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BILATERAL FATIGUE OF THE ANTERIOR TIBIALIS IN INDIVIDUALS WITH MULTIPLE SCLEROSIS

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BILATERAL FATIGUE OF THE ANTERIOR TIBIALIS IN INDIVIDUALS WITH MULTIPLE SCLEROSIS

A DISSERTATION APPROVED FOR THE
DEPARTMENT OF HEALTH AND EXERCISE SCIENCE

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Abstract

Multiple sclerosis (MS) is one of the most common progressive neurological diseases in young adults and is characterized by neurologic disruption within the central nervous system. Fatigue has been reported as one of the most debilitating symptoms in MS patients. Due to limited ankle mobility in MS patients during walking, investigating potential relationships between dorsiflexion strength asymmetry (SA) and walking ability is necessary to better understand the impact on quality of life in MS patients. PURPOSE: To investigate bilateral differences in strength and fatigability during isometric/isokinetic dorsiflexion in MS patients, and determine the relationship between SA and functional performance. Methods: 13 MS patients (MS Group: 8 females, 5 males) and 13 individuals without MS (NON-MS: 8 females, 5 males) participated in the current study. Maximal isometric and isokinetic contractions were conducted to determine peak torque (PT) and other muscle performance variables (voluntary contraction time (VCT), time-rate of muscle tension development (TRTD), and muscle tension-maintaining capacity (MTMC)). Subjects also performed fatiguing isometric and isokinetic exercise on separate days, and fatigability recovery was measured to investigate the effect of fatigue on PT and the muscle performance variables. Functional performance tests were conducted determine the relationship between isometric/isokinetic SA and walking ability. RESULTS: The MS group exhibited significant limb-limb PT differences during isometric ($p = 0.01$) and all isokinetic contraction speeds ($p < 0.02$) maximal contractions. The MS group also exhibited significantly greater SA than the NON-MS group ($p = 0.03$). There were no significant

limb-limb differences or between group differences during the fatiguing tests. There were significant limb differences in PT before the isometric and isokinetic fatigue tests (p = 0.03, < 0.001 respectively) and after two minutes of recovery (p = 0.04, 0.002 respectively) in the MS group. The MS group exhibited lower performance in the functional performance tests, and there was a strong relationship between isometric/isokinetic SA and walking ability. CONCLUSION: There are no bilateral differences in fatigability in MS patients; however there are bilateral strength differences in dorsiflexion PT in MS patients. Dorsiflexion SA in MS patients is greater than in individuals without MS, and the dorsiflexion SA in MS patients has a strong relationship with walking performance.

Chapter 1. Introduction

Multiple sclerosis (MS) is one of the most common progressive neurological diseases in young adults (11). The cause of this disease is not yet clear, but is characterized by neurological disruptions associated with abnormal immune-mediated response within the central nervous system (CNS) which damage and sometimes destroy myelin, oligodendrocytes, and axons (13). The consequence of damage to the CNS is dysfunctional nerve conduction, which translates into slowed and even blocked nerve single transmission to and from the CNS. The symptoms associated with the disturbance to the CNS can compromise central and peripheral function (67). Additionally, symptoms can vary from person to person and include fatigue, skeletal muscle weakness, bowel and bladder dysfunction, and even mood disturbances. Skeletal muscle weakness and fatigue have been reported by individuals with MS as being some of the most profound and bothersome symptoms (11).

Muscle weakness and fatigue has been shown to directly limit daily function and contributes to general fatigue, which causes lower quality of life (QOL) in most individuals afflicted with the disease (4, 6, 11, 13). Symptomatic (general) fatigue (feeling of tiredness or lassitude) has been reported as the symptom most common and disabling in MS patients (11) which is different than skeletal muscle weakness and fatigue. The two types of fatigue are different in etiology but due to the overlapping consequences it is hard to distinguish them as separate symptoms. Muscle fatigue is best defined as difficulty in initiating or sustaining voluntary activities, which can cause

reduced exercise tolerance (13). It is widely known that people with MS often experience muscle fatigue during exercise as well as activities of daily living (ADL) (3, 6, 59, 82), but the mechanisms responsible are unclear and hard to test due to the overlapping nature of fatigue. Mechanisms of muscle fatigue can be separated into central and peripheral mechanisms. Central fatigue corresponds to the inability to sustain central drive to spinal motor neurons as a result of the myelin, oligodendrocyte, and axon destruction (13, 67). This central impairment leads to decrements in force production, and muscle activation (15, 46, 67, 93). Peripheral fatigue in MS has been associated with the loss of force-generating capacity within the skeletal muscle as a result of muscle weakness and fatigue (59, 67, 82). Peripheral disruption within the skeletal muscle in MS patients leads to a decrease in oxidative capacity, slowing of muscle contractile properties, impaired contraction coupling, and muscle atrophy (15, 36, 47, 66, 94). Collectively, these central and peripheral impairments can cause alterations in balance, gait, and exercise tolerance which may lead to decrements in QOL (3, 6, 11, 63).

Recent evidence has shown bilateral differences in function and performance, i.e. asymmetry, in the legs can be very detrimental to QOL due to the numerous activities that require bilateral function, such as walking and balance (6, 12, 21, 31). It has been observed that MS patients exhibit bilateral differences in oxygen consumption (VO_2), peak workloads, and leg strength whereas individuals without MS display a non-significant difference between legs (15, 46). Research focusing on bilateral differences in lower limbs is scarce in the MS population. Larson et al. (2013)

conducted experimentation on MS patients, and quantified muscular strength of the quadriceps in each leg individually. The researchers found that the difference in strength between the strong and weak leg in MS patients, was significantly larger than that of the healthy individuals, which was also associated with a significantly lower VO_2 peak in the weaker leg of the MS patients (46). These bilateral differences may contribute to the slower walking speed in MS patients (46). A case study conducted by White and Dressendorfer (94) showed that an MS patient experienced significantly weaker quadriceps in the left leg than the right, with a peak strength of 70 and 90 Nm, respectively. This led to a 30% lower VO_2 peak in the weaker left leg (94). However, these initial studies are severely limited in terms of sample size and statistical power. Further statistically robust research on asymmetry in MS patients may allow for more specific rehabilitation and exercise interventions. Although current exercise interventions have shown limited improvement of QOL in MS patients, assessing asymmetry may elicit more substantial effects on ADL and QOL.

Exercise in individuals with MS has been shown to provide many benefits including cardiorespiratory fitness, muscle strength and endurance, reduced systemic fatigue, and enhanced ability to perform ADL (93). More importantly, exercise does not appear to cause increases in the rate of progression or the severity of the disease (63). Resistance training in MS has been shown to improve strength, functional capacity, gait kinematics, and fatigue indices which all lead to a small improvement in QOL (31, 63, 93). However, when functional measures such the 25-foot walking test (25W), three minute step test, and the timed up-and-go test (TUG) are conducted,

there seems to be little if any improvements (20, 21, 63, 93). One aspect to consider is that the exercise interventions have not focused on training and physical performance limitations, specifically bilateral leg differences. Therefore aerobic capacity, strength, and other physical improvements that occur after exercise intervention in MS patients may be more pronounced if limb asymmetry was taken into consideration.

When compared to healthy subjects, MS patients demonstrate reduced speed and stride length during walking (6). Benedetti and colleagues evaluated the walking gait of MS patients by measuring the lower limb kinematic variables, foot-ground reaction forces, and lower limb muscle activity during self-paced walking and compared the results to that of healthy subjects (6). Walking velocity was reduced in MS patients by 35.7 cm/s during self-paced walking, primarily due to reductions in stride length and cadence. Researchers also recognized arrhythmic gait in MS patients, evident by significantly different stance durations between the right leg and left leg (6). This finding might be misleading as not every MS subject's right leg is stronger than left, or vice versa. The kinematics of gait in MS patients was also significantly different from healthy subjects, with varied ankle and knee angles during many of the stages of walking (6). The tibialis anterior muscle plays a pivotal role in motor gait, responsible for ankle dorsiflexion, and is activated in the latter portion of the loading period. It also contributes to ankle stabilization and the transfer of the weight to the lateral border of the foot (6).

Many MS patients experience a phenomenon called "foot drop," or difficulty lifting the front portion of the foot (6). It has been shown that MS patients have altered ankle muscle recruitment and limited ankle motion during walking, although knee motion is relatively normal (64). Gait kinematics has been shown to improve with resistance training in MS patients (31). It has also been demonstrated that fatiguing exercise of the anterior tibialis muscle enhances corticomotor excitability, which causes subsequent strength loss (82). A decrement in strength and control of the anterior tibialis after resistance exercise in individuals with MS may lead to subsequent decrements in walking, balance, and other ADL. Walking ability and endurance may be affected not only by muscular strength, but also by the aerobic capacity of the muscle. Improved knowledge of how the anterior tibialis interacts with fatigue and asymmetry in MS patients may provide clinicians a better understanding of how to treat and alleviate symptoms.

Purpose

The purposes of this study were to investigate whether individuals with multiple sclerosis exhibit: (1) bilateral differences in dorsiflexion strength (both isometric and isokinetic), and fatigue during exercise; and (2) decrement in performance during the functional tests (timed up-and-go test, 6-minute walk test, and 25-foot walk test) compared to individuals without multiple sclerosis.

Research Questions

1. Are there bilateral differences in isometric/isokinetic strength of the dorsiflexors in individuals with multiple sclerosis? Are bilateral differences in isometric/isokinetic strength of the dorsiflexors greater in individuals with multiple sclerosis compared to individuals without multiple sclerosis?
2. Are there bilateral differences in the fatigability of the dorsiflexors in individuals with multiple sclerosis after fatiguing isometric/isokinetic exercise? Are bilateral differences in the fatigability of the dorsiflexors greater in individuals with multiple sclerosis compared to individuals without multiple sclerosis?
3. Are there correlations between isometric/isokinetic dorsiflexion strength asymmetry and walking performance in individuals with multiple sclerosis that would not be correlated in individuals without multiple sclerosis?

Hypotheses

1. Multiple sclerosis patients will exhibit bilateral differences in isometric/isokinetic strength of the dorsiflexors and these differences will be greater than those observed in individuals without multiple sclerosis.
2. Multiple sclerosis patients will exhibit bilateral differences in fatigability of the dorsiflexors and these differences will be greater than those observed in individuals without multiple sclerosis.

3. Multiple sclerosis patients will exhibit correlations between isometric/isokinetic strength asymmetry of the dorsiflexors and walking performance and these correlations will not be present in individuals without multiple sclerosis.

Research Sub-Questions

1. Is there a difference in performance of the three functional performance measures between individuals with multiple sclerosis compared to individuals without multiple sclerosis?

Sub-Hypothesis

1. Multiple sclerosis patients will exhibit decrements in functional performance compared to individuals without multiple sclerosis.

Significance

Fatigue is one of the most reported symptoms related to many neurological diseases, including multiple sclerosis. To date, very few researchers have explored the effects of multiple sclerosis related muscle asymmetry. Thus, comparing bilateral differences and the peripheral muscular responses to fatiguing exercise may help shape current exercise and rehabilitation interventions in multiple sclerosis patients. These findings will have implications for developing interventions that help prevent injuries in multiple sclerosis patients and subsequently improve quality of life.

Delimitations

The delimitations for the following study were:

1. The findings of this study are applicable to healthy individuals and with multiple sclerosis between the ages of 20-65.
2. Multiple sclerosis patients had neurologist confirmed diagnosis of multiple sclerosis, with an extended disability status scale score (EDSS) less than or equal to 6.0
3. The findings of this study are applicable to the anterior tibialis muscle.
4. Multiple sclerosis patients were free from relapse for at least 3 months.
5. Multiple sclerosis patients were not currently using prednisone or other steroids for disease exacerbation within 3 months of the study
6. Individuals without asymmetric orthopedic limitations.
7. Individuals without multiple risk factors for cardiovascular diseases.

Limitations

The limitations for the following study were:

1. The participants were willing volunteers from the Norman and Oklahoma City areas and do not represent a true random sample.
2. Because testing occurred on multiple testing visits and fatigue is variable and unpredictable in multiple sclerosis patients, initial fatigue in multiple sclerosis patients may differ between testing visits.

3. Medications, symptom management, and disease modification may have varied between multiple sclerosis patients.
4. Results will not apply to multiple sclerosis patients that have an EDSS score > 6.0.
5. Individuals without multiple sclerosis were matched with the multiple sclerosis patients in age, gender, and physical activity.

Assumptions

The assumptions of the following study include:

1. Participants gave maximal effort for all muscular fitness testing and functional testing.
2. Participants provided accurate medical information and health history.
3. All participants were honest when filling out fatigue questionnaires.
4. Participants complied with the directions and guidelines provided prior to testing. This includes refraining from exercise, caffeine, and food.

Operational Definitions

1. Bilateral Asymmetry: Differences between the sides of the body (46).
2. Body Composition: The total amount and distribution of fat mass and fat-free mass that makes up a human body (32).
3. Central Drive: Efferent motor neuron outputs to working skeletal muscles (68).

4. Central Fatigue: Any impairment or disruption of the central nervous system that contributes to the overall condition of fatigue in physical activity (13).
5. Dual-Energy X-Ray Absorptiometry (DXA): A full body x-ray device that elicits x-ray beams that absorb different energy levels and allow the measurement of fat mass and fat-free mas in the human body (32).
6. Fatigue: Difficulty in initiating or sustaining voluntary activities. This includes the lack of central nervous system drive to the muscle, central fatigue, and fatigue in the muscle itself, peripheral fatigue (13).
7. Kin-Com Dynamometer: An electromechanical device used to provide resistance during isokinetic and isometric muscular contractions. This device will provide force and torque measurements during the different fatiguing exercise protocols (5).
8. Kurtzke Expanded Disability Status Scale (EDSS): An incremental numerical scale used to assess the disability level of an individual with MS, from 1-10 (44).
9. Matched Control Subjects: Subjects in the control group, which will be matched by average age, gender, and physical activity level to MS subjects (46).
10. Multiple Sclerosis (MS): An inflammatory degenerative autoimmune disease of the central nervous system (42).

11. Peripheral Fatigue: Any impairment in the muscle that leads to fatigue during physical activity (13).
12. Relapsing Remitting: A clinical course of multiple sclerosis characterized by disease relapses and stages of either full recovery or a deficit after recovery with no progression of disease symptoms during the recovery stages (58).
13. Strength Asymmetry: A strength ratio using isometric or isokinetic peak torque where the value for the weaker limb is divided by the stronger limb. Zero percent asymmetry indicates complete symmetry and 100% indicates maximal asymmetry (15).
14. Timed Up and Go Test: This is a functional test of central drive and used to assess lower extremity motor function in the upper motor neuron diseases, such as MS. Individuals will be timed beginning seated in a chair, asked to rise, then walk 3 meters forward, turn around, and walk back to the chair and sit down (57).
15. Quality of Life (QOL): An umbrella term to describe a number of outcomes important within an individual's life (63).
16. 6-Minute Walk Test (6MW): This is a functional test and used to assess cardiopulmonary function and has been used in neurological populations. Participants walk as fast and as far as possible without rest or encouragement for 6 minutes (79).
17. 25-Foot Walk Test (25FW): This is a functional test used to assess an individual's walking ability and leg function based on a timed 25-foot walk.

Gait speed has been shown to be a reliable and useful measure of walking ability (23).

Chapter 2. Review of Literature

The following review of literature is organized into subsections (2.1-2.3). Each subsection will review some key literature in a study-by-study manner with a summary at the end of the review of literature to tie the key articles together before Chapter 3, methods.

2.1 Pathology, Diagnosis, and Progression of Multiple Sclerosis

Multiple sclerosis (MS) is a progressive and degenerative autoimmune disease of the central nervous system (CNS) and is characterized by demyelination, destruction of myelin which covers axons, which disrupts the electrical signals carried to and from the CNS (84). MS is considered an autoimmune disease as T-cells react against proteins in the myelin, predominantly myelin oligodendrocyte glycoprotein which can cause alteration in axons signals and even cause the axon to become transected (49). The destruction of the CNS and disruption of nerve transmissions can lead to sensory and motor disturbances which ultimately can lead to decreased functional capacity and overall quality of life (QOL) in individuals with MS (3, 6, 11).

Symptoms related to MS vary from person to person, and are not always dependent on the progression of the disease. Symptoms can include headaches, respiratory symptoms, bladder dysfunction, difficulty speaking or with sight, vertigo, and pain. The more commonly studied symptoms are those affecting motor function specifically, muscle weakness, and fatigue as they directly impact ADLs and QOL (63).

Additionally these symptoms tend to be the most physically debilitating symptoms of MS (50).

The pathology and progression of MS is still not well understood, which makes this disease difficult to identify and manage on a long term basis. The use of magnetic resonance imaging (MRI) has allowed for a more accurate diagnosis of the disease because clinicians are now able to verify lesions (a consequence of demyelination and disturbance to axons) within the brain and the CNS. The specific progression of the disease is more subjective, but stringent criteria has helped clinicians to more accurately determine the course of the disease and identify the subtype of MS used to help with disease management.

Lublin & Reingold (1996)

These researchers set out to reassess the terminology used to describe the subtypes for MS. A survey was created by the Advisory Committee on Clinical trials of New Agents in MS of the National Multiple Sclerosis Society and was administered to clinicians with a total of 125 completed surveys for analysis. The survey focused on MS symptoms and relapses also known as "attacks" and how they changed over time. An MS related "attack" can be difficult to identify as it relates to changes in disease symptomology. However there are numerous factors that can exacerbate symptoms such as new medications and over-heating are just two examples (29). The difference between a relapse (attack) and an exacerbation of symptoms is a relapse is caused by new damage to the CNS. During a relapse new symptoms might occur as well as

worsening of current symptoms that lasts more than 24 hours without any explanation for a sudden change, i.e. a new medication.

While the definitions for the various subtypes were not made with direct clinical evidence such as lesions observed from magnetic resonance imagery (MRI), these researchers felt confident that through acute and chronic changes and frequency of "attacks" experienced by MS patients would a better way to define its progression. Following analysis of the survey four subtypes are described below:

Relapsing-Remitting (RR) MS is defined as multiple disease relapses with full recovery or with some residual deficits after recovery. During the time between relapses and during subsequent recovery individuals will experience no increase in disease progression.

Primary-Progressive (PP) MS is defined as a continuous progression of the disease, with occasional plateaus that may also provide temporary improvements of the disease. This disease progression is nearly continuous, with no distinct relapses and only minor fluctuations.

Secondary-Progressive (SP) MS is defined as having a similar progression as RR at the onset of the disease followed by progression of the disease with possible relapse, plateaus, and temporary remission. This progression of MS is often seen when an individual has had RR progression for a long period of time. The latter progression of SP MS is more varied.

Progressive-Relapsing (PR) MS is defines as a continuous progression of the disease from onset, with short periods of relapse. This relapse period may or may not include some recovery, and during the periods between relapse individuals experience continuous progression. This type of MS is similar to RR, only instead of no progression of the disease between relapse, PR MS continuously will worsen between relapse.

McDonald et al. (2001)

There is no one test to identify if an individual has MS. Currently, for an individual to be diagnosed with MS they must meet certain clinical and para-clinical evaluations. This study outlined the new recommended diagnostic criteria for MS disease diagnosis. These guidelines were set guided by the International Panel on the Diagnosis of MS during a meeting in 2000. One of the major additions was the inclusion of the ability to detect brain abnormalities using MRI technology which was not previously used to diagnose MS.

The new criteria for disease diagnosis requires an individual's brain MRI must meet three of the four following criteria: one gadolinium-enhancing lesion, one infratentorial lesion, one juxtacortical lesion, and three periventricular lesion, with lesions ordinarily being at least 3 mm long. Lesions are commonly found in the spinal cord in MS patients; however these lesions must only be used as supplementary evidence if a brain scan provides incomplete information.

In addition to brain abnormalities individuals must have experienced some sort of MS related symptomology. The initial onset of symptoms come and go and are commonly called "attacks" (16). An individual needs to have had two or more attacks with clinical evidence of two or more lesions. These guidelines make diagnosis of MS less subjective, and can help to eliminate alternative diagnoses. These criterions are for ages 10-59 years, and anyone younger or older than this age range clinicians must take special care to ensure a proper diagnosis. Many other neurological disorders can mimic MS, especially those with similar symptoms; the use of the clinical tests is a necessity in its diagnosis.

Weinshenker et al. (1989)

Tracking changes in an individual's disease has been a way to try and quantify the progression of MS. The current study evaluated 1,099 patients from the MS Clinic at the University of London, Canada and included a wide variety of patients that were followed on average for 12 years during the course of their disease. Any patient diagnosed with clinical MS was included in the study, as to not bias the severity of the population studied. Researchers observed that MS was most prominent in females (66%) with a mean age of onset to be 30.5 years. In addition 65.8% of individuals were classified as RR at the onset of disease, 14.8% as RP, and 18.7% to have a chronically progressive form of MS. Researchers were able to demonstrate the frequency of conversion from remitting to progressive course of the disease since they followed individuals for multiple years. Most individual's disease changed to the more

progressive form within 1-5 years of diagnosis (32%) more than half of patients entered the progressive form within the first decade of the disease diagnosis (57%). However, some individuals didn't experience any further progressive of MS until after having the disease for more than 26 years (9%). Individuals that had a progressive course of MS from the onset was most common in those who were not diagnosed with MS until later in life with 63% of those aged 40-49 with progressive MS at onset, and 74.5% of those greater than 49 years at onset.

There is a difference between disease onset and diagnosis due to wide variation between when an individual is diagnosed and when the onset (first symptoms) occurs. Despite these limitations with the large number of subjects and wide variety of disease courses and levels of disability, this study appears to provide a better understanding of the distribution of disease course and its progression in the MS population.

