive performance was assessed by the Paced Auditory Serial Addition Test (PASAT) component of the MSFC, and did not change following 12 weeks of TBRST or BWSTT; however, 24 weeks of BWSTT resulted in improvements in PASAT scores which approached significance ($p = 0.06$). At 12 week follow-up, PASAT scores returned towards baseline levels. Two long-term exercise interventions have evaluated cognitive performance in persons with MS and did not observe significant improvements following training.^{6,8} One intervention was primarily home-based exercise, which resulted in improvements that approached significance ($p = 0.08$) over non-exercising controls; the other intervention had a low training frequency (i.e., 1 session/week). Taken together, long-term exercise, which is supervised and performed several times per week may be necessary for improving cognitive performance in persons with MS.

Fatigue and QoL were assessed in this dissertation using the Modified Fatigue Impact Scale (MFIS) and the Multiple Sclerosis QoL-54 (MSQoL-54), respectively. Adapted exercise had the greatest overall impact on outcomes of fatigue and QoL. BWSTT and TBRST paradigms resulted in significant improvements in fatigue and QoL, both overall and within subscale scores. Unlike improvements in cognition which may require longer training interventions, improved fatigue and QoL may occur with shorter training durations. When long-term BWSTT was discontinued, significant effects of the intervention remained for mental QoL outcomes, but not for physical QoL or fatigue.

BWSTT must be maintained long-term to obtain the full benefits of this exercise modality. Symptoms of fatigue are experienced more frequently and to a greater extent by persons with progressive MS,^{9,10} which was evident from baseline fatigue scores in both investigations. The strong impact of adapted exercise on fatigue reduction in this population is, therefore, of great importance and presents an alternative strategy for fatigue management.

Self-efficacy, assessed by the Multiple Sclerosis Self-Efficacy (MSSE) scale, was included in the comparative training intervention. Interestingly, neither training modality impacted the functional MSSE scale; however, BWSTT had a stronger, although non-significant, impact than TBRST on the MSSE control scale. BWSTT may provide a different training experience than TBRST for persons with mobility impairments as it allows participants to walk upright, an activity in which they would be severely or completely restricted from participation. TBRST did not allow for this same experience as exercise was accomplished from a seated position, and consequently may not have provided participants with the same sense of control and empowerment over their disease.

7.1.3.3 Brain Health

BDNF and brain imaging parameters were included in the first investigation in this dissertation as measures for evaluating the effects of exercise on underlying disease processes. Twenty-four weeks of BWSTT resulted in non-significant increases in serum BDNF levels, significant reductions in iron deposition in deep brain structures, and some significant changes in brain metabolites and diffusion metrics which may suggest less

tissue damage. Together, these results provide some preliminary evidence in a small sample that adapted exercise may impact circulating neurotrophic factor concentrations and brain health. Consequently, adapted exercise interventions may impact underlying disease processes in persons with progressive MS, in addition to exerting beneficial effects on physical and mental function. The diversity of the potential benefits of exercise highlights the uniqueness of exercise as a multi-faceted intervention strategy for persons with MS.

7.2 STUDY LIMITATIONS

Although the studies included in this dissertation address a clear void in current research regarding exercise in persons with MS, there are several limitations of this body of work. One of the primary limitations of this research is the small sample of participants. This work targeted a specific subset of patients with MS: individuals with progressive MS with a high level of disability. Due to the highly specific target group, the population from which the sample was drawn was very limited. The training modalities examined in this investigation also required considerable personnel assistance compared to typical exercise training modalities. BWSTT, in particular, is a highly specialized intervention requiring two to three trainers at all times to carry out. The labour-intensive nature of BWSTT limits the application of this intervention in large samples of participants. TBRST, although less labour-intensive than BWSTT, typically requires the assistance of one trainer. The sample sizes of the studies in this dissertation were similar to comparable interventions in this population. A BWSTT intervention with exclusively progressive MS patients with high disability (EDSS = 7.0-7.5) had a sample size of 4.¹¹

Other BWSTT interventions with persons with MS have included more participants (n = 13-19), although the samples were generally less impaired and included patients with relapsing and progressive disease courses.^{1,2,12} The only study to date to examine the cardiorespiratory response to TBRST in persons with MS similarly included 6 participants,¹³ and a TBRST intervention in patients with stroke had a sample size of seven.¹⁴