Trapp et al. 1998

This study investigated the pathologic changes in the axon of individuals with MS. Previously it was thought that axons were spared of destruction; however neurologic disability had been correlated with atrophy of the spinal cord, cerebellum, and cerebral cortex in individuals with MS. Brain tissue of 11 patients with either acute, primary, or secondary progressive MS, ranging in age from 18 to 62 years, who were either active or chronically active were included in the study. Researchers found

that axon termination was most pronounced in active lesions, while chronically active lesions also exhibited axonal terminated ovoids mainly at the edges of the lesion.

It is believed that in RR stages of MS the axons are able to restore conduction. The appearance of axonal transection in the progressive stage of the disease may be indicative of an axon destruction threshold that MS patients are unable to recover from. Chronic demyelination may also lead to axon termination, as indicated by the terminal axon ovoids in the center of the lesions. Axons away from the lesions also experienced some degree of alteration. Past research has found N-Acetyl aspartate to be reduced in regions of no visible lesions in individuals with MS, which may indicate that, a reduction in N-Acetyl aspartate be a precursor to future lesions.

Kurtzke 1983

Kurtzke Expanded Disability Status Scale (EDSS) (44). The researchers developed the disability status scale to measure maximal function of each MS patient as limited by neurological deficits (43). In the current study, the researchers set out to improve on this scale by including individual ratings of dysfunction among functional groupings. These scores are based on a standard neurological examination of the 7 functional systems (44). The functional systems are each independent of one another and reflect neurologic impairment in MS. These functional systems include pyramidal, cerebellar, brain stem, sensory, bowel & bladder, visual cerebral total and cerebral mentation. Each of the functional systems lie on a scale of 0-5 or 0-6, where 0 is normal function and the latter identifies the most severe effect of this function. The

EDSS score expanded on the initial disability status scale. EDSS is a rating of 0-10, where a score of 0 is normal neurological function and 10 is death due to MS. The rating on the EDSS scale takes into account grading on the individual functional systems. At scores of less than 4.0 indicate an individual with full ambulation. At the level of 4.0, an individual will have functional system grades that may be high, but also now ambulation will also be evaluated. At each score above 4.0 the MS patient will not only have higher score on functional system scales, but also progressively have impaired ambulation. An EDSS score of less than 5.5 is indicative of a patient able to walk without aid for at least 100 meters (44). Scores at or above 6.0 will describe a patient that must use assistance to walk, and will progressively decrease the length of walking prior to resting. This new EDSS scale provides additional information to allow physicians and researchers a better evaluation of the effect the disease has on MS patients. The next section will focus specifically on muscle fatigue and the current evidence on the potential mechanisms contributing to muscle fatigue.

2.2 Muscle Fatigue in Multiple Sclerosis (Central and Peripheral Mechanisms)

The origin of skeletal muscle fatigue may be centrally mediated which seems appropriate in a neuromuscular disease that causes lesions in the myelin and axons of the central nervous system (CNS). In other words the electrical signals sent to and from the CNS could be delayed, slower and or incomplete which suggests the mechanism for muscle fatigue is of central origin as opposed to the muscle (peripheral). Alterations in skeletal muscle characteristics and function in individuals

with MS may play a role in the underlying cause of muscular fatigue. Example of peripheral alterations include but are not limited to, possible impaired oxidative capacity, fiber type composition, reduction in cross bridge number and density resulting in lower force, and impaired calcium release from the sarcoplasmic reticulum (18, 25, 36, 66, 82). The next section is the seminal papers focusing on mechanisms of muscle fatigue related to central and peripheral disturbances. The final section outlines new areas of research to further the understanding of central and peripheral disturbances as it relates to the etiology of MS and how one limb or side of the body might have more or less disturbances which suggests that studies should focus on differences between limbs as it might enhance our understanding of the impact central and peripheral disturbances have on muscle fatigue.

Sharma et al. (1995)

The main purpose of this study was to explore muscle fatigue in individuals with MS. Force activation and energy metabolism of the anterior tibialis was assessed in MS patients and healthy subjects during voluntary force production and an exercise protocol to induce muscle fatigue using electrical stimulation (the leg tested was not specified). 28 individuals with MS (mean age of 44 years) with a mean EDSS of 5.1, ranging from 2-8 and 14 healthy subjects (mean age of 34 years) participated in the study. Prior to the exercise protocol electrical stimulation of the peroneal nerve was used to determine compound muscle action potential (CMAP), twitch tension (TT), tetanic force (TF), and MVC was assessed both voluntarily and via electrical

stimulation. The exercise protocol to induce muscle fatigue consisted of supramaximal tetanic stimulation of the peroneal nerve every three seconds for nine minutes. During exercise, the CAMP, ratio of last of first CMAP of the tetanic train, TF, and rate of rise of TF were assessed every minute. Following exercise (recovery) the same measures assessed during exercise were assessed at 1, 5, 10 and, 15 minutes. Metabolic data was assessed during exercise using magnetic resonance spectroscopy (P-MRS) to measure phosphocreatine (PCr), inorganic phosphate (Pi), and intracellular pH.

Prior to exercise the CMAP amplitude, TT, TF, and MVC (both voluntarily and via electrical stimulation) were significantly reduced in the MS patients compared to healthy subjects. During exercise CMAP amplitude increased in MS patients to 112.6 ± 3.5% of initial and decreased in controls to 98.5 ± 2.5%, p= 0.06. Rate of rise in TF was significantly lower in MS patients compared to healthy subjects before, during exercise, and during recovery. Metabolically once the muscle was fatigued Pi had a significantly greater increase compared to healthy subjects. PCr was significantly lower between groups during exercise, with the MS patients experiencing greater loss of PCr. Similarly, intracellular pH decreased more in MS patients compared to healthy subjects. Following 15 minutes of recovery there were no differences between groups for all metabolic measurements.

The data from this study suggests that muscle fatigue in MS patients might be related more to peripheral changes at the muscular level. Since fatigue was induced

using stimulation of the peripheral nerve the lower potentiation of twitch tension in MS patients and longer half-relaxation time of tetanic force is suggestive of a peripheral impairment, possibly in the excitation-contraction coupling. In addition the observation of impaired energy metabolism exhibited by an exaggerated metabolic response during exercise compared to healthy subjects is suggestive of a metabolic role in muscle fatigue in individuals with MS. The deficits seen in maximal tetanic (39% lower than controls) and voluntary (38% lower) forces suggest peripheral alterations as opposed to central mechanisms which was supported from the groups being similar in the metabolic measures prior to exercise. These finding suggest that individuals with MS could have elevated levels of muscle fatigue from muscle weakness or reduced muscle size.

Ng et al. (1997)

CNS deficits in MS patients can cause a decreased maximal motor unit firing rate and inadequate motor unit recruitment (74). If an individual is unable to adequately recruit enough motor units for a given movement, this may cause an increased central motor drive to carry out the movement which can contribute to muscle weakness and fatigue. The purpose of the current study was to determine if patients with MS exhibit excessive motor drive during voluntary isometric maximal contractions (MVC) and during fatiguing exercise.

Fourteen patients with MS (mean age of 46.1 years) with an average EDSS score of 2.5 and eighteen healthy subjects (mean age of 44.4 years) took part in this

study. Subjects performed MVC's as well as a bout of fatiguing exercise of the dorsiflexors, during which surface EMG of the anterior tibialis was measured. The leg tested was determined by MVC. If unequal strength was observed the weaker leg was tested. Subjects performed graded submaximal contractions to induce fatigue in increments of 10% of MVC, from 10-90% MVC, which was followed immediately by a final MVC. Fatigue was assessed by measuring the difference in force produced from the initial MVC and the final MVC following the fatiguing submaximal contractions.

MVC strength data did not show a significant difference between MS and controls (130.0 ± 14.4 vs. 155.5 ± 13.8 N, respectively). However, EMG data showed significantly higher rates of relative force for submaximal contractions from 10-70% in the MS group compared to healthy subjects. In addition significantly higher EMG/force slopes were observed between groups. This might indicate a greater relative central motor drive in MS patients to achieve the same relative force of healthy subjects. The results of this study suggest that an increased central motor drive is present in MS patients with a mild/moderately impaired disease during submaximal isometric contractions as evidence from both higher level of EMG activity and higher EMG/force relationships.

One of the more interesting mechanisms suggested for explaining the increased central motor drive was the possibility of a "reorganization" of motor drive by alterations in motor unit firing. It was unclear as to the exact mechanism

responsible for the increase in central motor drive but the "reorganization" of motor drive is suggestive of central impairment as opposed to peripheral alterations.

Kent-Braun et al. (1997)

Intramuscular changes associated with MS have been similar to that of chronically sedentary individuals, which has been related to increased levels of muscular fatigue (37). Therefore the purpose of the present study was to assess skeletal muscle characteristics in patients with MS and determine if the changes were similar to those seen in sedentary individuals. Nine patients with MS (mean age of 47 years with a median EDSS of 4 ranging from 2-6) and eight health age-matched subjects (mean age of 42 years) participated in the study. Symptomatic fatigue was assessed using a questionnaire called the fatigue severity scale (FSS). Dorsiflexor muscle strength was measured by MVC. MRI measured the fat-free cross sectional area (CSA) of the anterior compartment. Finally, P-MRS data and muscle biopsies were obtained from the resting tibialis anterior. It was not stated which leg was tested in this study.

MS patients reported significantly more symptomatic fatigue than healthy subjects using the FSS. After MVCs of the dorsiflexors were normalized to fat-free CSA, MS patients exhibited statistically similar strength compared to healthy subjects (104.9 ± 22.0 vs. 173.3 ± 28.0 N, $p > 0.09$, respectively) despite the MS patients being significantly less active than healthy subjects. However, the fat free CSA of the

anterior compartment was 30% lower which was significantly lower in MS patients, which typically indicates atrophy in the dorsiflexor muscles.

Muscle biopsies revealed MS patients had significantly fewer muscle fibers for all fiber types compared to healthy subjects, type I (66 ± 6 vs 76 ± 6%) type IIa (28.2 ± 5.9 vs. 19.2 ± 1.8), and type IIax (6.3 ± 1.7 vs. 4.9 ± 1.4). Succinate dehydrogenase (SDH) an enzyme associated with oxidative capacity was significantly lower in MS patients in all fibers types compared to healthy subjects. No significant differences in glycerol phosphate dehydrogenase (GDPH) were observed suggesting that the groups were similar in glycolytic activity. However, the ratio of SDH/GDPH which assess the overall capacity for oxidative vs glycolytic metabolism were significantly lower for all fiber types in the MS group compared to healthy subjects. In other words fibers in the MS group rely on relatively more anaerobic means during exercise creating the potential for early muscle fatigue.

Overall this data suggests that individuals with MS show characteristics similar to those seen in disuse models and that these alterations could contribute to increased levels of muscle fatigue which affect function and the ability to perform ADL. The authors suggested that the differences in muscle characteristics might be from reduced maximal discharge rates and altered or incomplete motor unit activation, alterations in central motor drive.

Castro et al. (1998)

Earlier studies have shown that MS patients exhibit lower levels of succinic dehydrogenase and SDH/ α-glycerol-phosphate-dehydrogenase than healthy subjects, suggesting impaired aerobic capacity (36). Increased energy demand for a muscle to contract could cause elevated levels of muscle fatigue. An indirect way to assess energy demands of contraction is to measure myofibrillar actomyosin CA^{2+} ATPase (qATPase) activity (22). Seven MS patients and five healthy subjects participated in the current study. Muscle biopsies of the tibialis anterior (leg tested was unspecified) were taken to measure qATPase activity in addition to myofibrillar actomyosin ATPase staining intensity (hATPase) to determine fiber-type specific qATPase activity. Maximal rate of force development during superimposed dorsiflexion exercise was measured as well.

The activity of qATPase in the tibialis anterior exhibited the following hierarchical arrangement, IIax > IIa > I. No significant differences between groups were found for maximal rate of force development and fiber type qATPase activity. There was a positive significant correlation between hATPase staining intensity and qATPase activity for type II muscle fibers ($r = 0.551$; $P < 0.001$) with no significant differences between MS patients and healthy subjects.

This data suggests that muscle contractions in MS patients do not exhibit altered energy demands, and thus muscle fatigue in MS patients is not reflected by increased energy demands. This is in disagreement with past work by the same

researchers, in which it was found that MS patients exhibit reduction in aerobic enzyme activity (36).

Garner & Widrick (2003)

Previous evidence suggested that muscle fatigue in MS could be from peripheral disturbances (36, 67). Therefore the purpose of this study was to investigate cross-bridge mechanisms, isoform content, calcium activated force, and shortening velocity in the vastus lateralis. Six patients with MS who had been diagnosed with MS for ~ 13.5 years with an EDSS score of 4.75 (ranging from 4.0-6.0) and six age-matched healthy subjects. Muscle biopsies were taken from the vastus lateralis of the weaker leg in MS subjects, and the non-dominant leg of healthy subjects. Isometric MVC was assessed to determine muscular strength. Daily physical activity was evaluated by using a pedometer for 14 consecutive days.

The results of the study showed that MS patients exhibited significantly lower knee extensor torque/kg than healthy subjects, approximately 45% lower and were significantly less active than the healthy subjects. The groups had similar fiber type compositions; however MS patients had significantly less type IIa myosin heavy chain isoforms. In the group of MS patients, type I and type IIa fibers produced less peak calcium activated force than in the healthy subjects, and this is attributed to smaller CSA of both fiber types, and a decline in tension of type I fibers. As inorganic phosphate and pH increased, MS patients experienced a reduction in calcium activated force.

Peak calcium activated force is a function of the actomyosin cross bridge and the average force per cross bridge shortening velocity. The reduction of calcium activated force suggests a reduction in cross bridge number, density, and average force as indicated by atrophy of both fiber types and decline in tension of type I fibers. This data suggests impaired cross bridge mechanisms during contractions in MS patients, and impaired mechanisms differ depending on fiber type. The authors were not able to tease out if the changes observed were due to inactivity or from central mechanisms such as alterations in motor unit excitability.

NG et al. (2004)

This study investigated peripheral and central impairments in MS patients and how they were related to functional capacity. Eighteen MS patients with a median EDSS score of 3.2, as well as eighteen age-matched healthy subjects. Exercise testing consisted of MVC and electrically stimulated maximal contractions of dorsiflexion in the right leg, with EMG measurements made to determine compound muscle action potential (CAMP) as a test of peripheral muscle function. Muscle twitch and tetanic force were measured and electrically evoked muscle force-frequency to determine muscle contractile properties which are also measurements of peripheral muscle function. Central motor function was measured by having subjects perform a toe-tap test, measuring the central activation ratio, and rapid voluntary force development at 40% MVC. Cross sectional area (CSA) of the tibialis anterior was measured using MRI, which allowed calculating specific strength calculated as MVC/muscle CSA.

Symptomatic fatigue was evaluated by use of the fatigue severity scale and a visual analog fatigue scale.

MS patients were able to perform significantly less toe taps than healthy subjects, approximately 50% less. The maximal rate of force development was significantly slower in MS patients, and MS patients had significantly lower central activation ratios. These tests indicate central motor dysfunction as a mechanism for muscle fatigue. The MS group was significantly weaker despite having similar CSA of the tibialis anterior. Electrically stimulated CAMP and twitch force were similar between groups, although the MS group demonstrated slower force relaxation. The force-frequency relationship was significantly shifted to the left, showing higher percent of maximal force for a given stimulation frequency. These data indicate that weakness during the MVC in MS patients may be of central origin because there was no decreased force during stimulated contractions. Central impairment was not related to symptomatic measures of fatigue. Therefore the peripheral adaptations may be secondary to changes in central motor drive and disuse in MS patients.

Andreasen et al. (2009)

Exercise-induced loss of voluntary muscle strength is associated with muscle fatigue, and arises due to peripheral alterations at the muscle or due to a lack of central motor drive (87). Compared to individuals without MS it has been shown that individuals with MS may have to increase levels of central muscle activation given similar levels of effort (% MVC) (87). Therefore the current study investigated the

relationship between symptomatic fatigue using the Fatigue Severity Scale and central muscle activation in patients with MS. The study included 60 MS patients that were divided into three groups; 19 of those with primary fatigue (mean age of 43 years), 20 with secondary fatigue (mean age of 39 years), and 21 with non-fatigue (mean age of 39 years). The groups were defined using the fatigue severity scale; the non-fatigue group included those individuals with a score lower than 4.0, and those scoring greater than 4.0 were divided into primary fatigue if no other fatigue-related complications were present and secondary fatigue if other fatigue-related complications were present. All patients had an EDSS score of less than 3.5 indicative of little physical disabilities that may mimic the symptoms of fatigue; mean EDSS score for primary fatigue was 2.5, mean score for secondary fatigue was 2.0, and mean score for non-fatigue was 2.0. Walking ability was measured using a six-minute walk test. MVC was performed on the quadriceps of the right leg only, followed by twitch-interpolated supramaximal stimulation to determine central activation. Fatiguing exercise consisted of eight MVC's held for 4 seconds each, with 2 seconds of rest between contractions, followed by a 15 second MVC with twitch interpolation superimposed at the end of the last MVC. The non-fatigue group also was able to walk a significantly longer distance than the two fatigue groups. Baseline MVC was similar between all groups. Patients with secondary and primary fatigue had significantly lower central activation ratios, than the non-fatigue group. Central activation was decreased during the fatiguing exercise test in all groups, with no difference between groups.

The primary finding of this study was that MS patients with higher levels of symptomatic fatigue using the FSS had greater impairment in the ability to activate their muscles. This might suggest that an underlying cause of fatigue in patients with MS is impaired cortical motor activation, which may lead to difficulty with motoneuron drive and an inability to produce maximal force. However it is still unclear as to whether adaptations in both central and peripheral control in MS patients may be an underlying cause of muscular fatigue and weakness, and limited exercise capacity.

Malagoni et al. (2014)

Many patients with chronic diseases have been shown to have impaired resting muscle oxygen consumption ($rmVO_2$) in the legs. $rmVO_2$ is a measurement which describes the muscle's ability to extract oxygen from blood (61). MS patients have been shown to have lower aerobic capacity than in healthy subjects, and it is has been suggested to be due to inability to extract oxygen. The current study set out to evaluate differences in $rmVO_2$ of the gastrocnemius muscle between individuals with MS compared to healthy subjects. Twenty-eight MS patients (mean age of 42.7 years) participated in the current study, all of whom had an EDSS score less than 6.0. Twenty-two healthy age-matched subjects (mean age of 36 years) were also tested. $rmVO_2$ of the gastrocnemius as measured using NIRS, which provided measurements of oxy and de-oxyhemoglobin concentrations of the gastrocnemius muscle in both legs. Researchers inflated a cuff around the thigh to induce venous occlusion, and the cuff was released after 30 seconds. $rmVO_2$ was then calculated by averaging the rate

of increase following occlusion from both legs, when appropriate. Functional mobility was also assessed by having subjects perform a six-minute walk test.

$rmVO_2$ was significantly higher in MS patients than in healthy subjects ($p = 0.003$). The MS patients were separated into low walking ability and high walking ability groups based on six-minute walk performance using 450 meters as criteria to separate groups. It is not clear as to how the cut-off point of 450 meters was determined. The MS patients with low walking ability had significantly higher $rmVO_2$ than the high walking ability group of MS patients and healthy subjects. The higher $rmVO_2$ in the group who walked less than 450 meters might suggest a compensatory mechanism of the periphery to sustain mobility.

2.3 Muscle Function and Fatigue Asymmetry

MS patients experience symptoms of muscle weakness and paresis that typically affects the body asymmetrically (45-47, 94). Due to the heterogeneity of the disease, MS patients may exhibit varied severity of symptoms between limbs. An individual may experience greater fatigue, loss of strength, or motor control due to the disease (45-47). Currently, there is little research that has focused on its potential effect on muscle fatigue and function. Asymmetry has even been observed in an MS patient who exhibited high levels of aerobic fitness (94). Despite the knowledge that MS can asymmetrically affect muscles very few studies have assessed limb to limb differences in MS patients compared to healthy individuals. There will be two subsections to 2.3. The first section tests both limbs as either right to left or non-

dominant to dominant. Again the comparison might be a bit misleading as MS can affect the dominant limb in some individuals and non-dominant in a different individual. The second subsection compares the more affected, weaker limb to the less affected stronger limb.

2.3A Asymmetry *(right to left; non-dominant to dominant)*

Lambert et al. (2001)

MS patient's exhibit reduced muscle strength compared to healthy individuals at both low and high speeds of dynamic contractions (5). It is well known that MS patients often experience symptomatic fatigue, but less is known of the interaction of muscle strength and fatigue during dynamic exercise. Fifteen MS patients (mean age of 38.8 years) with an average EDSS score of 3.5 and fifteen matched healthy individuals (mean age of 33.1 years) participated in the current study. Whole body plethysmography was used to determine body density which was utilized to determine percent body fat and fat free mass in all subjects. Strength was tested on both lower limbs performing maximal isokinetic leg extensions and flexions at five different speeds (30^{o}, 60^{o}, 90^{o}, 120^{o} and 180^{o}/sec). Muscle fatigue was assessed by performing 30 concentric knee extension and flexion contractions at 180^{o}/sec of the dominant leg. A fatigue index was calculated as the work performed during the latter 15 contractions divided by the work performed during the first 15 contractions.

No significant differences were observed when comparing peak force between dominant and non-dominant legs in both groups. When peak torque was adjusted for

age and body mass individuals with MS were significantly weaker compared to controls for non-dominant extension (16.9%), dominant flexion (25.7%), and non-dominant extension (20.8%) for all speeds tested. When measures of strength were adjusted for fat free mass and age individuals with MS were significantly weaker compared to controls across speeds for the non-dominant extensors (12.8%), the dominant flexors (20.2%), and the non-dominant flexors (21.3%). Finally muscle fatigue using the fatigue index was significantly different between groups for the knee flexors of the dominant leg (9.8% lower in MS). The average work output during the 30-contractions was significantly lower in the MS group at 34.5% ($p = 0.0003$) for knee flexion. Whereas knee extension was not significantly different at 13.3% lower in the MS group ($p = 0.085$). When measures of strength were adjusted for age, body mass and fat free mass, individuals with MS were significantly weaker than matched healthy subjects. This suggests that muscle weakness and fatigue in MS patients is not described by less muscle mass, but rather force/muscle mass (muscle quality). Despite testing both limbs this study did not observe differences between limbs in either group.

Chung et al. (2008)

Muscle weakness and fatigue may play a role in postural control as well, and any imbalance in lower limbs may have a larger effect on postural control and balance in MS patients. Therefore the aim of this study was to measure strength and limb-loading asymmetries in MS patients, along with postural control and symptomatic

fatigue. The study consisted of twelve women with MS (mean age of 55 years) with and average EDSS score of 4 (ranging from 2-6) and twelve age-matched healthy subjects (mean age of 53 years). Symptomatic fatigue was assessed using the fatigue severity scale (FSS) and the visual analog fatigue scale. Peripheral sensory was assessed by placing a tuning fork on each foot and measuring the time of perception. Toe-taps were measured as an index of central motor drive (87). A 25-foot walk test was also used as an index of functional performance. Strength of the dorsiflexor and quadriceps was assessed in both legs by performing an isometric MVC. Strength asymmetry was assessed by performing three isotonic contractions at 45% peak isometric torque. Postural stability was also assessed with force plates, while subjects stood quietly for 20 seconds.

The right leg of MS patients performed significantly less toe-taps than the healthy subjects, and both legs exhibited significantly longer perceived vibration than the healthy subjects. Walk times were also significantly longer in MS patients than in the controls. Power asymmetry in the quadriceps was greater in MS patients than in healthy subjects, but not in the dorsiflexors. Knee extensor power was significantly correlated to fatigue and walk times in MS patients. This data suggests that strength asymmetry in MS patients is related to fatigue, slowed gait, and postural instability. It is not known what the cause of each variable is, but may be that all variables interact with one another to cause the eventual physical dysfunction and lower quality of life in MS patients. In addition the researchers compared right leg to left leg. It is not clear

as to which leg was weaker since the right limb could have been more affected than the left and vice versa.

Thickbroom et al. (2006)

This study investigated the corticomotor response and perceived effort of repeated contractions of the first dorsal interosseous (a muscle intrinsic to hand movement) in patients with MS compared to healthy subjects. In other words this study investigated the differences in fatigability, subjective ratings of fatigability, and central changes in MS patients compared to healthy subjects.

Twenty three patients with MS (age ranging from 25-51) whose EDSS scores were less than 3.5 and 14 healthy subjects (age ranging from 22-58) participated in the study. The subjects performed 7 second voluntary isometric contractions of the first dorsal interosseous at 40% of MVC, with 3 seconds of rest in between contractions for 20 minutes in both the dominant and non-dominant hand. Rating of perceived exertion (RPE) was recorded during the third contraction of each minute using the Borg's scale. Voluntary muscle activity was recorded using EMG surface electrodes. Transcranial magnetic stimulation (TMS) was used during the last contraction of each minute to elicit motor evoked potential (MEP) responses of the first dorsal interosseous at 30% above threshold level.

MVC was similar between hands for both groups at baseline. However when comparing healthy subjects and MS patients the MVC force was ~13% lower for both hands at baseline which was statistically significant. During exercise similar levels of

force decrements were observed (75.8 ± 5.1% vs. 71.5 ± 3.0% of baseline, respectively). Ten minutes following exercise both groups showed strength improvements however the MS patients showed significantly lower levels of recovery from baseline compared to healthy subjects (84.0 ± 2.3% vs. 92.6 ± 3.5%, respectively). During the first 5 minutes of exercise the groups exhibited similar RPE ratings; however the MS group reported higher RPE ratings during the remainder of the exercise task, including significantly higher levels during the final 5 minutes of exercise. The MEP response to TMS was significantly lower in MS patients, and MEP amplitude increased proportionally more in the MS group than healthy subjects during exercise. This data suggests that patients with MS exhibit enhanced central motor drive and perception of effort during submaximal exercise. The increased RPE occurred in patients with MS, although fatigability as measured by the decrement in MVC force was not different during the exercise protocol. Because both groups increased MEP amplitude during exercise, this suggests that a similar central response to fatigue is occurring in both groups, but more excessive in MS patients. This may be occurring due to the demyelination that affects MS patients, resulting in more cortical activity to exert similar amount of force. The increase in cortical activity and central drive appears to cause higher levels of perceived exertion in MS patients. However it is unclear as to the consistency of their findings as they compared right to left and non-dominant to dominant not more affected (weaker) to less affected (stronger) .

2.3B Asymmetry *(more affected (weaker) to less affected (stronger))*

White & Dressendorfer (2005)

This was a case study of a 38 year old woman with relapsing remitting MS that was extremely active, jogging and cycling two days/week each. This patient complained of left leg weakness during intense exercise, and her lower-limbs appeared to have asymmetric muscle mass but were not assessed in this study. A graded exercise on a treadmill and on a cycle ergometer was conducted to determine maximal oxygen uptake (VO_{2max}), and blood samples were drawn to analyze lactate concentration. Single-leg cycling was also performed to determine inter-limb differences. Maximal isokinetic testing of the quadriceps at 60^{o}/sec was performed to assess maximal muscle strength. Treadmill running was also videotaped to analyze gait abnormalities.

The individual exhibited very good aerobic capacity when whole body measurements were taken, but showed considerable differences between legs. The left leg, which was the leg the subject had identified as the leg experiencing weakness during exercise, had much lower values for many physiological measurements during the single-leg cycling tests. When the left and right legs were compared VO_{2peak} was 0.77 L (30%) less in the left leg, resulting in less peak workload (150 watts in left leg vs. 170 watts in right leg). Maximal ventilation, heart rate, and blood lactate values were all lower in the left leg as well. During the treadmill test, gait and stride velocity was normal until the individual reached later stages of the protocol. Maximal isokinetic

voluntary contraction of the left quadriceps produced 22% less torque than the right quadriceps which confirmed the participant's complaint of weakness in the left leg during exercise.

The limited strength in the left leg may have caused the right leg to adapt to working more during aerobic activities. The right leg performed 85% of whole body VO_{2max}, while the left leg only performed 60%. This suggests that the right leg may have compensated to a weaker left leg by increasing oxygen extraction during exercise. However this was a case study it provides evidence of the potential impact asymmetry could have on function and performance.

Larson & White (2011)

Reduced mobility has been shown to be associated with increased risk of osteoporosis in elderly individuals (52). Low bone density may increase bone fracture risk in patients with MS (91). Commonly bone mineral density is assessed by measuring one proximal femoral hip, however MS patients exhibit asymmetrical symptoms associate with the disease. For this reason, researchers in this study assessed bone mineral density in MS patients by measuring both limbs. Researchers measured 23 MS patients, 21 of which were females. All MS patients were diagnosed with relapsing-remitting MS and had a mean EDSS score of 3.34. Patients self-identified which leg was more affected by the disease prior to the study.

Bone density was measured at the femoral neck of both legs using dual-energy x-ray absorptiometry (DXA). There was no significant difference between the right and

left femoral necks, however when researchers evaluated bone mineral density based on the self-reported symptoms in each leg, the more affected leg had significantly lower femoral neck bone mineral density. The difference in bone density between legs in MS patients may be associated with atypical bone remodeling due to muscle weakness and atrophy of the musculature on the weakened leg. This data provide evidence that both legs/hips should be measured in MS patients to allow for more accurate detection of bone mineral density. More accurate detection of bone loss in MS patient will provide clinicians better knowledge how to accurately prescribe rehabilitation to individuals.

Larson et al. (2013)

The current study set out to quantify and investigate asymmetry in lower-limb performance and metabolism in MS patients during cycling exercise. Eight MS patients (mean age of 51.6 years) and seven healthy subjects (mean age of 49.4 years) participated in the study, and all MS patients had an EDSS score of less than 6.5 indicating low levels of disability with a mean score of 2.6. Muscle strength in each limb was assessed in the quadriceps using isometric MVC. Each participant performed continuous ramp exercise on a cycle ergometer to determine VO_{2peak}. Participants performed single-leg cycling in each leg to VO_{2peak} of each leg. Functional performance was assessed by using a six-minute walk test. A DXA scan was performed in both groups to assess lean mass and fat mass in the lower-limbs, which were not different between legs or groups. MVC, peak workload, and VO_{2peak} were statistically different

between legs in MS patients, and no difference in the healthy subjects. The distance covered by MS patients was significantly less than the healthy subjects in the six-minute walk test. Researchers also observed a significant correlation between groups in the six-minute walk test and leg differences in peak workload. There was a much larger bilateral difference in MS patients when the lower-limb performance was measured during single-leg cycling then MVC. The peak workload difference between legs in MS patients was 28%, and the difference between legs during MVC was 18.2%. The weaker leg in MS patients may be limiting aerobic exercise tolerance and performance, as indicated by the significant correlation between six-minute walk distance and peak workload difference between legs.

Rudroff et al. (2014)

Impaired walking ability is common in MS patients, and often resistance training is prescribed help improve muscle strength and endurance (17, 20, 21, 31, 93). EMG has often been used to analyze muscle activity during motor tasks; however some patients with MS have impaired central activation (67). The current study set out to analyze glucose uptake and strength of MS patients during a walking test, and measure any asymmetries present. The researchers tested 4 women with MS and a mean EDSS score of 3.0, and 4 healthy female subjects. MVC was measured for the knee extensors and flexors and the dorsiflexors of each leg. Each participant would then have a 22 gauge i.v. catheter placed into the antecubital vein of the right arm to deliver a tracer of [^{18}F]-FDG. Strength testing was followed by 15 minutes of treadmill walking at a comfortable walking speed. Two minutes into the walking test the

subjects were infused with the tracer. After the walking test, individuals were placed in the PET/CT scanner to measure [^{18}F]-FDG uptake in leg muscles. The subjects were placed in 20 to 21 bed positions, and the PET-CT scanned the whole body of each subject for 1.5 minutes per bed position. Regions of interest (ROI) of the legs were measured to analyze the muscle tissue within each leg. This included four large ROI of the knee extensor, knee flexor, hip flexor, and plantar flexor muscle groups, as well as 16 smaller ROIs to measure individual muscle groups.

Significant differences between leg differences in strength was observed in the MS group for only the knee flexors (51 N difference), however a similar absolute strength difference was seen in the knee extensors of the MS patients as well (46 N difference). Plasma glucose levels prior to infusion of [^{18}F]-FDG were similar between MS and healthy subjects. Glucose uptake of the knee flexor and hip flexor were significantly greater for MS patients. Glucose uptake of the MS group exhibited asymmetrical differences of the knee and hip flexors. Specifically, the semitendinosus muscle of the stronger leg had higher glucose uptake in MS patients than the weaker leg. Although the sample size was small, this study provides insight into how skeletal muscle metabolism in MS patients may affect walking ability due to leg asymmetry of glucose uptake. Overall the asymmetry in [^{18}F]-FDG and strength in the MS group suggests an increased metabolic cost during activities such as walking which may play a pivotal role in premature fatigue during activities of daily living.

Larson et al. (2014)

This study examined unilateral lower-limb cycling exercise to measure performance asymmetry between legs. Eight MS patients (mean age of 51.1 years) and seven age and sex matched healthy subjects (mean age of 49.4) participated in the current study. A DXA was performed to quantify lean and fat mass in each of the lower-limbs. Isometric MVC of the quadriceps muscle was performed to test strength in each leg. Graded exercise was performed on a cycle ergometer to measure VO_{2peak}, and single-leg cycling was performed using 20% of whole body VO_{2peak} for each leg to test exercise tolerance. The mean EDSS score for the MS patients was 2.6, indicating low levels of disability. There was no significant difference between groups during whole body VO_{2peak}, peak workload, or peak lactate. MS patients did exhibit a significantly lower peak heart rate during whole body exercise compared to healthy subjects. Although VO_{2peak} and peak workload were not significantly different between groups, they both had large effect sizes, -0.98 and -0.97, respectively. There was no significant difference in MVC strength between legs or between groups. During submaximal single-leg cycling the MS patients performed significantly more work with the stronger leg, while the healthy subjects experienced no difference between legs. The between leg difference for work performed was significantly greater in MS patients than in healthy subjects. The differences in work performed by each leg in MS patients may be due to the decrement in central motor drive, affecting the body asymmetrically. Because many activities of daily living require coordination of both lower limbs, such as walking, bilateral asymmetries may cause MS patients to favor

one side more than the other resulting in further development of bilateral asymmetries. The weaker leg in MS patients may limit aerobic capacity and cause premature muscle failure.

Summary

The above literature discusses the impact MS has on physiologic function, and subsequent impairments that limit QOL. Many of the physiologic alterations that occur relate to fatigue in MS patients, which may affect the patient's ability to walk and perform ADL (3, 6, 11, 63). Although it is known that MS patients exhibit asymmetry in symptoms related to the disease, little research has been done on this topic. A better understanding of the asymmetrical alterations that occur in MS patients may provide better rehabilitation and care that is more specific to each individual. Currently much of the emphasis has been on testing and improving strength of quadriceps and hamstrings in MS patients, however researchers have found little impact on walking ability after quadriceps and hamstring resistance training (20, 21, 63, 93). This may be due to gait abnormalities occurring in other muscles of the leg musculature, specifically the anterior tibialis. Many MS patients exhibit a foot drop phenomenon during motor gait which may lead to slowed walking speed and impaired walking capacity (57). Identifying the relationship between walking capacity and strength/endurance of the anterior tibialis of MS patients may provide a better understanding of how to optimally treat and rehab these patients.

Chapter 3: Methodology

Introduction

This chapter presents the methodology for the current study. This includes a description of the participants, their inclusion and exclusion criteria, the design of the study, data collection procedures, instrumentation to be used, and how the data was analyzed.

Participants

Thirty volunteers, both male and female between the ages of 20-65 were recruited to participate in the current study. Thirteen of these individuals were diagnosed with MS (MS Group); while the other seventeen were individuals without MS (NON-MS Group) matched for gender, age, and physical activity. Subjects were age matched $\pm$ 4 years, and physical activity was assessed using information from the health status questionnaire. Due to an inability to match with an MS patient, four of the subjects in the NON-MS group were not included in the data analyses of the current study. Each subject was provided details of the study design prior to participation and informed consent approved by the University of Oklahoma Institutional Review Board (IRB #: 6802) was obtained from each subject. They also were all notified that we first needed physician's clearance for safe participation and each subject filled out a health status questionnaire, medical history questionnaire, Kurtzke questionnaire, and a questionnaire to determine physical activity readiness (PAR-Q). Individuals with MS were recruited through the Oklahoma Medical Research

Foundation's MS Excellence Center and through local support groups. Individuals without MS were recruited from the Norman and Oklahoma City metro area via word of mouth, flyers, and email.

Inclusion Criteria

Eligibility for the current study was based upon the following requirements. Participants were required to be:

1. Individuals within the 20-65 age range.
2. Non-smokers or individuals who had quit smoking within last 6 months.
3. Individuals with MS with a physician's diagnosis of MS and free from relapse for the previous three months. An individual was considered to have relapsed if they experienced a period of worsening symptoms lasting more than 24 hours and had been prescribed steroids.
4. Individuals with physician's clearance. This was obtained for all exercise tests included in the current study by both individuals with MS and individuals without MS.
5. Individuals with MS with an Expanded Disability Status Scale (EDSS) score of $\leq$ 6.0. This score is considered minimal to moderate disability, and the individual is still able to walk 100 meters without rest.
6. Individuals who had no past history of lower limb orthopedic asymmetries (hip replacement, knee surgery, etc.) or other significant lower limb bilateral asymmetries.

7. MS patients not currently using prednisone or other steroids to manage symptoms.

Exclusion Criteria

Individuals with the following characteristics were excluded from participating in the current study:

1. Men and women outside the age range 20-65 years.
2. Smokers.
3. Any individual with past orthopedic injuries that would create an asymmetry in their lower limbs.
4. Any individual with metabolic, cardiovascular, or respiratory diseases that may provide undue variability in the data.
5. Any individual with MS that has had a relapse in the previous 3 months.
6. Any individual with MS that has an EDSS score > 6.0.
7. Any MS patient that was currently using prednisone or other steroids for symptom management.

Experimental Design

This study utilized a cross-sectional design. Subjects came to the laboratory for five visits, a screening/familiarization visit followed by four testing visits. All testing visits were separated by at least 48 hours. Visit 1 consisted of the subjects filling out and signing the informed consent and HIPPA forms, as well as filling out the health

status questionnaire, medical history questionnaire, Kurtzke questionnaire, and physical activity readiness questionnaire (PAR-Q). Subjects also filled out a symptomatic fatigue assessment and the Modified Fatigue Impact Scale (MFIS). The subjects underwent a DXA scan to assess whole body composition and lower-leg composition, and participated in familiarization with the Kin-Com dynamometer. For each limb, subjects underwent a maximal voluntary isometric contraction (MVC) of the anterior tibialis muscle on visit 2, as well as maximal voluntary isokinetic contractions (MVIC) during ankle dorsiflexion/plantarflexion at four speeds: 30^{o}/sec, 60^{o}/sec, 90^{o}/sec, and 120^{o}/sec. Very few studies have incorporated isokinetic testing of the dorsiflexors in MS patients, and thus the velocities chosen were based on those that have commonly been used in testing of healthy subjects, older adults, and stroke patients (30, 39). The order of which leg was tested and the contraction speeds tested was randomized for visit 2. In visit 3 and 4, subjects performed isometric and isokinetic fatiguing exercise, respectively. During the isometric fatigue test in visit 3, subjects were asked to maintain the target force level of 30% of MVC until force dropped below 90% (i.e. 27% MVC) for 2 seconds or more than 2 instances (66). During the isokinetic tests in visit 4, subjects were asked to maintain a target force level of 30% of MVIC at 60^{o}/sec until force drops below 90% (i.e. 27% MVC) (30, 66). Visit 5 consisted of the subjects performing all three functional tests, and each test was performed twice after familiarization. The three functional tests included 6-minute walk test (6MW), 25-foot walk test (25W), and a timed up and go test (TUG). Every day during the duration of the testing, subjects were given Rochester Fatigue

Diary (RFD) to assess daily fatigue. These fatigue diaries were filled out by the subjects even on the days they did not visit the testing laboratory.

Control Variables

Testing of each subject was performed at the same time of day throughout the course of the study. Subjects were asked to abstain from caffeine, exercise, and alcohol for 12 hours prior to each testing visit and be 2-3 hours post-prandial prior to testing. Hydration status was determined prior to all exercise testing using a refractometer (VEE GEE Refractometer CLX-1, Kirkland, WA); values of 1.004-1.029 USG were required to conduct testing (34). If an individual could not reach these values within 30 minutes of entering the lab, researchers rescheduled the testing visit. The subjects were also given Rochester Fatigue Diary (RFD) for each day during the duration of the study. The RFD was provided to each subject for every day, even days no testing was conducted. The RFD is a measure of lassitude that the subjects determined for each hour of the day. If a participant exhibited higher levels of fatigue during the days prior to testing than normal, the subject was asked to reschedule the testing visit, as to not provide any unwanted variability. The Modified Fatigue Severity Scale (MFIS) was also utilized to monitor fatigue on the day of testing. MFIS is a 21-item questionnaire, measuring physical, social, and cognitive symptomatic fatigue, which uses summated rating Likert scale to access the impact of fatigue on everyday life (80). We focused our attention for this study on the physical subscale of the MFIS.

If a subjects' score deviated more than 2.5 standard deviations from their mean they were rescheduled for testing on a different day.

Table 1. Protocol Outline.

	Protocol	Time
Visit 1	1. Informed Consent 2. Questionnaires 3. Symptomatic Fatigue Assessment 4. DXA Scan 5. MVC and MVIC Familiarization	Approximate Time: 90 minutes
Visit 2	1. MVC Test 2. MVIC at 30°/sec 3. MVIC at 60°/sec 4. MVIC at 90°/sec 5. MVIC at 120°/sec (speeds randomized) 6. Repeat 1-5 for Opposite Leg (randomized)	Approximate Time: 120 minutes
Visit 3	1. Perform MVC 2. Perform Isometric Fatiguing Exercise at 30% MVC 3. Perform MVC 4. Repeat Steps 1-3 on Opposite Leg (randomized)	Approximate Time: 90 minutes
Visit 4	1. Perform MVIC 60°/sec 2. Perform 60°/sec Isokinetic Fatiguing Exercise at 30% MVIC 3. Perform MVIC 60°/sec 4. Repeat Steps 1-3 on Opposite Leg (randomized)	Approximate Time: 90 minutes
Visit 5	1. Perform Timed 25-Foot Walk Test 2. Perform 6-Minute Walk Test 3. Perform Timed Up-And-Go Test	Approximate Time: 90 minutes

Visit 1: Screening Visit

Prior to enrollment, physician's clearance was required of all subjects. On the initial visit to the laboratory (Screening Visit), subjects were screened to ensure that all inclusion and exclusion criterion was met. Subjects were given ample time to read and ask questions regarding both the consent and HIPPA forms approved by the Institutional Review Board of the University of Oklahoma. Upon signing the consent form, subjects then completed the following questionnaires: a health status questionnaire, a physical readiness questionnaire (PAR-Q), symptomatic fatigue assessment called the modified fatigue impact scale (MFIS), and Kurtzke self-administered expanded disability status scale. Following the completion of these forms, standing height and weight were assessed, followed by a Dual Energy X-Ray Absorptiometry scan to assess body/lower-leg composition. Familiarization of the isometric and isokinetic dorsiflexion movements was performed for both legs on the initial visit as well.

Questionnaires

The health status questionnaire and a PAR-Q provided the researchers the necessary information about any past health complications that indicate that the subject might be at increased risk by participating in the current study. The health status questionnaire form also included any medications the subject was taking, as well as summary information on the frequency, duration, intensity and types of exercise each participant had performed in the previous 6 months. The Kurtzke self-

administered expanded disability status scale (EDSS) allowed the MS patients to assess disease severity related to eight neurologic categories and walking function.