Another limitation of the current work is the lack of a non-exercising control condition. Due to the disease course of progressive MS, it would be expected that over time this patient population would acquire further disability or maintain the same level of disability, rather than experiencing disease remission.¹⁵ Inclusion of a control condition would allow us to determine if non-exercising participants experienced any improvements or decrements in the same outcomes over time. This would further allow us to determine if a lack of change in outcome measures in the exercise group could be interpreted as an improvement, as it is possible the control group may worsen over the same period time. For example, a significant decrease in MSCF scores (i.e., worsening disability) was observed in non-exercising MS controls over a 24 week intervention period.⁶

The research in this investigation further included a limited number of outcome assessments, although many were novel for this population. The outcomes included in the current investigations are some of the most commonly used to assess physical and mental function in persons with MS and in most cases are MS-specific. Inclusion of additional outcome measures, such as balance, spasticity, spatiotemporal gait parameters, and

alternative cognitive tasks, such as the symbol digit modalities test, may provide additional information on the potential benefits of BWSTT and TBRST for persons with progressive MS. Furthermore, the use of self-report measures, such as fatigue and quality of life, may also represent a limitation due to the subjective nature of these questionnaires. Lastly, while the aim of this research was to target patients with progressive MS with severe mobility impairment, the specificity of this sample greatly limits the generalizability of the study findings.

7.3 FUTURE DIRECTIONS OF EXERCISE INTERVENTIONS FOR PERSONS WITH MS

The study of exercise in persons with MS is an area of research in its infancy and several important questions remain to be addressed. Findings from the investigations within this dissertation provide promising initial results for the effects of adapted exercise interventions for persons with progressive MS with mobility impairment. It is now prudent to evaluate these interventions in larger samples with appropriate control conditions. As BWSTT is labour-intensive and often limited in availability, executing an RCT with this modality may be challenging. One approach for undertaking a RCT may be using a multi-staged, multi-centre intervention over a longer time period. In regards to TBRST, this was the first investigation to examine the long-term effects of this exercise modality in persons with MS; consequently, many questions remain to be addressed. Long-term, controlled TBRST interventions with patients with MS in general, as well as with those with progressive MS specifically, should be the focus of future research in this area.

Studies of the effects of exercise in persons with MS have only begun to examine the potential impact of physical activity on disease processes with the implementation of outcomes such as blood biomarkers and brain imaging. Further rigorous investigation of the effects of acute and chronic exercise on markers of disease activity will be imperative to determine the disease-modifying potential of exercise interventions. Inclusion of additional blood biomarkers and the development of more sophisticated and sensitive brain imaging techniques will no doubt provide a greater understanding of the effects of exercise interventions. The particularly intriguing finding from this dissertation that exercise reduced iron deposition in deep brain structures following long-term BWSTT should be further investigated from a cross-sectional and prospective perspective. An initial investigation of the association between regional brain iron deposition and fitness levels in a large sample of persons with MS may provide an indication of the strength of this relationship and may further direct prospective research in this area.

It has been challenging to establish and implement appropriate assessment tools to evaluate the many physical and mental symptoms of MS, as well as the impact of exercise on these outcomes. The development of tools to assess neurological disability which are sensitive to changes over time has been particularly challenging, necessitating the development of measures in this area.¹⁶ The inclusion and/or development of alternative outcomes for the assessment patients with MS with severe disability may further be warranted, as traditional measures may not be appropriate, applicable, or valid markers in patients with such severe ambulatory limitations. Evaluation of traditional and alternative outcome assessments for this patient group should be explored.

It has also been observed that comorbidities commonly occur among persons with MS.¹⁷ Future studies should evaluate the effects of exercise for reducing risk of chronic health conditions, and consequently disability in persons with MS, which may represent an important benefit of exercise participation. The impact of comorbid health conditions may be of even greater importance for persons with PPMS due to a later age at disease diagnosis than persons with RRMS.

While it is important to fully understand the effects of exercise in persons with MS from cellular mechanisms to functional abilities, it is also important to examine how exercise is prescribed and delivered to the general MS population. A survey of health-care preferences of a large group of patients with MS revealed that the area where most individuals with MS would like more health advice is concerning exercise.¹⁸ Information about exercise was desired more than advice about medications or other health complications. These findings highlight the need for further research focused on the development of tools that can easily be administered and incorporated in a community-based setting for patients with MS to become and stay physically active.

7.4 OVERALL CONCLUSIONS

This thesis addressed many limitations of current research regarding exercise and MS, from the patient population, to novel exercise outcomes and training modalities. BWSTT and TBRST represent viable and safe adapted exercise solutions for patients with progressive MS which may result in a number of physical and mental health benefits. Both BWSTT and TBRST interventions significantly improved fatigue levels and QoL. BWSTT may be superior to TBRST for improving disability and physical

function, although this requires further long-term evaluation. Long-term BWSTT may also improve cognitive performance and brain health. Conversely, TBRST provided a greater cardiovascular challenge than BWSTT, and was generally rated as a more preferable training modality by participants. Although the effects of discontinuing TBRST were not evaluated, most beneficial effects of BWSTT were not maintained at post-exercise follow-up.