Modified Fatigue Impact Scale (MFIS)

MFIS is a 21-item questionnaire, measuring physical, social, and cognitive symptomatic fatigue, which uses a Likert scale to access the impact of fatigue on everyday life (60). This questionnaire has the subjects describe their own fatigue by answering a variety of questions on a scale of 0-4; 0 being never experiencing this fatigue symptom or 4 being almost always experiencing this fatigue symptom. The questionnaire is scored on a subscale of physical, cognitive, and psychosocial fatigue based on specific questions, as well as a total score. This questionnaire was administered on every testing visit and if the physical subscale of the MFIS was 2.5 standard deviations higher than the previous scores the subjects were asked to reschedule the testing visit to a later date when fatigue levels normalize (46-47).

Rochester Fatigue Diary (RFD)

The RFD is a measure of lassitude in MS patients. The RFD consists of 24 vertical bars for each subject to rate the severity of fatigue on a visual analog scale at each hour of the day (80). The location of the hourly mark is translated to 0 (maximal fatigue) to 100 (no fatigue) and then averaged for a daily fatigue score (80). Sleep is given a score of zero. The advantage of RFD is that it allows the subject to assess their own lassitude and is less subjective to recall bias of other fatigue questionnaires (80). The RFD was given to subjects to take home for every day during the duration of the

testing and was measured each testing session. The variation of fatigue was monitored similar to the MFIS, any drastic change in scores for more than 48 hours along with changes in MFIS would require the subject to reschedule the testing visit to a later date when the fatigue levels normalize (46-47).

Standing Height

Height was measured to the nearest 0.5 cm using a stadiometer (Seca Model 242, Chino, CA). The subjects were asked to remove their shoes and place their heels together and stand up tall with their head aligned in the sagittal plane.

Body Mass and Body Mass Index

Body mass was measured to the nearest 0.1 km using a digital electronic scale (Tanita Model WB-627A, Tokyo, Japan) with subjects wearing light/minimal clothing and no shoes. The body mass index (BMI) was calculated as the body mass in kilograms divided by the standing height in meters squared (kg/m^2).

Body Composition

Total body and lower-leg composition was measured using a whole body Lunar DXA dual-energy x-ray absorptiometry (DXA) scanner (with software version 13.60.033, GE-Lunar Prodigy Advanced, Madison, WI) for the following variables; tissue (% fat), fat mass (kg), lean mass (kg). The purpose of this test was to compare whole body composition and composition of the lower-legs. Daily calibration was performed using a manufacturer produced phantom of a known density providing scan

accuracy. Pre-scan calibration quality assurance indicated a low correlation of variance (< 0.2%). Subjects were asked to wear clothing without any metal pieces (ex. zippers, buttons) and all attenuating materials and shoes were removed before testing. Subjects were positioned in the center of the DXA table in the supine position using standardized positioning; the arms close to the sides of the body and with legs secured by Velcro straps. Subjects too wide for the scanning bed had each side of the body tested separately and composition of both sides of the body were added together to estimate body composition. Assessment of the lower-legs was used to determine any significant differences in lean mass of the legs between and within groups which can alter the interpretation of the strength data (46-47). From the full body scans, separate regions of interest were made for the lower-legs, using the tibiofemoral joint of the knee and the subtalar joint of the ankle as landmarks. The region of interest for each lower-leg was quality checked by two separate researchers to ensure accuracy. Subjects had their hydration tested prior to the DXA scan. If a female subject was premenopausal, a urinary pregnancy test (SA Scientific Ltd 087525, Northalke, IL) was conducted during the first testing visit prior to the DXA scan as well.

Isometric and Isokinetic Familiarization

After the DXA scan on visit 1, the subject was then fitted and familiarized to the dynamometer that was used for isometric and isokinetic dorsiflexion testing in the study. All testing was performed using a KinCom dynamometer (KinCom model: KC125AP, Isokinetic International, East Ridge, TN 37412). The KinCom utilizes a load

cell and tachometer that will measure the direction and amount of force being applied to the apparatus by the subject. This includes measuring the rotational speed of the lever arm. Subjects were seated in the dynamometer and appropriate adjustments were made to ensure comfort and proper fit. All settings were recorded and remained the same for all remaining testing and training sessions. All subjects were secured in place using the safety straps around the testing leg. Each subject was positioned in the supine position on the Kin-Com bench with the knee in 10^{o} flexion (maintained by placing a rolled towel under the knee). This angle was chosen because 10^{o} of flexion is approximately the maximal knee extension angle during walking (95-96). The foot was then placed in the ankle apparatus and positioned so that the midway point between the lateral and medial malleolus was aligned with the axis of rotation on the Kin-Com. The length of the foot from the fifth metatarsal bone to the lower extremity of the external malleolus was measured to define the lever arm length for all subjects. The foot angle was set to 120^{o} plantar flexion (66). The subjects were then asked to perform submaximal voluntary dorsiflexion contractions both isometrically and isokinetically until they felt comfortable with the device. The subjects were fitted and familiarized for both legs during this visit.

Visit 2: Strength Testing

The maximal voluntary isometric contraction (MVC) and maximal voluntary isokinetic contraction (MVIC) testing were conducted during visit 2. All testing was performed using a KinCom dynamometer (KinCom model: KC125AP, Isokinetic

International, East Ridge, TN 37412). Subjects began by performing an MVC, in which subjects were given three warm up contractions, asking subjects to produce self-perceived 25%, 50%, and 75% contraction of full exertion, with 60 seconds of rest in between. Upon completion of the warm up, subjects performed three MVC's. Subjects were instructed to push against the load cell as hard and as fast as they could for five seconds and be given 120 seconds between attempts (66). Verbal instructions and encouragement was given to subjects by the researchers during the contractions. Upon completion of MVC's with the initial leg tested, subjects were given 5 minutes of rest before performing the MVIC testing with the same leg at four different speeds; 30^{o}/sec, 60^{o}/sec, 90^{o}/sec, and 120^{o}/sec. The order of the speeds performed was randomized for each subject. Subjects performed three warm up sets, followed by three maximal repetitions for three sets at each speed with 120 seconds of rest between each set. Subjects were asked to perform the MVIC as quickly and as forcefully as possible and verbal instructions and encouragement was given to subjects throughout testing. The subjects were then removed from the dynamometer, and researchers set up the dynamometer for testing on the opposite leg. After 15 minutes of rest, the subject was set up into the dynamometer the same as previously described, and followed the same testing procedure for MVC and MVIC of the opposite leg. The order of legs tested was randomized for each subject.

Visit 3-4: Fatigue Testing

After the strength testing visit, subjects returned to the laboratory for visit 3 and 4 for additional testing following the same instructions as during Visit 1. All testing sessions took place at the same time of day, and were separated by at least 48 hours. RFD from the previous days between visits and MFIS of the training day were analyzed prior to the start of testing for each visit.

Fatigue Testing

On visits 3-4, subjects performed fatiguing exercise protocols on the Kin-Com dynamometer of isometric and isokinetic exercise, respectively. The fatiguing exercise bouts were performed on the anterior tibialis, and subjects were positioned similarly to how they were for the MVC and MVIC testing on visit 2, using the same recorded marks and seat adjustments. Prior to the isometric fatiguing exercise of visit 3, subjects were given three warm ups at 25%, 50%, and 75% of perceived full exertion, with 60 seconds of rest in between. Upon completion of the warm up, subjects performed three MVC's. Participants were instructed to push against the load cell as hard and as fast as they could for five seconds and be given 120 seconds between attempts (66). After the MVC's, the subjects performed isometric fatiguing exercise. Subjects were asked to maintain the target force level of 30% of MVC until force dropped below 90% (i.e. 27% MVC) for 2 seconds or more than 2 occasions (66). Upon termination of the isometric fatigue testing, the subjects immediately performed a MVC, with two subsequent MVC's separated by 60 seconds. This maximal testing was

performed to measure the difference in central drive after the fatiguing exercise. The subjects were then given 15 minutes to rest before performing the exercise with the opposite leg. The isokinetic protocol was performed on visit 4 in a similar manner as the isometric fatiguing exercise, but at 60^{o}/sec contractions. The order of which leg was tested first was randomized for each visit.

Visit 5: Functional Testing

On visit 5, subjects performed all three functional tests to assess physical function. These tests were performed to mimic movements that have carry-over to everyday activities. The functional tests included; the timed up-and-go test, the 25-foot walk test, and the 6-minute walk test. All subjects were also be familiarized with each functional test prior to testing, due to the learning effect associated with all three tests (69**,** 83). Each test will be described further below:

Timed Up-and-Go Test

One of the functional performance tests performed on visit 5 was the timed up-and-go test (TUG). The TUG was initially developed to study disturbance in dynamic balance and as a measure of functional mobility (57, 72). The TUG has been shown to be a valid and reliable assessment of functional mobility in individuals with MS (12, 69). The test requires the subject to start sitting in a standard chair (seat height 46 cm, and arm height 67 cm) with their backs against the chair, arms resting on the chair's arms. On the word "go" the subject stands up from the chair, walks 3 m, turns, and walks back to the chair, and sits down (57). The subject was timed from the

minute he or she lifted the pelvis from the chair until he or she returned with the pelvis to the chair. Subjects rested for 3 minutes between attempts, and both trials were recorded by the researchers, with the time rounded to the nearest .1 seconds.

25-Foot Walk Test

Another functional performance test performed on visit 5 was the 25-foot walk test (25W). The 25W is a quantitative mobility and leg function performance test based on a timed 25 foot walk (23). The 25W is the first test administered as part of the multiple sclerosis functional composite (MSFC) (23-24). The MSFC is similar to EDSS scale, in that it allows a quantitative assessment of the impact of MS on neurological status (25 foot walk/100m). Gait speed has been shown to be a useful and reliable functional measure of an individual's walking ability (56). Following National MS Society guidelines, the 25W was administered with clear markings indicating a 25 foot walk course (24). Subjects were instructed to remain standing with their toes just behind the starting line. Researchers instructed the subject as to where the course ends. Researchers then provided the same instructions to each subject:

"I'd like you to walk 25 feet as quickly as possible, but safely. Do not slow down until after you've passed the finish line. Ready? Go."

Timing began when the lead foot was lifted off the ground and passes the starting line. The researcher walked alongside the subject during the test and stopped timing when the back foot crossed the 25 foot mark. Subjects were then provided 3

minutes of rest before performing the test again. All trials were recorded by the researchers, with the walk time rounded within 0.1 seconds (24).

6-Minute Walk Test

The final functional performance test performed on visit 5 was the 6-minute walk test (6MW). The 6MW test was originally used as an assessment of cardiopulmonary function (9). In recent years the 6MW has been used in neurological populations (28). The 6MW has been shown to be a feasible, reproducible and reliable functional measure in individuals with MS (27). Subjects walked as fast and as far as possible without rest or encouragement for 6 minutes. The 6MWT was performed indoors, along a long, flat, straight, corridor with a hard surface. The walking course must be 30 m in length. A 100-ft hallway is therefore required, with the length marked every 3 m. The turnaround point was marked with an orange safety cone. The following instructions were read to each subject:

"The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

You will be walking back and forth around cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I am going to show you. Please watch the way I turn without hesitation."

The researchers demonstrated by walking one lap themselves. Researchers demonstrated how to walk and pivot around the cone briskly. Subjects began walking after the researchers said, “Go” and continued walking for 6 minutes. When the 6 minutes ended, the subjects were told to stop and the distance covered was recorded.

Data Management and Analyses

Data Management

Data was stored in the Human Performance and Body Composition Lab at the University of Oklahoma. All data and documents were stored in a locked filing cabinet that only approved research personnel had access to. Each subject had their own data collection folder to store all data collection sheets. Each subject was assigned a number used for data analysis. No identifying subject markers were used other than the assigned subject number with any data. All information from the DXA scans were printed off and stored. All exercise performed on the Kin-Com dynamometer was recorded and saved using the Biopac data analysis software (Biopac Systems MEC 100: Biopac Systems Inc., Holliston, MA), and recorded for each subject on data collection sheets. The analysis included a low frequency filter and all measurements were made to the nearest .01 seconds. All functional performance testing were also recorded on data collection sheets each visit. Separate sheets were used for each subject for each visit.

Data Analyses

Dorsiflexion Peak Torque and Voluntary Contraction Time

Peak torque (PT) measurements during dorsiflexion isometric contractions on visit 2 and 3 were quantified by multiplying the maximal force produced by the length of the lever arm. Peak torque was measured to determine the maximal dorsiflexion strength of the individuals. Similarly, during isokinetic contractions on visit 2 and 4 torque for dorsiflexion was quantified by multiplying the maximal force produced by the lever arm. The limb with the highest PT value each visit was defined as the "strong limb" and the lower PT value as the "weak limb" for the given visit. The defined strong and weak limbs were used to assess limb differences in all other analyses for that visit. All torque measurements were made in $N \cdot m$.

$$\text{Torque } (N \cdot m) = \text{force } (N) \times \text{lever arm } (m)$$

After careful visual analysis of the torque curves, PT was selected as the highest torque value achieved in the three trials. Once selected, the trial that elicited the peak torque value was analyzed to determine Voluntary Contraction Time (VCT). VCT is a common measurement made to determine the speed at which an individual can achieve PT (76). VCT for the isometric contractions in visit 2 and 3 was measured as the time from a point corresponding to 10% PT to the point PT was achieved (76). VCT for the isokinetic contractions in visit 2 and 4 was measured as the time from plantarflexion PT to dorsiflexion PT during the second repetition (14).

Time-Rate of Muscle Tension Development

Rate of force production during isometric contractions on visit 2 and 3 were quantified by assessing the time-rate of muscle tension development (TRTD). TRTD is the rate of force production during an isometric contraction and is used as a measure of central drive in MS patients (14, 67). This measure is made by taking the maximal torque produced and dividing it by the time required to reach peak torque.

$$\text{TRTD } (N \cdot m/s) \text{ (14)} = \text{Peak Torque } (N \cdot m) \div \text{VCT (s)}$$

Muscle Tension-Maintaining Capacity

Muscle tension-maintaining capacity (MTMC) was assessed using the "Integral" function in the Biopac software. MTMC was measured to determine the subject's capability to maintain maximal force over the course of MVC. The MTMC measurement was made by quantifying the area under the curve for 4 seconds of the isometric contractions, beginning when peak torque was achieved, on visit 2 and 3 (14). If there was not 4 seconds after the subject achieved peak torque, analysis was made using the latter 4 seconds of the isometric contraction. The integral function used to quantify MTMC is shown below.

$$\int_0^4 \mathrm{PT} = \mathrm{MTMC}$$

Strength Asymmetry

Strength asymmetry (SA) was calculated for isometric torque and isokinetic torque on visits 2-4. SA has previously been quantified by researchers for a better representation of asymmetry in multiple sclerosis patients (15). SA is quantified as the strength ratio, where the PT value of the weaker limb is divided by the PT value of the stronger limb. 100% asymmetry indicated maximal asymmetry, whereas 0% indicated even distribution of torque.

$$\text{Strength Asymmetry (15)} = [1 - (\text{Weak Limb} \div \text{Strong Limb})]\text{x}100$$

Statistical Analysis

An a priori analysis indicated that a sample size of 12 participants would be necessary to detect a significant limb-limb interaction using a dependent (paired samples) t-test and between group interaction using independent t-tests with an alpha of 0.05, a power of 0.80, and an estimated effect size of 1.2 and 1.1 respectively. These calculations were based on effect sizes of MVC data measuring differences between legs, effect size of 1.2, and between groups, effect size of 1.1 (46).

All analyses were performed using SigmaPlot Software 12.5 (Systat Software, San Jose, CA). Independent t-tests were used to assess subject characteristics between groups. Independent t-tests were also used to compare mean differences between groups for isometric SA during visit 2.

Two-way repeated measures ANOVA was utilized to assess the group x limb interaction for lower leg composition in visit 1, and isometric PT, VCT, TRTD, and MTMC in visit 2. A two-way repeated measures ANOVA was utilized to examine the limb x speed interactions for isokinetic PT within each group and to assess group x speed interaction for isokinetic SA between groups. A two-way repeated measures ANOVA was utilized to assess the group x limb interaction for fatigue time, and fatigue reps during visit 3 & 4. A two-way repeated measures ANOVA was also performed to assess the group x time interaction for SA between groups during measurements made before the fatigue test (PRE), immediately after the fatigue test (POST), and two minutes after the fatigue test (REC). A two-way repeated measures ANOVA was also performed to assess the limb x time interaction within each group for the following measurements during visits 3 & 4; PT, VCT, TRTD, and MTMC. When significant interactions and effects were found, Student-Newmans-Keuls stepwise multiple comparisons were used to determine where specific between and within-group differences were located.

Independent t-tests were also used to assess group mean differences for 25W time, gait speed (calculated by dividing 25 ft. by the time it took to complete the 25W), TUG time, and 6MW distance from Visit 5. Linear correlation analyses were used to examine the relationships between all three functional tests and SA as well as EDSS in the MS group. All data was expressed as mean $\pm$ standard deviation. An alpha level of 0.05 was the criteria to establish statistically significant differences. Cohen's d effect sizes (d) were analyzed when appropriate. A value of < 0.19 was considered trivial,

0.20 - 0.49 was considered a weak effect, a value of 0.50 - 0.79 was considered a moderate effect, and a value of $\geq$ 0.80 was considered a strong effect.

Chapter 4: Results & Discussion

Results

Descriptive Data

Thirty subjects participated in this study, which included thirteen individuals with physicians diagnosed MS (MS Group) and seventeen individuals without MS (NON-MS group). Groups were matched for age, gender, and physical activity. Due to an inability to match four healthy individuals with an MS patient, these four subjects were omitted from data analyses. Therefore, twenty-six subject data were analyzed for this study. There were five males and eight females (n = 13) in the MS group (mean ± SD: age = 50.3 ± 9.1 yrs, height = 172.8 ± 5.4 cm, body mass = 99.7 ± 17.9 kg) and five males and eight females (n = 13) in the NON-MS Group (mean ± SD: age = 50.8 ± 8.5 yrs, height = 166.4 ± 10.7 cm, body mass = 79.5 ± 13.5 kg). Descriptive and anthropometric data for both groups are listed in Table 2. The MS group consisted of one subject with physicians' diagnosis of primary progressive MS and twelve subjects with physicians' diagnosis of relapsing remitting MS. The Expanded Disability Status Scale (EDSS) score of 3.5 ± 1.8 indicates a moderate impairment in the MS patients. Rochester Fatigue Diaries and Modified Fatigue Impact Scale were assessed and analyzed prior to each testing session to ensure similar levels of fatigue. No visits had to be rescheduled due to increased fatigue. The MS group had significantly greater amounts of body mass (mean ± SD: MS vs. NON-MS = 99.7 ± 5.4 kg vs. 79.5 ± 13.5 kg, p = 0.003), body fat percentage (mean ± SD: MS vs. NON-MS = 46.1 ± 7.6% vs. 37.3 ±

12.4%, p = 0.04) and fat mass (mean ± SD: MS vs. NON-MS = 45.05 ± 13.7 kg vs. 29.7 ± 13.6 kg, p = 0.008).

Table 2. Participant Characteristics

Variable	NON-MS n = 13	MS n = 13	*p*
Age (yrs)	50.8 ± 8.5	50.3 ± 9.1	0.88
Height (cm)	166.4 ± 10.7	172.8 ± 5.4	0.07
Body Mass (kg)	79.5 ± 13.5	99.7 ± 17.9	0.003*
Body Mass Index (kg/m^2)	29.0 ± 6.1	33.5 ± 6.0	0.07
Body Fat (%)	37.3 ± 12.4	46.1 ± 7.6	0.04*
Lean Mass (kg)	47.5 ± 9.4	51.4 ± 7.4	0.24
Fat Mass (kg)	29.7 ± 13.6	45.0 ± 13.7	0.008*
Physical Activity (min/wk)	188.1 ± 83.2	141.9 ± 142.1	0.32
EDSS	N/A	3.5 ± 1.8	N/A

Data are mean ± SD. EDSS, expanded disability status scale. *$p < 0.05$ represents a statistically significant difference across group means.

Lower-leg composition data is presented in Table 3. Results of the two-way repeated measures ANOVA indicated no significant group x leg interaction for lean mass, fat mass or fat percentage in the lower-legs ($p < 0.05$). There was a significant group effect for fat mass (F = 12.2, p = 0.001, $\eta^2 = 0.20$) and fat percentage (F = 7.5, p = 0.009, $\eta^2 = 0.13$) in the lower legs. Post-hoc analysis indicated that the MS group had a significantly greater amount of fat mass in the right lower-leg (mean ± SD: MS vs NON-MS = 1.4 ± 0.6 kg vs. 0.9 ± 0.4 kg, p = 0.02, d = 0.98) and the left lower-leg (mean ± SD: MS vs NON-MS = 1.4 ± 0.6 kg vs. 1.0 ± 0.4 kg, p = 0.03, d = 0.78). Post-hoc analysis indicated that the MS group had a significantly greater percent body fat in the left

lower-leg than the Non-MS group (mean ± SD: MS vs NON-MS = 38.6 ± 9.4 % vs. 30.6 ± 11.0%, p = 0.05, d = 0.78). Within and between groups comparisons showed no difference in lean mass for the right and left lower-leg.

Table 3. Lean and Fat Mass of the Lower Legs

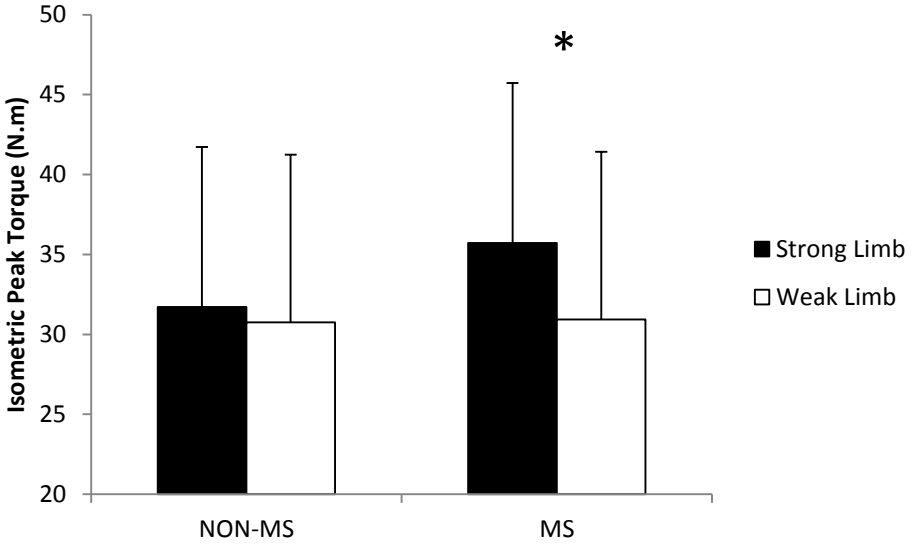
	Non-MS			MS		
Variable	Right Limb	Left Limb	*p*	Right Limb	Left Limb	*p*
Lean Mass (Kg)	2.2 ± 0.7	2.2 ± 0.7	0.74	2.1 ± 0.3	2.2 ± 0.4	0.51
Fat Mass (kg)	1.0 ± 0.4	0.9 ± 0.4	0.11	1.4 ± 0.6*	1.4 ± 0.6*	0.85
Lower-Leg Fat (%)	31.5 ± 11.3	30.6 ± 11.0	0.20	38.8 ± 9.4	38.6 ± 9.4*	0.65

Data are mean ± SD. *$p < 0.05$ represents a statistically significant difference between groups.

Maximal Torque Testing

The results from the two-way repeated measures ANOVA indicate a significant group x limb interaction for peak torque (F = 5.9, p = 0.02, $\eta^2 = 0.20$). There was also a significant limb effect for peak torque (F = 13.4, p = 0.001, $\eta^2 = 0.36$). Post-hoc analysis showed a significant mean PT difference within the limbs of the MS group (mean ± SD: Strong vs Weak = 35.7 ± 9.4 vs. 30.9 ± 10.2, p < 0.001, d = 0.87; Figure 1).

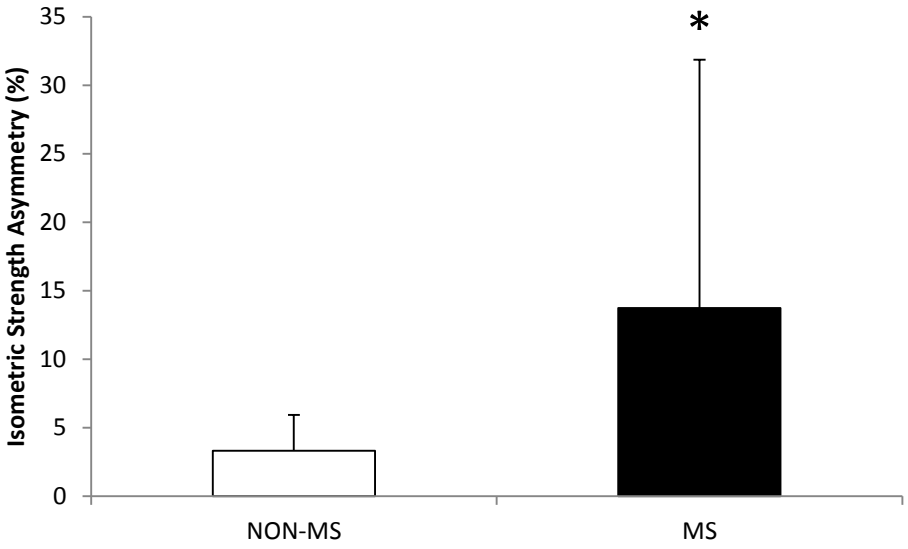
Figure 1. Mean Group Isometric Peak Torque of each Limb.



Values are means ± SD. * $p < 0.05$ represents statistically significant difference between limbs

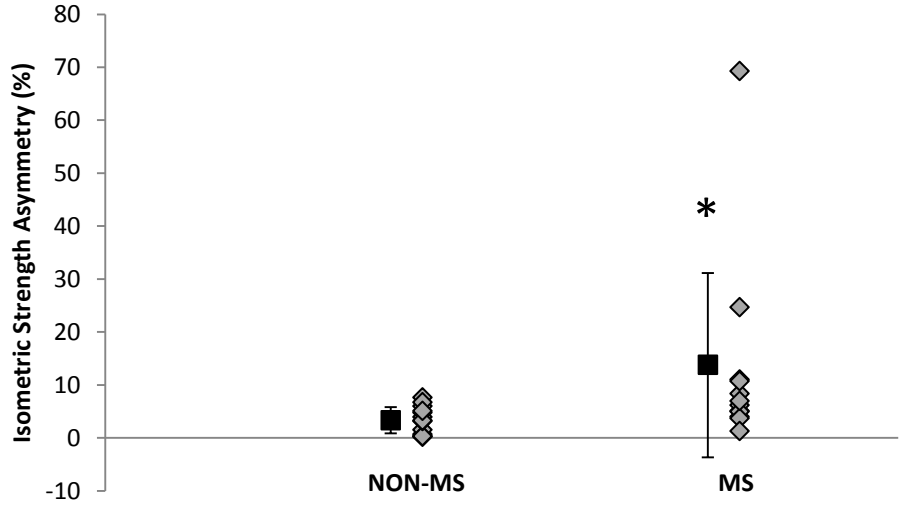
Figure 2 shows the isometric SA of both groups from visit 2. Independent t-tests of the isometric SA showed that MS patients exhibited significantly greater asymmetry than the NON-MS group (mean ± SD: MS vs NON-MS = 13.7 ± 18.1 vs. 3.3 ± 2.6, p = 0.03 d = 0.84). Isometric SA of each individual subject is presented in Figure 3.

Figure 2. Mean Group Isometric Strength Asymmetry



Values are means ± SD. * $p < 0.05$ represents statistically significant difference between groups

Figure 3. Individual Isometric Strength Asymmetry Response



Values are means ± SD. * $p < 0.05$ represents statistically significant difference between limbs

Table 4 shows the isokinetic PT values for limbs within each group for each speed tested, 30^{o}/sec, 60^{o}/sec, 90^{o}/sec, and 120^{o}/sec. The results from the two-way limb x speed repeated measures ANOVA indicated that there was no significant limb x speed isokinetic PT interaction in the MS group. However, there was a main effect for speed ($F = 51.8$, $p < 0.001$, $\eta^2 = 0.96$) and a main effect for limb ($F = 13.4$, $p = 0.003$, $\eta^2 = 0.87$) in the MS group. Post-hoc analysis showed a significant isokinetic PT mean difference, as the speed of the contraction increased PT decreased, between all speeds in the strong limb; 30^{o}/sec-60^{o}/sec, 30^{o}/sec-90^{o}/sec, 30^{o}/sec-120^{o}/sec, 60^{o}/sec-90^{o}/sec, 60^{o}/sec-120^{o}/sec, and 90^{o}/sec-120^{o}/sec (Figure 4a). There was also a mean PT difference in the weak limb, as the speed of the contraction increased PT decreased, between all speeds except between 90^{o}/sec-120^{o}/sec (Figure 4a). The post-hoc analysis indicated a significant mean difference between limbs at all four speeds. Mean difference between speeds for each limb within the MS group is found in Table 5.

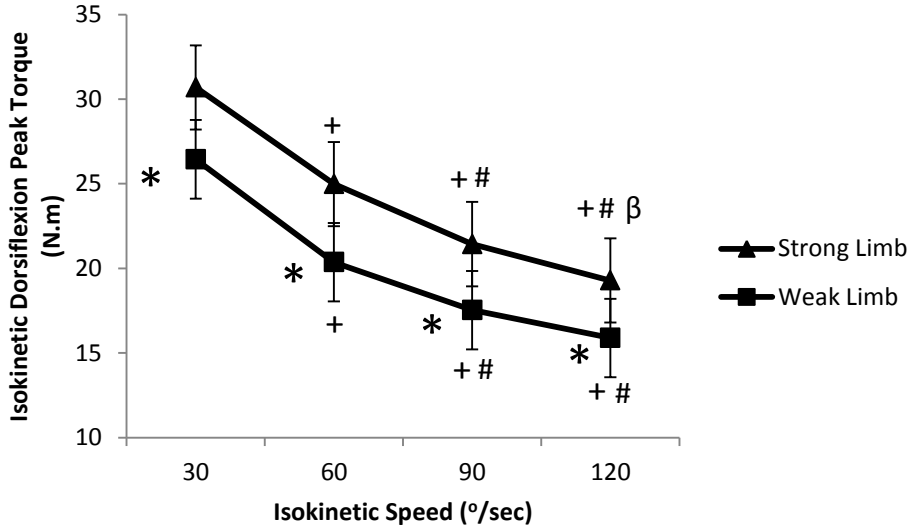
Table 4. Isokinetic Dorsiflexion Peak Torque

	NON-MS				MS			
Variable	Strong Limb	Weak Limb	*p*	d	Strong Limb	Weak Limb	*p*	d
Isokinetic 30°/sec PT (N·m)	27.9 ± 9.6	25.5 ± 8.9	<0.001*	0.27	30.7 ± 6.5	26.4 ± 9.5	0.003*	0.54
Isokinetic 60°/sec PT (N·m)	22.9 ± 7.7	20.9 ± 7.5	<0.001*	0.27	25.0 ± 5.6	20.4 ± 7.3	0.001*	0.74
Isokinetic 90°/sec PT (N·m)	20.3 ± 7.1	18.2 ± 6.4	<0.001*	0.32	21.4 ± 4.8	17.5 ± 6.2	0.005*	0.73
Isokinetic 120°/sec PT (N·m)	18.2 ± 6.8	15.5 ± 6.1	<0.001*	0.43	19.3 ± 3.0	15.9 ± 5.2	0.012*	0.83

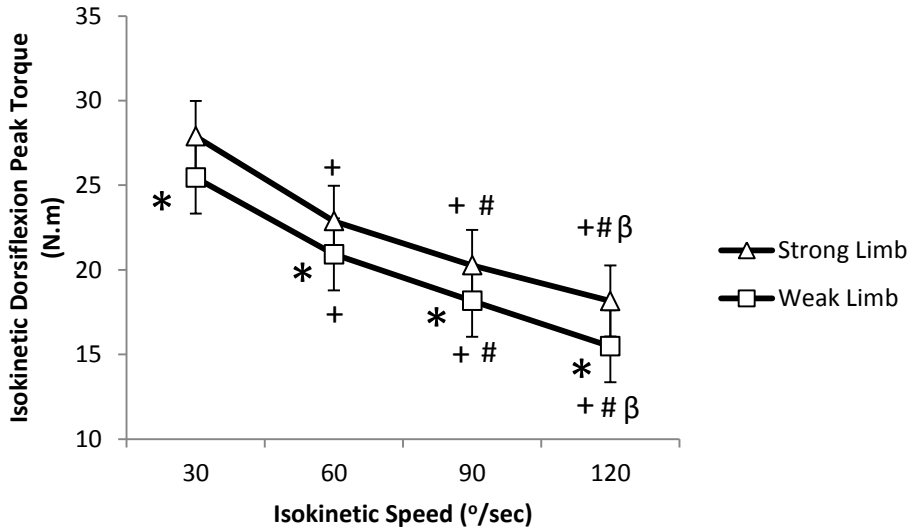
Data are mean ± SD. PT, peak torque. *$p < 0.05$ represents a statistically significant difference between limbs.

Figure 4. Mean Isokinetic Dorsiflexion Peak Torque for each Speed of each Limb

4a – MS



4b – NON-MS



Values are means ± SD
* $p < 0.05$ represents statistically significant limb difference.
+ $p < 0.05$ represents statistically significant difference from 30°/sec.
# $p < 0.05$ represents statistically significant difference from 60°/sec.
β $p < 0.05$ represents statistically significant difference from 90°/sec.

Table 5. Mean Difference between each Contraction Speed for Multiple Sclerosis

	MS					
Variable	Strong Limb	*p*	d	Weak Limb	*p*	d
30^{o}/sec-60^{o}/sec PT (N·m)	5.7 ± 0.8	<0.001*	2.11	6.1 ± 0.8	<0.001*	2.77
30^{o}/sec-90^{o}/sec PT (N·m)	9.3 ± 0.8	<0.001*	3.31	8.9 ± 0.8	<0.001*	2.70
30^{o}/sec-120^{o}/sec PT (N·m)	11.4 ± 0.8	<0.001*	2.93	10.6 ± 0.8	<0.001*	2.68
60^{o}/sec-90^{o}/sec PT (N·m)	3.6 ± 0.8	0.001*	2.18	2.8 ± 0.8	0.001*	1.18
60^{o}/sec-120^{o}/sec PT (N·m)	5.7 ± 0.8	<0.001*	2.16	4.5 ± 0.8	<0.001*	1.43
90^{o}/sec-120^{o}/sec PT (N·m)	2.1 ± 0.8	0.04*	0.79	1.6 ± 0.8	0.11	0.67

Data are mean difference ± SE. PT, peak torque. *$p < 0.05$ represents a statistically significant mean difference.

The results from the two-way limb x speed repeated measures ANOVA indicated that there was no significant limb x speed isokinetic PT interaction in the NON-MS Group. However, there was a main effect for speed ($F = 92.6$, $p < 0.001$, $\eta^2 = 0.98$) and limb ($F = 39.784$, $p < 0.001$, $\eta^2 = 0.52$). Post-hoc analysis showed a significant isokinetic PT mean difference, as the speed of the contraction increased PT decreased, between all speeds in the strong and weak limbs; 30^o/sec-60^o/sec, 30^o/sec-90^o/sec, 30^o/sec-120^o/sec, 60^o/sec-90^o/sec, 60^o/sec-120^o/sec, and 90^o/sec-120^o/sec (Figure 4b). Post-hoc analysis also showed a significant mean PT difference between limbs at all four speeds for the NON-MS group. Mean difference between speeds for each limb within the NON-MS group is found in Table 6.

Table 6. Mean Difference between each Contraction Speed for NON-MS

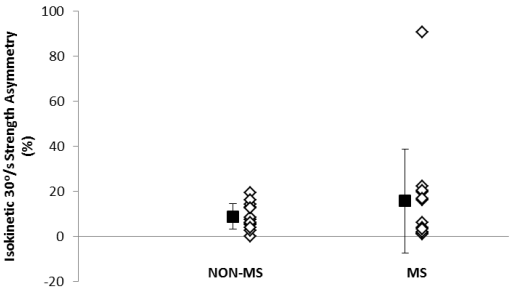
	NON-MS					
Variable	Strong Limb	*p*	d	Weak Limb	*p*	d
30^{o}/sec-60^{o}/sec PT (N·m)	5.0 ± 0.3	<0.001*	3.73	4.5 ± 0.3	<0.001*	3.74
30^{o}/sec-90^{o}/sec PT (N·m)	7.6 ± 0.3	<0.001*	5.43	7.3 ± 0.3	<0.001*	4.02
30^{o}/sec-120^{o}/sec PT (N·m)	9.7 ± 0.3	<0.001*	4.20	10.0 ± 0.3	<0.001*	4.89
60^{o}/sec-90^{o}/sec PT (N·m)	2.6 ± 0.3	<0.001*	1.67	2.8 ± 0.3	<0.001*	2.55
60^{o}/sec-120^{o}/sec PT (N·m)	4.7 ± 0.3	<0.001*	2.28	5.4 ± 0.3	<0.001*	3.91
90^{o}/sec-120^{o}/sec PT (N·m)	2.1 ± 0.3	0.003*	1.27	2.7 ± 0.3	<0.001*	1.57

Data are mean difference ± SE. PT, peak torque. *$p < 0.05$ represents a statistically significant mean difference.

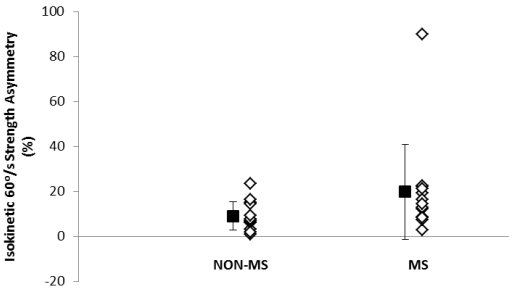
Figure 5 shows the individual isokinetic SA values for each group at each speed tested. Two-way group x speed repeated measures ANOVA test for the isokinetic SA at all four contraction speeds indicated no significant group x speed interaction. For isokinetic SA, there was a trivial effect size between groups at the 120^{o}/sec speed (d = 0.16), weak effect size at the 30^{o}/sec speed (d = 0.39), and a moderate effect size at the 60^{o}/sec and 90^{o}/sec speeds (d = 0.66, 0.54 respectively). Isometric SA and Isokinetic SA's values from Visit 2 are shown in Table 7.

Figure 5. Individual Isokinetic Dorsiflexion Strength Asymmetry at each Speed

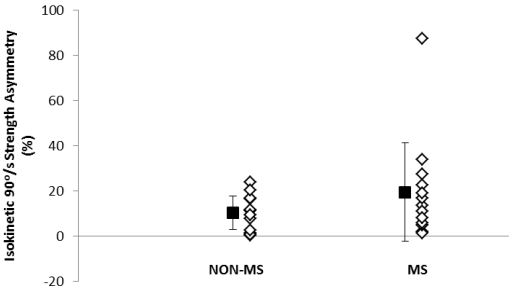
5a – 30°/sec



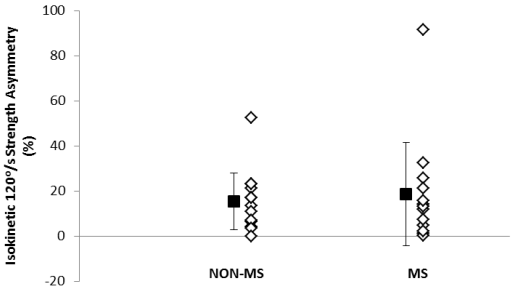
5b – 60°/sec



5c – 90°/sec



5d – 120°/sec



Values are means ± SD.

Table 7. Strength Asymmetry Values

Variable	NON-MS	MS	*p*	d
Isometric SA (%)	3.3 ± 2.6	13.7 ± 18.1	0.03*	0.84
Isokinetic 30°/sec SA (%)	8.8 ± 5.7	15.7 ± 24.0	0.33	0.39
Isokinetic 60°/sec SA (%)	9.1 ± 6.6	19.9 ± 22.0	0.10	0.66
Isokinetic 90°/sec SA (%)	10.3 ± 7.7	19.4 ± 22.7	0.18	0.54
Isokinetic 120°/sec SA (%)	15.4 ± 13.5	18.6 ± 23.9	0.68	0.16

Data are mean ± SD. SA, strength asymmetry. *$p < 0.05$ represents a statistically significant difference between groups.

Muscle Performance Variables

The muscle performance variables from the isometric contractions can be found in Table 8. The results of the two-way repeated measures ANOVA did not indicate a group x limb interaction for VCT. There was however a significant limb effect ($F = 5.7$, $p = 0.03$, $\eta^2 = 0.19$). The post-hoc analysis showed a significantly greater VCT in the strong limb of the MS group compared to the weak limb (mean ± SD: Strong vs Weak = 2.1 ± 1.5 vs. 1.2 ± 0.5, $p = 0.005$; Figure 6). Post-hoc analysis also indicated a significantly greater VCT in the strong limb of the MS group compared to the strong limb of the NON-MS group (mean ± SD: MS vs NON-MS = 2.1 ± 1.5 vs. 1.2 ± 0.5, $p = 0.009$; Figure 6). VCT showed a strong effect size between limbs in the MS group ($d = 0.91$) and a trivial effect size in the NON-MS group ($d = 0.12$).

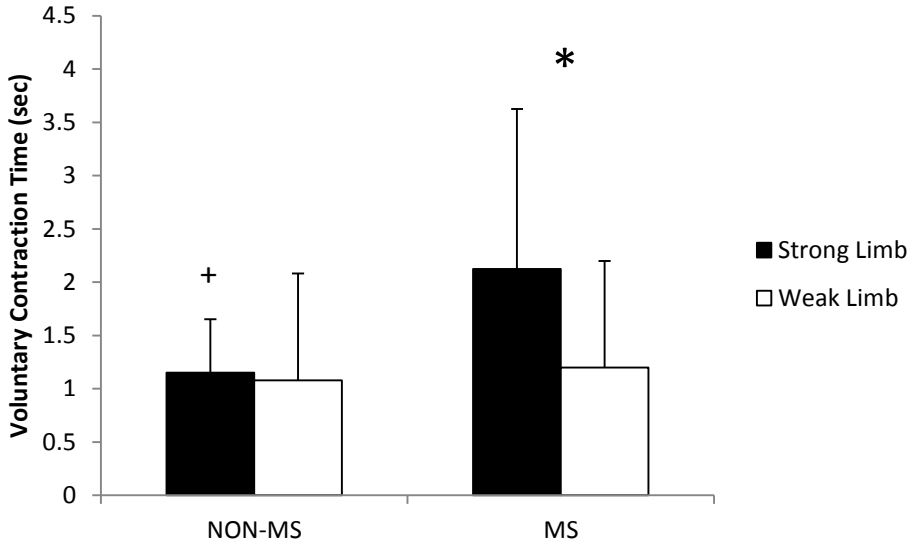
The results of the two-way repeated measures ANOVA did not indicate a group x limb interaction for TRTD. There was however a significant group x limb effect for MTMC ($F = 6.0$, $p = 0.02$, $\eta^2 = 0.20$). There was also a significant limb effect for MTMC ($F = 7.0$, $p = 0.01$, $\eta^2 = 0.23$). Post-hoc analysis indicated that the strong limb MTMC was significantly greater compared to the weak limb in the MS group (mean ± SD: Strong vs Weak = 130.5 ± 35.5 vs. 113.4 ± 41.0, $p < 0.001$; Figure 7). TRTD showed a weak effect size between limbs in the MS group and NON-MS group ($d = 0.39$, 0.23 respectively). MTMC showed a moderate effect size between limbs in the MS group ($d = 0.76$) and a trivial effect size within the NON-MS group ($d = 0.11$).