In conclusion, the results of this dissertation provide promising initial support for the impact of adapted exercise for patients with progressive MS. The results are also particularly promising in light of the level of disability of this patient group. Randomized controlled trials will now be the key to confirming these preliminary findings. Further support for the beneficial effects of adapted exercise for this patient population may lead to the implementation of additional services and support for accessible exercise opportunities. Additional evaluation of TBRST may also provide evidence for a cost-effective adapted exercise solution. As limited options for pharmacological intervention are available for patients with progressive MS, adapted exercise should be considered by patients and health care providers as an alternative disease management strategy.

7.5 REFERENCES

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7.6 APPENDICES

7.6.1. Appendix 1: Participant evaluation of exercise equipment questionnaire (Chapter 6).

Participant evaluation of exercise equipment

Equipment name: _____

Equipment type (check all that apply) : Resistance Flexibility
 Aerobic Other: _____

Evaluation of experience

WHAT NUMBER BEST REPRESENTS HOW YOU FEEL RIGHT NOW?

-5	-4	-3	-2	-1	0	+1	+2	+3	+4	+5
very bad		moderately bad		somewhat bad		somewhat good		moderately Good		very good

USING THE SCALE BELOW, INDICATE THE EXTENT TO WHICH EACH WORD DESCRIBES HOW YOU FEEL **RIGHT NOW**. RECORD YOUR RESPONSES ON THE LINE NEXT TO EACH WORD.

0 = do not feel	1 = feel slightly	2 = feel moderately	3 = feel strongly	4 = feel very strongly
-----------------	-------------------	---------------------	-------------------	------------------------

- | | | | | | | | |
|--------------|-------|--------------|-------|-----------------|-------|--------------|-------|
| 1. Calm | _____ | 4. Energetic | _____ | 7. Tired | _____ | 10. Peaceful | _____ |
| 2. Fatigued | _____ | 5. Worn-out | _____ | 8. Happy | _____ | 11. Upbeat | _____ |
| 3. Refreshed | _____ | 6. Relaxed | _____ | 9. Enthusiastic | _____ | 12. Revived | _____ |

During a typical exercise session...

	None at all						A lot
how much shoulder pain do you usually experience	1	2	3	4	5	6	7
how much bodily pain do you usually experience	1	2	3	4	5	6	7
how much physical discomfort do you usually experience	1	2	3	4	5	6	7

When using the _____

	None at all						A lot
How much shoulder pain did you experience	1	2	3	4	5	6	7
How much bodily pain did you experience	1	2	3	4	5	6	7
How much physical discomfort did you experience using the _____	1	2	3	4	5	6	7

	None at all						A lot
How much did you like using the _____	1	2	3	4	5	6	7

Opinions and Recommendations

How confident are you that you can use the _____

	Not at all confident			Completely confident			
without assistance	1	2	3	4	5	6	7
safely without causing injury	1	2	3	4	5	6	7

	Not at all	1	2	3	4	5	6	7	Very much
How useful would this piece of equipment be for improving your fitness to help you perform of your activities of daily living									

	Definitely not	1	2	3	4	5	6	7	Definitely yes
Would you recommend that exercise facilities purchase the _____									

	Never	1	2	3	4	5	6	7	Always
If the exercise facility you attended had this piece of equipment, how often would you use it									

In your opinion, who could safely use the _____ (check all that apply)

Exercise status	Injury Characteristics	Other
<input type="radio"/> New exercisers	<input type="radio"/> ASIA A <input type="radio"/> ASIA B <input type="radio"/> ASIA C <input type="radio"/> ASIA D	
<input type="radio"/> Experienced exercisers	<input type="radio"/> Paraplegia <input type="radio"/> Tetraplegia	
<input type="radio"/> Someone with low fitness levels		
<input type="radio"/> Someone with high fitness levels		

Do you have any other comments about the _____ to share?

Aerobic Equipment

In your opinion, what is the most appropriate use for this piece of equipment (check all that apply):

- Warm-up
- Aerobic training
- Cool down
- No use whatsoever
- Unsure

Assuming that you are very motivated and fit, in one exercise session, for how many minutes could you imagine yourself using the _____ without stopping?

- less than 5 min
- 5 min
- 10 min
- 15 min
- 20 min
- 25 min
- 30 min
- Other: _____