Table 8. Muscle Performance Variables

	NON-MS				MS			
Variable	Strong Limb	Weak Limb	*p*	d	Strong Limb	Weak Limb	*p*	d
Isometric VCT (s)	1.2 ± 0.5	1.1 ± 0.6	0.78	0.12	2.1 ± 1.5^{+}	1.2 ± 0.5	0.005*	0.91
TRTD (N·m/s)	30.1 ± 19.2	34.1 ± 21.5	0.43	0.23	22.9 ± 14.7	28.8 ± 17.8	0.19	0.39
MTMC (N·m)	110.5 ± 36.1	109.8 ± 39.2	0.89	0.11	130.5 ± 35.5	113.4 ± 41.0	<0.001*	0.76

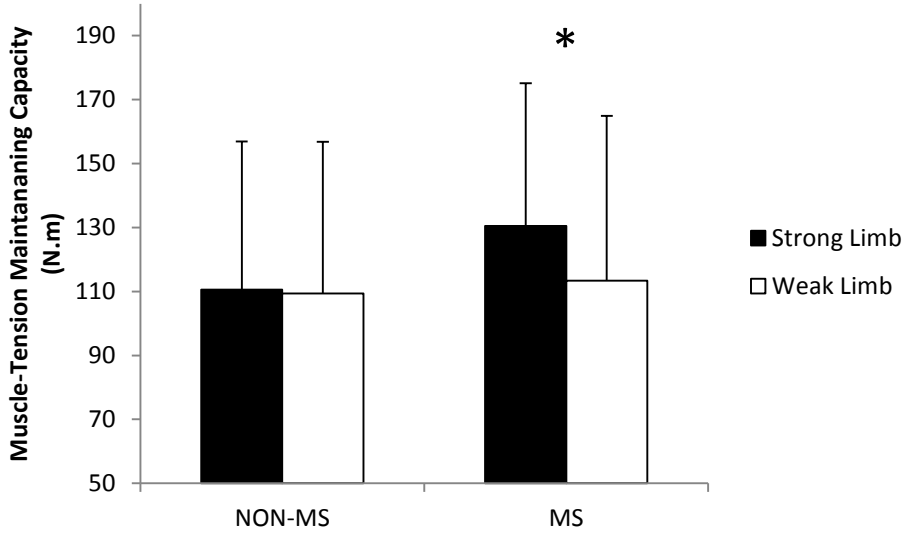
Data are mean ± SD. PT, peak torque; VCT, voluntary contraction time; TRTD, time-rate of muscle tension development; MTMC, muscle tension-maintaining capacity. *$p < 0.05$ represents statistically significant difference between limbs.
$^{+}$ $p < 0.05$ represents statistically significant difference between groups.

Figure 6. Mean Isometric Voluntary Contraction Time Value of each Limb between Groups



Values are means ± SD. * $p < 0.05$ represents statistically significant difference between limbs. $^{+}$ $p < 0.05$ represents statistically significant difference between groups.

Figure 7. Mean Muscle-Tension Maintaining Capacity Value of each Limb between Groups

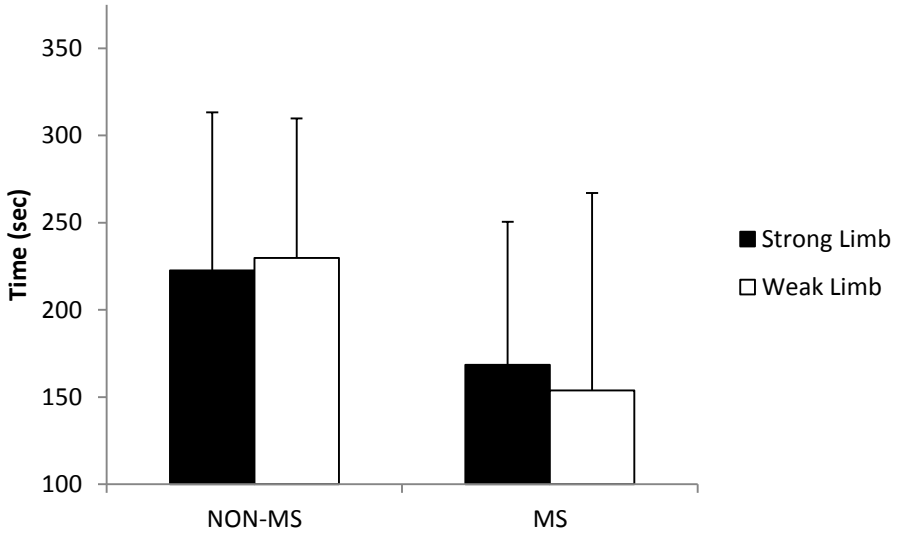


Values are means ± SD. * p <0.05 represents statistically significant difference between limbs.

Isometric Fatigue

Figure 8 shows the isometric fatigue test time for each limb in the two groups. The two-way repeated measures ANOVA results indicated that there was no group x limb interaction for isometric fatigue time. There was a moderate effect size for the difference in fatigue time in the strong limb (d = 0.63) and in the weak limb between groups (d = 0.78).

Figure 8. Mean Isometric Fatigue Time of each Limb between Groups

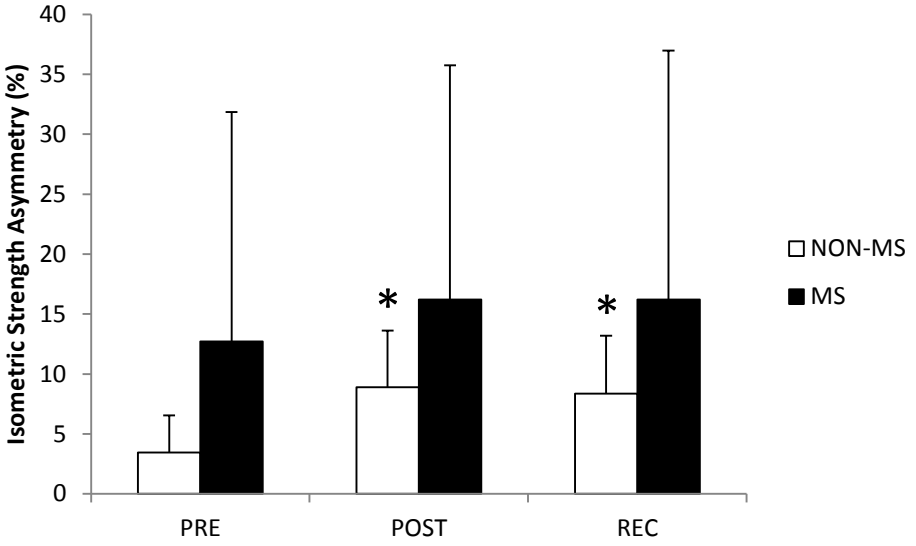


Values are means ± SD. * $p < 0.05$ represents statistically significant differences between groups.

Figure 9 shows the isometric SA for Visit 3 in each group. The results of the two-way repeated measures ANOVA indicated that there was no group x time interaction for isometric SA of the MVC before (PRE), immediately post (POST), and after 2 minutes of recovery (REC). However, there was a significant time effect ($F = 6.2$, $p = 0.004$, $\eta^2 = 0.14$). Post-hoc analysis indicated there were no significant group differences at any time point. There was a significant increase in SA in the NON-MS group between PRE-POST (mean ± SD: PRE vs POST = 3.5 ± 3.1 vs. 8.9 ± 4.7, $p = 0.03$) and PRE-REC (mean ± SD: PRE vs REC = 3.5 ± 3.1 vs. 8.4 ± 4.8, $p = 0.02$). There was a moderate effect size between groups for isometric SA at the PRE, POST, and REC time points ($d = 0.70$, 0.54, and 0.54 respectively). Figure 10a and Figure 10b represent

individual isometric SA at each time point for the MS group and the NON-MS group, respectively.

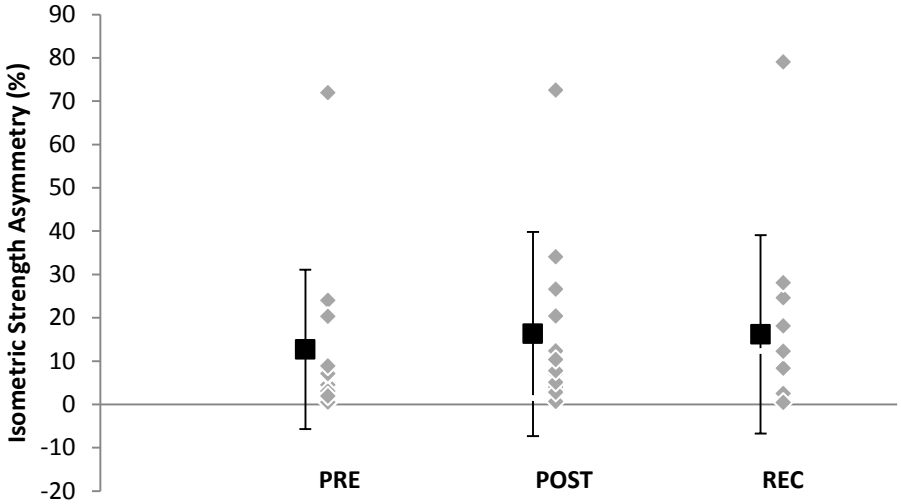
Figure 9. Mean Group Isometric Strength Asymmetry at each Time Point



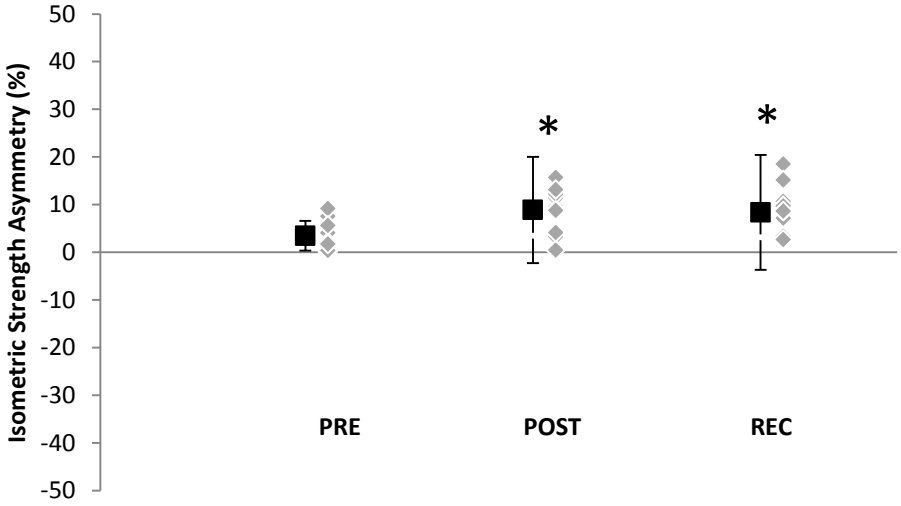
Values are means ± SD. * $p < 0.05$ represents statistically significant from the PRE value.

Figure 10. Individual Isometric Strength Asymmetry for each Time Point.

10a – Multiple Sclerosis



10b – NON-MS



Values are means $\pm$ SD. * $p < 0.05$ represents statistically significant from the PRE value.

Table 9 shows the isometric PT values of each limb at all three time points for both groups. The two-way repeated measures ANOVA indicated no limb x time interactions for isometric PT in the MS group. There was a significant time effect for isometric PT in the MS group ($F = 35.0$, $p < 0.001$, $\eta^2 = 0.91$). Post-hoc analysis indicated significant mean differences between all time points within the strong limb and the weak limb for the MS group (Figure 11a). Both limbs showed a significant decrease in PT after exercise and a significant increase after recovery, however still significantly less than before exercise. There was also a significant mean difference between limbs in the MS group for the isometric PT at the PRE time point (mean ± SD: Strong vs Weak = 36.9 ± 7.9 vs. 32.6 ± 10.6, $p = 0.03$) and at the REC time point (mean ± SD: Strong vs Weak = 33.0 ± 6.9 vs. 29.0 ± 10.0, $p = 0.04$). The two-way repeated measures ANOVA indicated no limb x time interaction for isometric PT in the NON-MS group. There was a significant time effect for isometric PT in the NON-MS group ($F = 24.2$, $p < 0.001$, $\eta^2 = 0.94$). Post-hoc analysis indicated significant mean differences between all time points within the strong limb and the weak limb for the NON-MS group (Figure 11b). Similar to the MS group, for the NON-MS group PT in both limbs significantly decreased after exercise and significantly increased after recovery, however still significantly less than before exercise values. The effect size for the interactions of each limb at each time point is shown in Table 10 and Table 11.

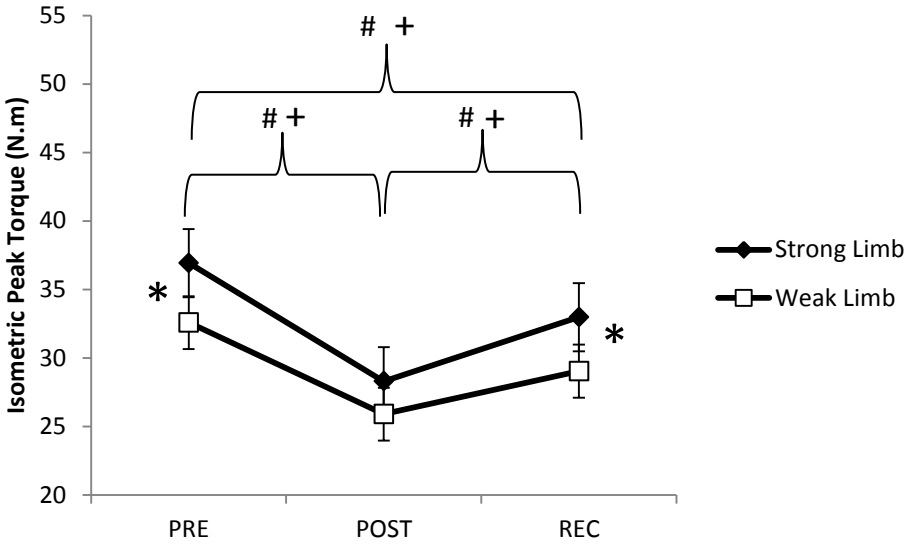
Table 9. Isometric Peak Torque and Muscle Performance Variables during Fatigue Testing

		NON-MS			MS		
		PRE	POST	REC	PRE	POST	REC
Isometric PT (N·m)	Strong	31.9 ± 10.8	24.3 ± 6.9^{+}	28.0 ± 8.6$^{+\#}$	36.9 ± 7.9	28.3 ± 6.8^{+}	33.0 ± 6.9$^{+\#}$
	Weak	30.8 ± 10.7	23.6 ± 6.7^{+}	27.6 ± 8.0$^{+\#}$	32.6 ± 10.6*	25.9 ± 9.3^{+}	29.0 ± 10.0$^{+\#}$*
Isometric VCT (sec)	Strong	1.1 ± 0.9	1.4 ± 1.2	N/A	1.1 ± 0.5	1.5 ± 0.8	N/A
	Weak	0.9 ± 0.5	1.1 ± 0.7		1.2 ± 0.8	1.1 ± 0.5	
TRTD (N·m/sec)	Strong	37.0 ± 26.0	27.2 ± 22.4	N/A	35.5 ± 15.5	20.7 ± 9.5^{+}	N/A
	Weak	38.2 ± 25.3	28.4 ± 23.4		34.2 ± 22.3	25.0 ± 14.2	
MTMC (N·m)	Strong	115.5 ± 37.2	90.6 ± 24.8^{+}	102.0 ± 30.4$^{+\#}$	134.0 ± 29.2	106.0 ± 28.1^{+}	117.4 ± 31.5$^{+\#}$
	Weak	113.6 ± 41.0	88.2 ± 25.1^{+}	100.8 ± 31.7$^{+\#}$	120.5 ± 45.1	93.3 ± 31.9^{+}	102.3 ± 38.1^{+}*

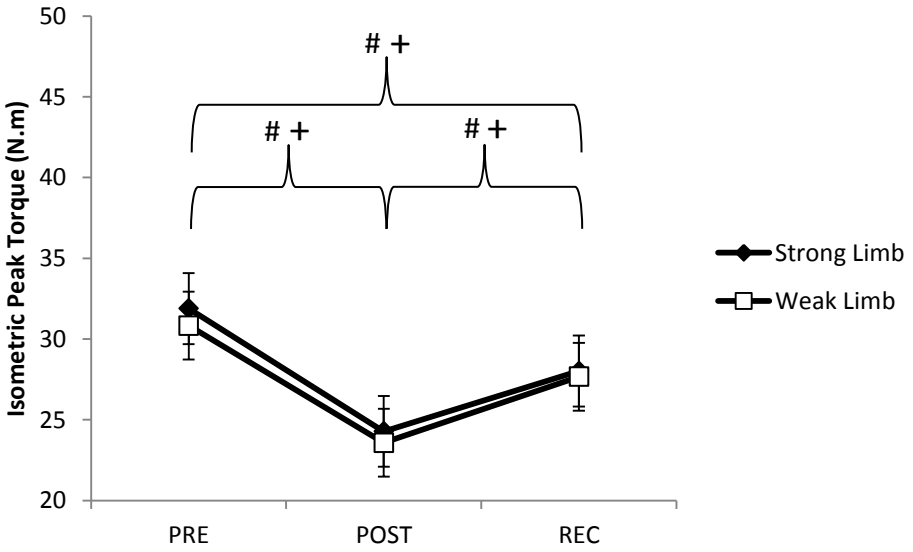
Data are mean ± SD. PT, peak torque; VCT, voluntary contraction time; TRTD, time-rate of muscle tension development; MTMC, muscle tension-maintaining capacity. * $p < 0.05$ represents statistically significant limb difference. $^{+}$ $p < 0.05$ represents statistically significant time difference from time point PRE. $^{\#}$ $p < 0.05$ represents statistically significant time difference from time point POST.

Figure 11. Mean Isometric Peak Torque at each Time Point

11a – MS



11b – NON-MS



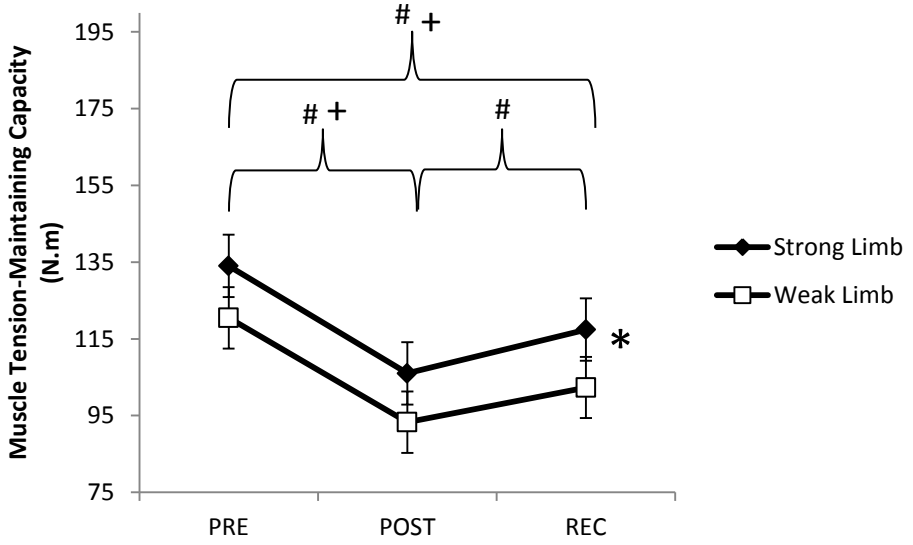
Values are means ± SD. * $p < 0.05$ represents statistically significant difference between limbs. # $p < 0.05$ represents statistically significant time difference in the strong limb. + $p < 0.05$ represents statistically significant time difference in the weak limb.

Muscle performance variables (VCT, TRTD, and MTMC) from the isometric fatigue testing are shown in Table 9. The two-way repeated measures ANOVA indicated no limb x time interaction for MTMC in either group. There was a significant time effect ($F = 26.3$, $p < 0.001$, $\eta^2 = 0.82$) and limb effect ($F = 4.9$, $p = 0.05$, $\eta^2 = 0.63$) in the MS group. Post-hoc analysis indicated MTMC significantly decreased PRE-POST and significantly increased POST-REC, however there was still a significant decrease PRE-REC in the strong limb. The weak limb MTMC significantly decreased PRE-POST, and was still significantly less PRE-REC (Figure 12a). Post-hoc analysis also indicated a significant mean difference between limbs at the REC time point in the MS group (mean ± SD: Strong vs Weak = 117.4 ± 31.5 vs. 102.3 ± 38.1, $p = 0.04$).

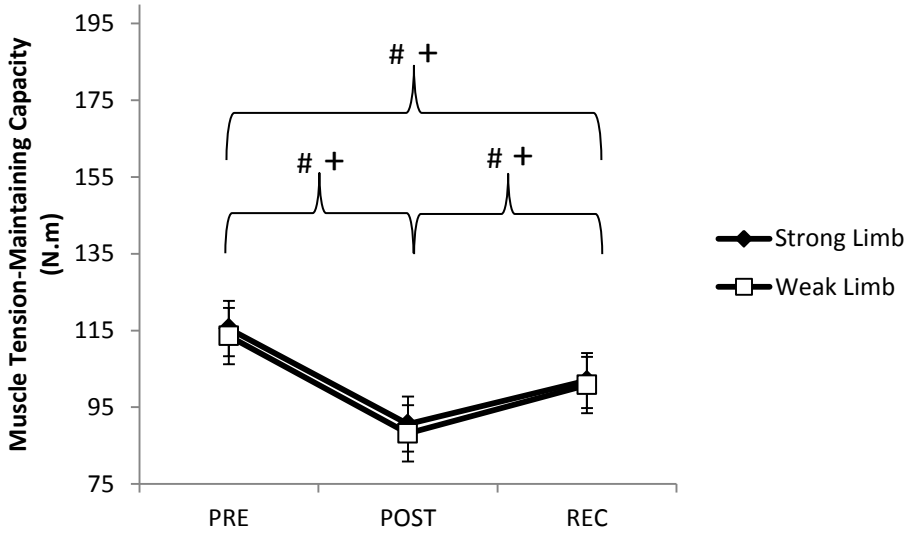
The two-way repeated measures ANOVA indicated a time effect in the NON-MS group for MTMC ($F = 19.7$, $p < 0.001$, $\eta^2 = 0.93$). Post-hoc analysis indicated MTMC significantly decreased PRE-POST and significantly increased POST-REC, however there was still a significant decrease PRE-REC within each limb (Figure 12b). The effect size for the interactions of each limb at each time point is shown in Table 10 and Table 11.

Figure 12. Mean Muscle Tension-Maintaining Capacity at each Time Point

12a – MS



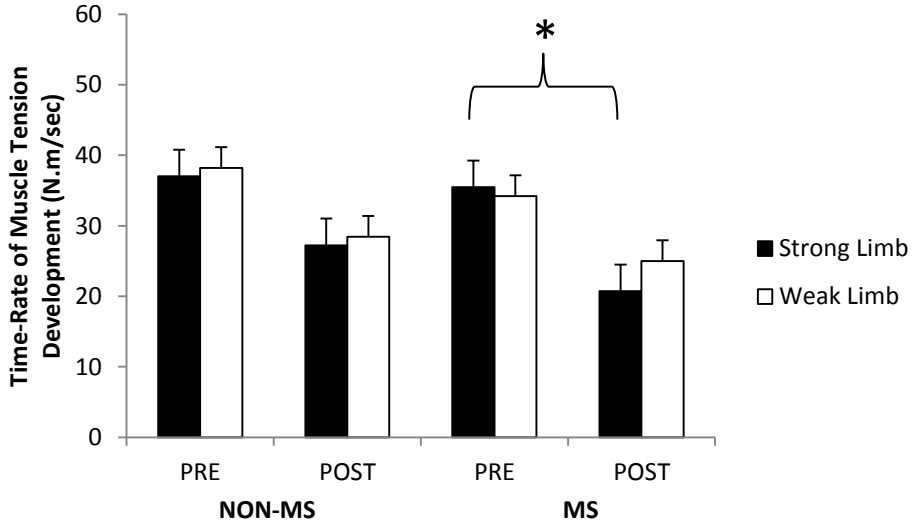
12b – NON-MS



Values are means ± SD. * $p < 0.05$ represents statistically significant limb difference. # $p < 0.05$ represents statistically significant time difference in the strong limb. + $p < 0.05$ represents statistically significant time difference in the weak limb.

The two-way repeated measures ANOVA indicated no limb x time interaction for VCT and no time or limb interaction in either group. Similarly, there was no limb x time interaction in either group for TRTD, however there was a significant time effect for TRTD in the MS group ($F = 7.6$, $p = 0.017$, $\eta^2 = 0.36$). Post-hoc analysis indicated a significant decrease within the strong limb from PRE-POST in the MS group (mean ± SD: PRE vs POST = 35.5 ± 15.5 vs. 20.7 ± 9.5, $p = 0.02$; Figure 13). The effect size for the limb differences at each time point in the MS group and the NON-MS group is shown in Table 10 and Table 11 respectively.

Figure 13. Mean Time-Rate of Muscle Tension Development in each Limb at each Time Point



Values are means ± SD. * $p < 0.05$ represents statistically significant time difference.

Table 10. Effect Size for Isometric Peak Torque and Muscle Performance Variables from Fatigue Testing in Multiple Sclerosis

	MS			
	Isometric PT (N·m) Cohen's d	Isometric VCT (s) Cohen's d	TRTD (N·m/s) Cohen's d	MTMC (N·m) Cohen's d
Strong PRE-POST	2.48+	0.46	0.80+	1.55+
Strong PRE-REC	1.38+	n/a	n/a	0.92+
Strong POST-REC	1.76+	n/a	n/a	0.88+
Weak PRE-POST	1.22+	0.13	0.54	1.61+
Weak PRE-REC	0.99+	n/a	n/a	1.26+
Weak POST-REC	1.02+	n/a	n/a	0.86
Limb PRE	0.82*	0.19	0.08	0.66*
Limb POST	0.42	0.50	0.26	0.54
Limb REC	0.56*	n/a	n/a	0.58

Data are Cohen's d. PT, peak torque; VCT, voluntary contraction time; TRTD, time-rate of muscle tension development; MTMC, muscle tension-maintaining capacity; Strong, strong limb; Weak, weak limb; Limb, limb difference. + $p < 0.05$ represents statistically significant time difference. * $p < 0.05$ represents statistically significant limb difference.

Table 11. Effect Size for Isometric Peak Torque and Muscle Performance Variables from Fatigue Testing in NON-MS Group

	NON-MS			
	Isometric PT (N·m) Cohen's d	Isometric VCT (s) Cohen's d	TRTD (N·m/s) Cohen's d	MTMC (N·m) Cohen's d
Strong PRE-POST	1.85^{+}	0.18	0.28	1.45^{+}
Strong PRE-REC	0.99^{+}	n/a	n/a	1.19^{+}
Strong POST-REC	1.62^{+}	n/a	n/a	1.18^{+}
Weak PRE-POST	2.22^{+}	0.22	0.11	1.89^{+}
Weak PRE-REC	0.90^{+}	n/a	n/a	1.72^{+}
Weak POST-REC	2.00^{+}	n/a	n/a	1.50^{+}
Limb PRE	0.33	0.22	0.07	0.18
Limb POST	0.17	0.23	0.04	0.13
Limb REC	0.14	n/a	n/a	0.09

Data are Cohen's d. PT, peak torque; VCT, voluntary contraction time; TRTD, time-rate of muscle tension development; MTMC, muscle tension-maintaining capacity; Strong, strong limb; Weak, weak limb; Limb, limb difference. + $p < 0.05$ represents statistically significant time difference. * $p < 0.05$ represents statistically significant limb difference.

Isokinetic Fatigue

Results of the isokinetic fatigue test are presented in Table 12. The two-way repeated measures ANOVA results indicated that there was no group x limb interaction for fatigue time or number of reps during the isokinetic fatigue test. There was a moderate effect size between groups in the strong limb for fatigue test time (d = 0.55) and a trivial effect size in the weak limb (d = 0.05).

Table 12. Isokinetic Fatigue Testing

	NON-MS			
Variable	Stronger Limb	Weaker Limb	*p*	d
Isokinetic Time (s)	126.7 ± 84.0	111.3 ± 51.4	0.21	0.57
Isokinetic Reps	84.0 ± 53.0	72.2 ± 33.8	0.19	0.48
	MS			
Variable	Stronger Limb	Weaker Limb	*p*	d
Isokinetic Time (s)	83.6 ± 72.9	116.0 ± 118.6	0.16	0.49
Isokinetic Reps	56.5 ± 44.4	78.3 ± 76.7	0.18	0.47

Data are mean ± SD.

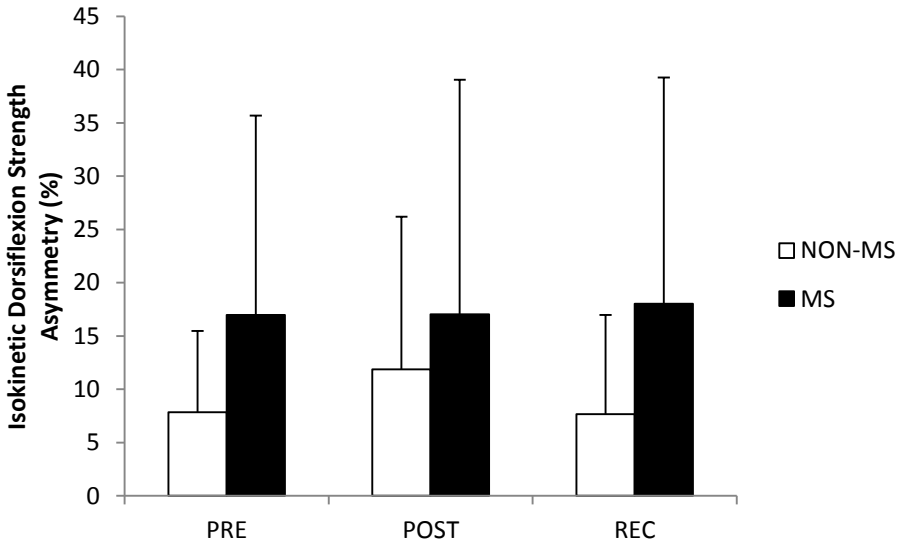
Group means for isokinetic SA at each time point are shown in Table 13. Results of the two-way repeated measures ANOVA indicated that there was no group x time interaction for SA when looking at PRE, POST, and REC (Figure 14). There was a moderate effect size between groups at the PRE time points (d = 0.64), weak effect size at the POST time point (d = 0.40), and moderate effect size at the REC time point (d = 0.74). Individual isokinetic SA responses at each time point are shown graphically in Figure 15a and Figure 15b for the MS group and NON-MS group respectively.

Table 13. Isometric and Isokinetic Dorsiflexion Strength Asymmetry in Fatigue Tests

	NON-MS			MS		
	PRE	POST	REC	PRE	POST	REC
Isometric PT SA (%)	3.4 ± 3.1	8.9 ± 11.6*	8.4 ± 12.5*	12.7 ± 19.1	16.2 ± 24.5	16.2 ± 23.8
Isokinetic PT SA (%)	7.8 ± 7.6	11.9 ± 7.6	7.7 ± 6.8	17.0 ± 18.7	17.0 ± 16.8	18.0 ± 18.7

Data are mean ± SD. PT, peak torque; SA, strength asymmetry. * $p < 0.05$ represents statistically significant difference from the PRE value.

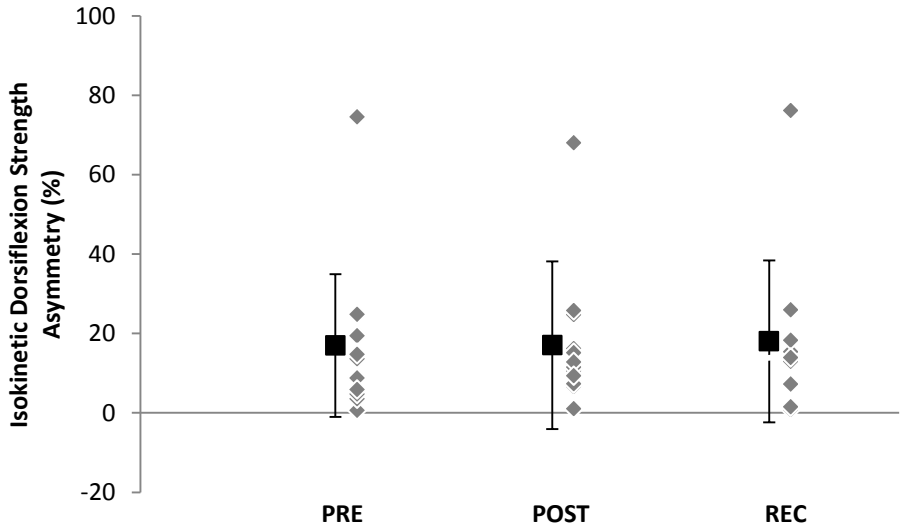
Figure 14. Mean Group Isokinetic Dorsiflexion Strength Asymmetry at each Time Point



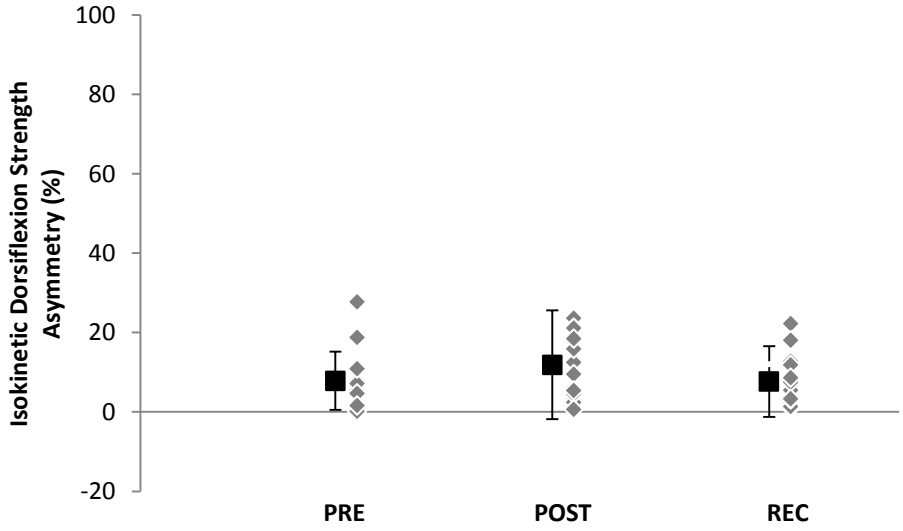
Values are means ± SD.

Figure 15. Individual Isokinetic Dorsiflexion Strength Asymmetry at each Time Point

15a – MS



15b – NON-MS



Values are means ± SD.

Isokinetic dorsiflexion PT values at each time point for both groups are shown in Table 14. The two-way repeated measures ANOVA indicated a limb x time interaction for isokinetic dorsiflexion PT in the MS group ($F = 3.5$, $p = 0.045$, $\eta^2 = 0.23$). There was a significant time effect as well ($F = 40.0$, $p < 0.001$, $\eta^2 = 0.92$) and post-hoc analysis indicated both limbs significantly decreased PT from PRE-POST, and significantly increased POST-REC, but still significantly less PRE-REC (Figure 16a). There was also a significant limb interaction in the MS group ($F = 13.9$, $p = 0.003$, $\eta^2 = 0.78$) and post-hoc analysis indicated a mean difference at the PRE time point (mean ± SD: Strong vs. Weak = 25.7 ± 6.7 vs. 21.8 ± 8.0, $p < 0.001$) and at the REC time point (mean ± SD: Strong vs. Weak = 22.9 ± 6.1 vs. 19.4 ± 6.4, $p = 0.002$). There was a moderate effect size in the MS group between limbs at the POST time point ($d = 0.59$) and a large effect size at the PRE and REC time point ($d = 1.25$, and 0.93 respectively).

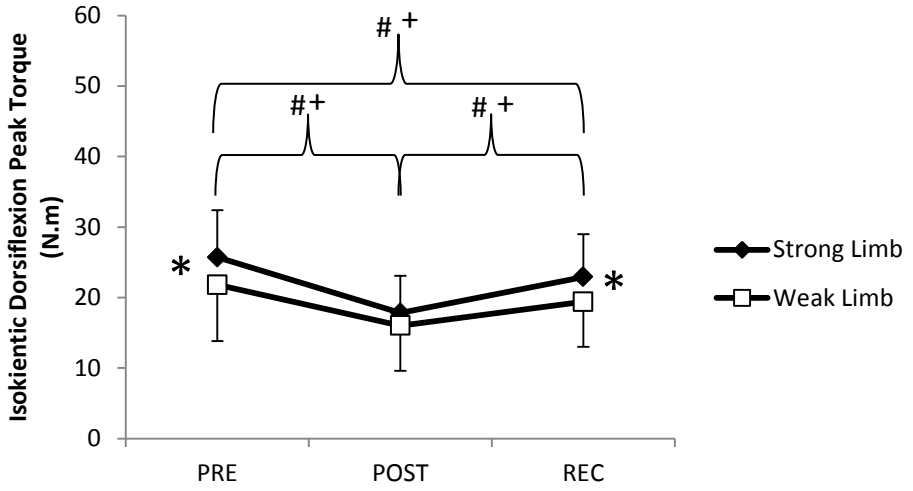
Table 14. Isokinetic Peak Torque and Voluntary Contraction Time during Fatigue Test

		NON-MS			MS		
		PRE	POST	REC	PRE	POST	REC
Isokinetic PT (N·m)	Strong	23.4 ± 7.9	14.6 ± 5.2[a]	19.9 ± 6.4[ab]	25.7 ± 6.7	17.8 ± 5.3[a]	22.9 ± 6.1[ab]
	Weak	21.8 ± 8.3*	13.5 ± 4.4[a]*	18.7 ± 5.8[ab]*	21.8 ± 8.0*	16.0 ± 6.4[a]	19.4 ± 6.4[ab]*
Isokinetic VCT(ms)	Strong	541 ± 102	632 ± 80.7[a]	537 ± 119[b]	578 ± 207	628 ± 181	587 ± 179
	Weak	536 ± 82.8	639 ± 121[a]	569 ± 59.2[b]	535 ± 64.0	632 ± 93.6[a]	552 ± 83.0[b]

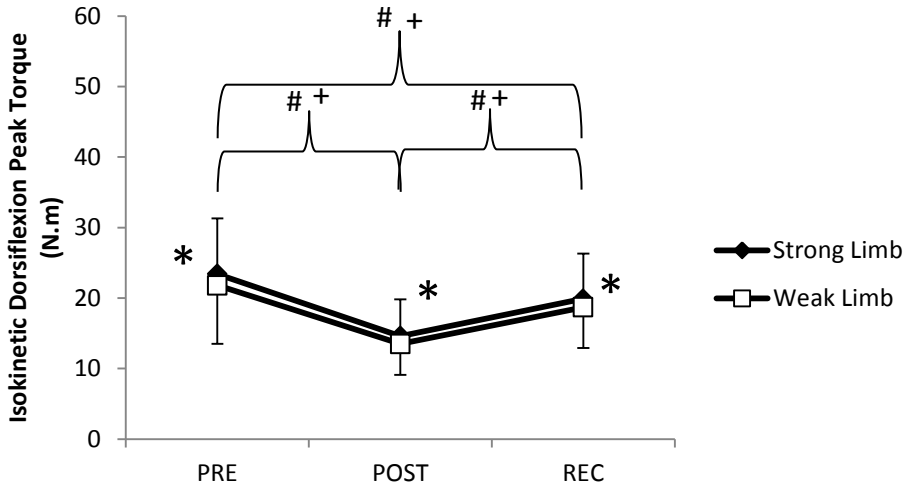
Data are mean ± SD. PT, peak torque; VCT, voluntary contraction time; TRTD, time-rate of muscle tension development. * $p < 0.05$ represents statistically significant limb difference. [a] $p < 0.05$ represents statistically significant difference from the PRE value. [b] $p < 0,05$ represents statistically significant difference from the POST value.

Figure 16. Isokinetic Dorsiflexion Peak Torque at each Time Point

16a – MS



16b – NON-MS



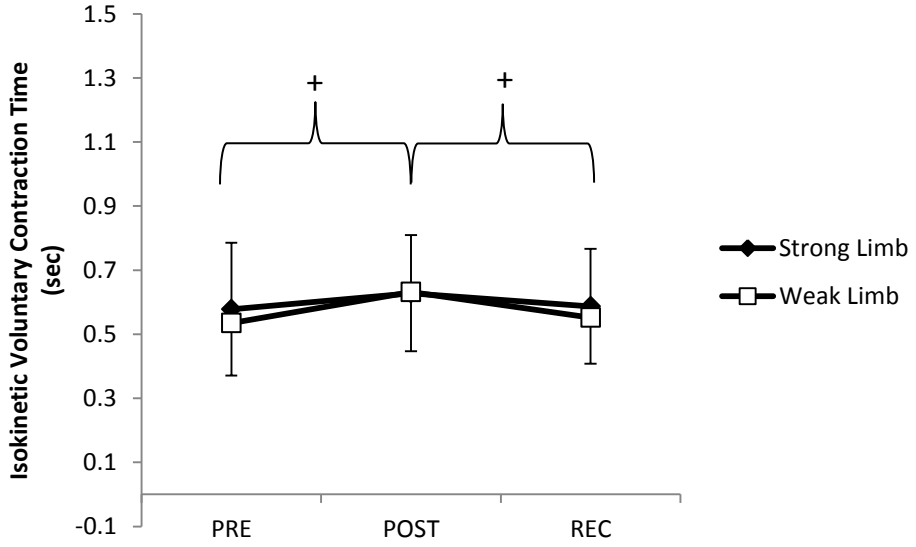
Values are means ± SD. Values are means ± SD. * $p < 0.05$ represents statistically significant difference between limbs. # $p < 0.05$ represents statistically significant time difference in the strong limb. + $p < 0.05$ represents statistically significant time difference in the weak limb.

There was no limb x time interaction for isokinetic dorsiflexion PT in the NON-MS group. There was however a significant time interaction ($F = 35.7$, $p < 0.001$, $\eta^2 = 0.98$) and post-hoc analysis indicated both limbs significantly decreased PT from PRE-POST, and significantly increased POST-REC, but still significantly less PRE-REC (Figure 16b). There was also a significant limb effect ($F = 11.0$, $p = 0.006$, $\eta^2 = 0.58$) and post-hoc analysis indicated a mean limb difference at the PRE time point (mean ± SD: Strong vs. Weak = 23.4 ± 7.9 vs. 21.8 ± 8.3, $p = 0.003$,), POST time point (mean ± SD: Strong vs. Weak = 14.6 ± 5.2 vs. 13.5 ± 4.4, $p = 0.04$), and REC time point (mean ± SD: Strong vs. Weak = 19.9 ± 18.7 vs. 18.7 ± 5.8, $p = 0.03$).

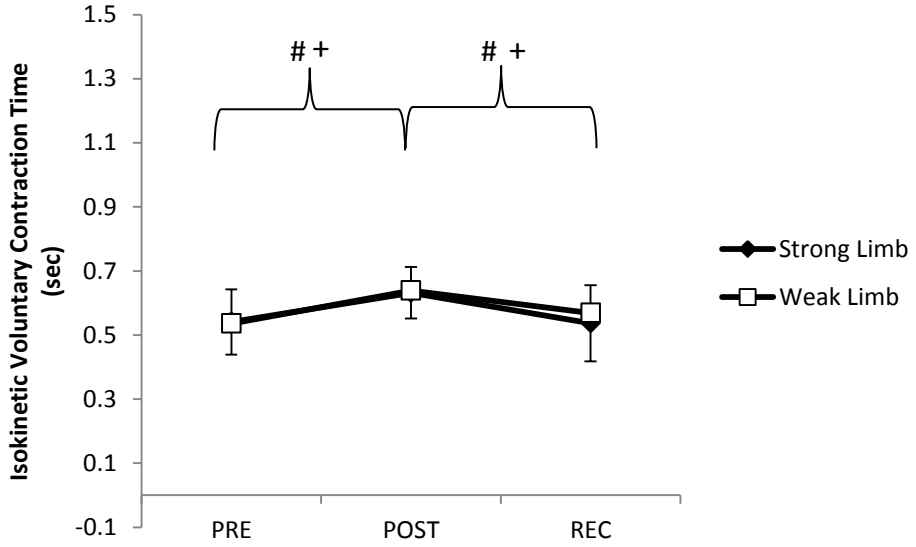
Table 14 shows the results of isokinetic VCT for each limb at each time point. The two-way repeated measures ANOVA indicated no limb x time interaction for isokinetic VCT in either group. There was however a significant time effect in the MS group ($F = 16.3$, $p < 0.001$, $\eta^2 = 0.36$). Post-hoc analysis indicated a significant increase in VCTPRE-POST and a significant decrease POST-REC in the strong limb of the MS group ($p = 0.001$ and 0.003 respectively; Figure 17a).

Figure 17. Isokinetic Dorsiflexion Voluntary Contraction Time at each Time Point

17a – MS



17b – NON-MS



Values are means ± SD. # $p < 0.05$ represents statistically significant time difference in the strong limb. + $p < 0.05$ represents statistically significant time difference in the weak limb.

There was a significant time interaction in the NON-MS group for VCT ($F = 19.1$, $p < 0.001$, $\eta^2 = 0.64$). Post-hoc analysis showed both limbs significantly increased PRE-POST and significantly decrease POST-REC ($p < 0.01$; Figure 17b). Effect size values for all time points for isokinetic VCT and PT from visit 4 are shown in Table 15.

Table 15. Effect Size for Isokinetic Dorsiflexion Peak Torque and Voluntary Contraction Time from Fatigue Testing

	NON-MS		MS	
	Isokinetic PT (N·m)	Isokinetic VCT (s)	Isokinetic PT (N·m)	Isokinetic VCT (s)
	Cohen's d	Cohen's d	Cohen's d	Cohen's d
Strong Limb PRE-POST	2.33*	1.60*	2.33*	0.54
Strong Limb PRE-REC	1.54*	0.05	1.50*	0.09
Strong Limb POST-REC	2.41*	1.36*	1.99*	1.54
Weak Limb PRE-POST	1.93*	1.00*	1.39*	0.99*
Weak Limb PRE-REC	1.29*	0.52	0.97*	0.19
Weak Limb POST-REC	2.23*	0.86*	1.30*	0.93*
Limb Difference PRE	1.28$^+$	0.07	1.25$^+$	0.23
Limb Difference POST	0.60$^+$	0.06	0.59	0.05
Limb Difference REC	0.64$^+$	0.54	0.93$^+$	0.22

Data are Cohen's d. PT, peak torque; VCT, voluntary contraction time. * $p < 0.05$ represents statistically significant time difference. $^+$ $p < 0.05$ represents statistically significant limb difference.

Functional Performance Tests

The results of the functional performance tests are presented in Table 16. Independent t-tests indicated there was a significant between group differences in all three functional performance tests. The MS group exhibited significantly greater time

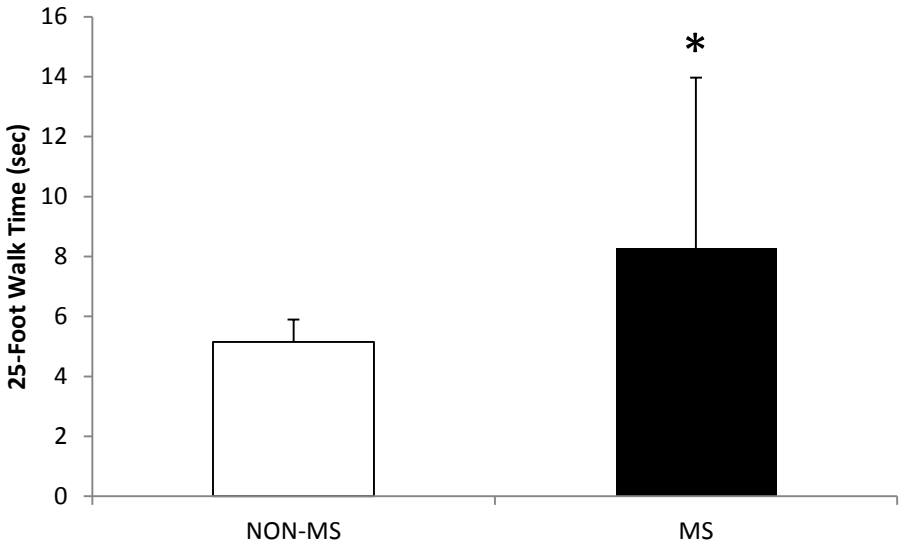
to perform the 25W test (mean ± SD: MS vs NON-MS = 8.3 ± 5.7 vs. 5.2 ± 0.7, p = 0.03; Figure 18), significantly decreased gait speed assessed by the 25W test (mean ± SD: MS vs NON-MS = 1.2 ± 0.4 vs. 1.5 ± 0.2, p = 0.01; Figure 19), significantly greater time to perform TUG test (mean ± SD: MS vs NON-MS = 10.7 ± 9.4 vs. 6.1 ± 1.1, p = 0.04; Figure 20), and significantly less distance covered during the 6MW test (mean ± SD: MS vs NON-MS = 418.5 ± 157.9 vs. 523.9 ± 67.9, p = 0.04; Figure 21) than the NON-MS group. There was a moderate between groups effect size for the TUG test (d = 0.72) and a large effect size for the 25W test, walking speed assessed by the 25W test, and the distance covered during the 6MW test (d = 0.80, 1.11, and 0.92 respectively).

Table 16. Functional Performance Testing

Variable	NON-MS	MS	*p*	d
25W Time (s)	5.2 ± 0.7	8.3 ± 5.7	0.03*	0.80
Gait Speed (m/s)	1.5 ± 0.2	1.2 ± 0.4	0.01*	1.11
TUG Time (s)	6.1 ± 1.1	10.7 ± 9.4	0.04*	0.72
6MW Distance (m)	523.9 ± 67.9	418.5 ± 157.9	0.04*	0.92

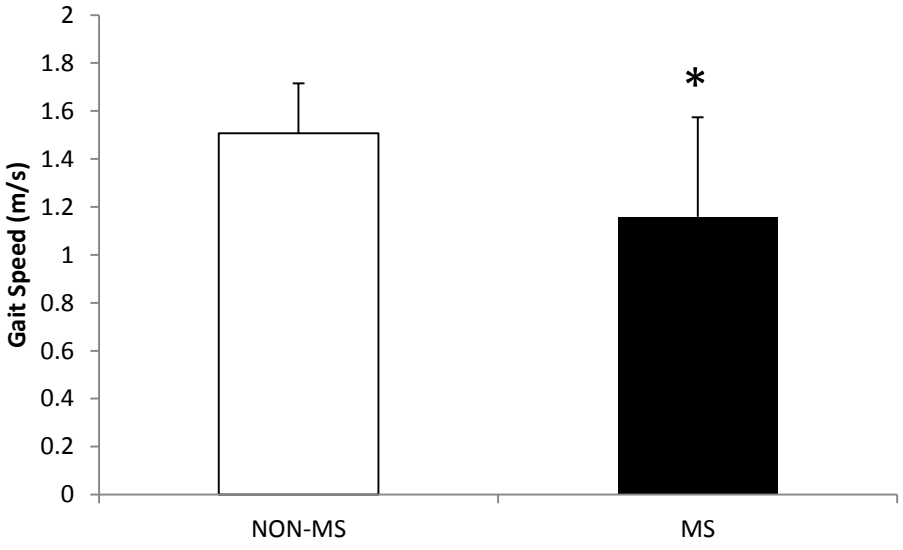
Data are mean ± SD; * $p < 0.05$ represents statistically significant group differences.

Figure 18. Mean Time Values of the 25-Foot Walk Test



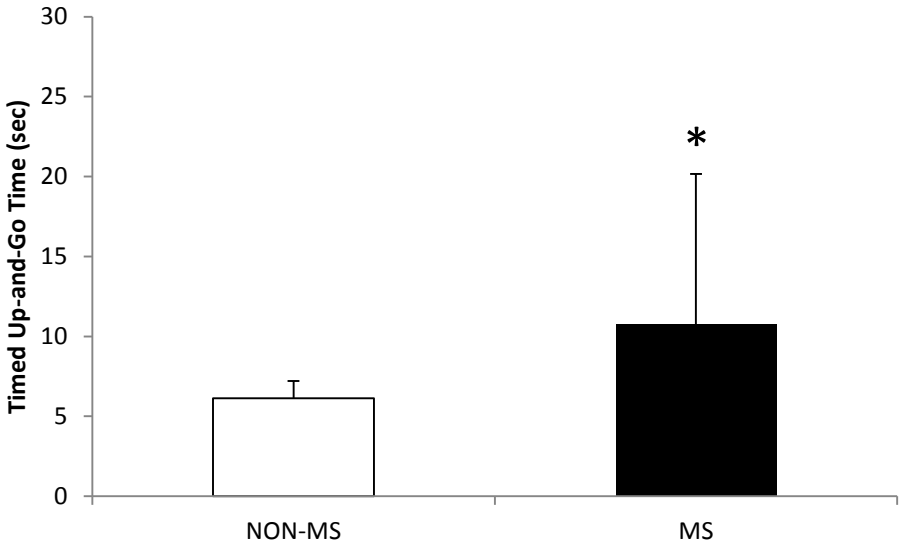
Values are means ± SD. * $p < 0.05$ represents statistically significant group difference.

Figure 19. Mean Gait Speed from the 25-Foot Walk Test



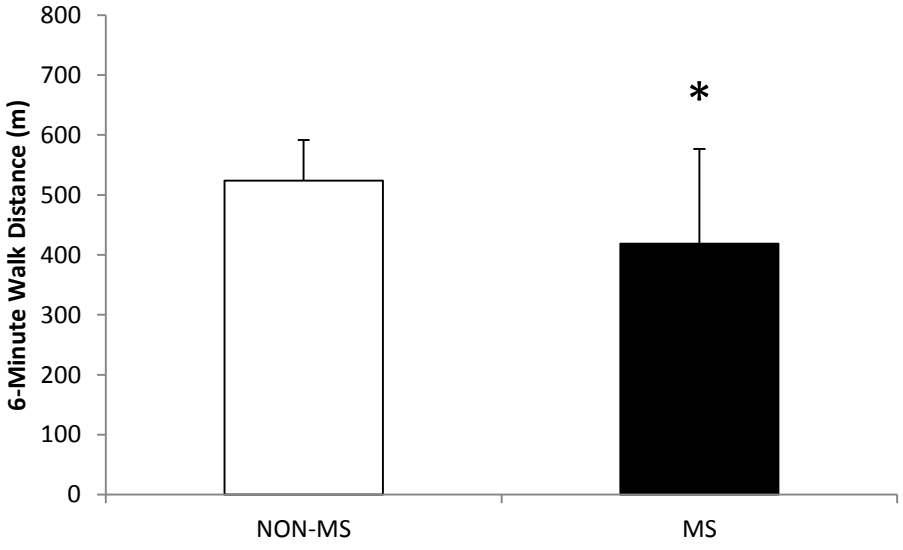
Values are means ± SD. * $p < 0.05$ represents statistically significant group difference.

Figure 20. Mean Time from the Timed Up-and-Go Test



Values are means ± SD. * $p < 0.05$ represents statistically significant group difference.

Figure 21. Mean Distance from the 6-Minute Walk Test



Values are means ± SD. * $p < 0.05$ represents statistically significant group difference.

Walking Performance and SA Relationship

Linear correlations were measured to assess the relationship between functional performance of the walking tests, EDSS, isometric SA and isokinetic dorsiflexion SA at 60°/sec. The results for all 26 pooled subjects are presented in Table 17. There was a significant correlation between all three functional performance measurements including gait speed and the isometric SA (Figure 22) and isokinetic SA (Figure 23).

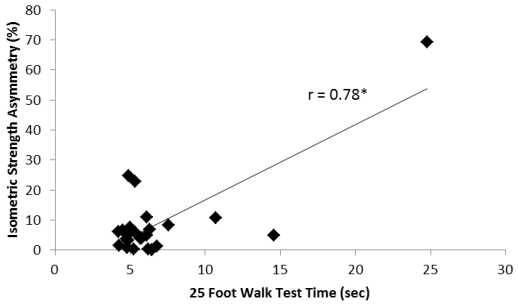
Table 17. Correlation Coefficients for the Relationship between Strength Asymmetry and Functional Performance Tests in all subjects (n = 26)

Pooled Subjects				
Variable	Isometric SA		Isokinetic Dorsiflexion SA	
	r	*p*	r	*p*
25W Time	0.78	<0.001*	0.89	<0.001*
Gait Speed	-0.52	0.006*	-0.68	<0.001*
TUG Time	0.65	<0.001*	0.78	<0.001*
6MW Distance	-0.47	0.02*	-0.62	<0.001*

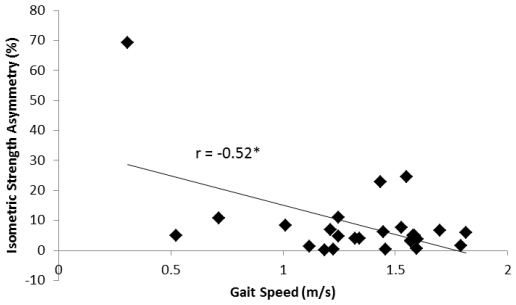
Data are linear r correlation coefficients. 25WT, 25 foot walk test; TUG, timed up and go test; 6MW, 6 minute walk test; SA, strength asymmetry; EDSS, expanded disability status scale. * $p < 0.05$ represents statistically significant correlations

Figure 22. Correlation Coefficients between Isometric Strength Asymmetry and Functional Performance Tests in both groups (n = 26)

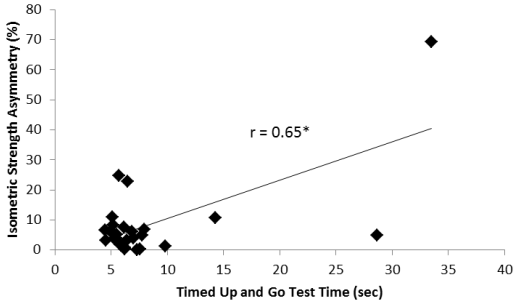
22a – 25-Foot Walk Test



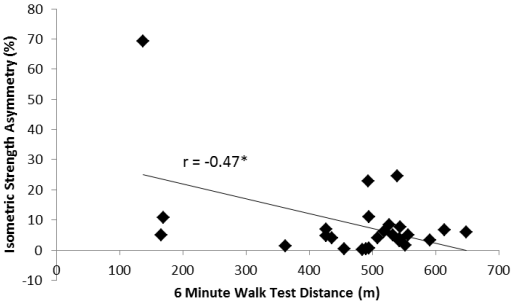
22b – Gait Speed



22c – Timed Up-and-Go Test



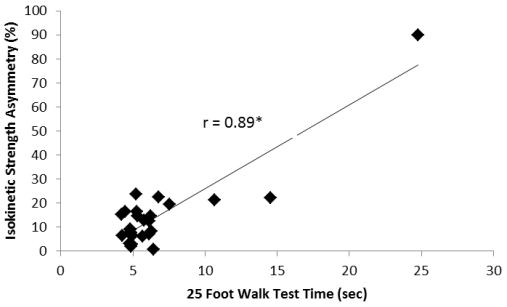
22d – 6-Minute Walk Test



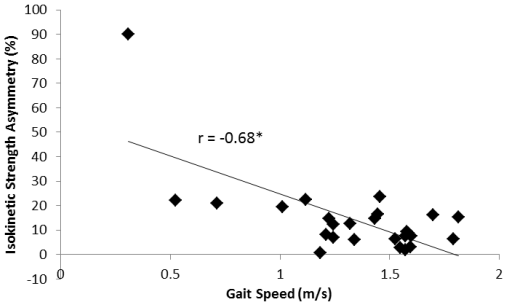
Values are means ± SD. * p <0.05 represents statistically significant correlation.

Figure 23. Correlation Coefficients between Isokinetic Strength Asymmetry and Functional Performance Tests in both groups (n = 26)

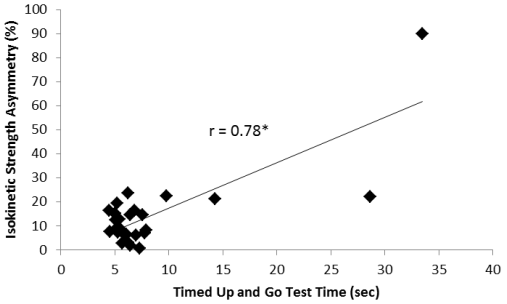
23a – 25-Foot Walk Test



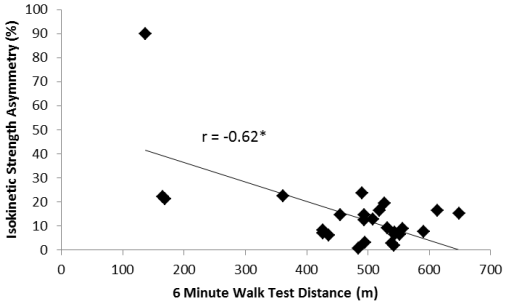
23b – Gait Speed



23a – Timed Up-and-Go Test



23b – 6-Minute Walk Test



Values are means ± SD. * $p < 0.05$ represents statistically significant correlation.

Groups were separated to investigate the linear correlation in each group separately. In the NON-MS group, there were no significant correlations between any of the functional performance tests and isometric/isokinetic dorsiflexion SA (Table 18). Results of the MS group correlations are shown in Table 19. In the MS group, there was a significant positive correlation between the 25W test and TUG for isometric SA (r = 0.76 and 0.61 respectively; Figure 24). There was a significant positive correlation between the 25W test and TUG for isokinetic dorsiflexion SA (r = 0.93 and 0.81 respectively) and a significant negative correlation between gait speed and 6MW for isokinetic dorsiflexion SA (r = -0.76 and -0.67 respectively; Figure 25). Results of the MS group EDSS correlation coefficients are shown in Figure 26. When comparing functional performance tests to EDSS, there was a significant positive correlation between 25 W test and TUG (r = 0.69 and r = 0.72 respectively). There was also a significant negative correlation between EDSS and gait speed (r = -0.75) and 6MW distance (r = -0.78).

Table 18. Correlation Coefficients for the Relationship between Strength Asymmetry and Functional Performance Tests in NON-MS (n = 13)

	NON-MS			
Variable	Isometric SA		Isokinetic Dorsiflexion SA	
	r	*p*	r	*p*
25W Time	-0.40	0.18	-0.17	0.57
Gait Speed	0.38	0.20	0.17	0.58
TUG Time	-0.45	0.12	-0.29	0.34
6MW Distance	0.47	0.11	0.22	0.48

Data are linear correlation coefficients. 25WT, 25 foot walk test; TUG, timed up and go test; 6MW, 6 minute walk test; SA, strength asymmetry; EDSS, expanded disability status scale. * $p < 0.05$ represents statistically significant correlation.

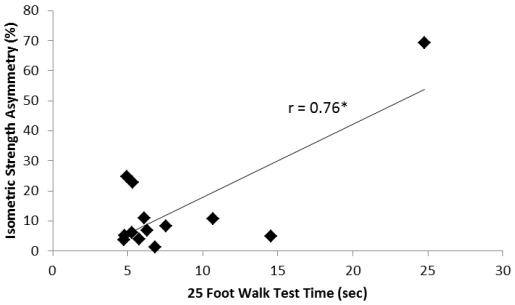
Table 19. Correlation Coefficients for the Relationship between Strength Asymmetry and Functional Performance Tests in Multiple Sclerosis (n = 13)

	MS					
Variable	Isometric SA		Isokinetic Dorsiflexion SA		EDSS	
	r	*p*	r	*p*	r	*p*
25W Time	0.76	0.002*	0.93	<0.001*	0.69	0.009*
Gait Speed	-0.50	0.08	-0.76	0.002*	-0.75	0.003*
TUG Time	0.61	0.03*	0.81	<0.001*	0.72	0.005*
6MW Distance	-0.43	0.14	-0.67	0.01*	-0.78	0.002*

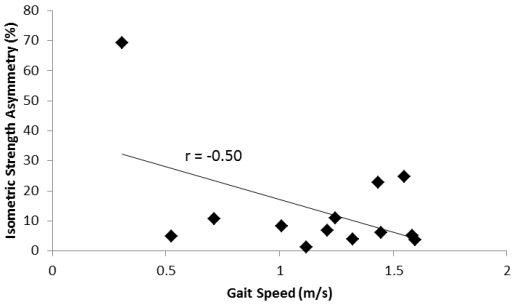
Data are linear correlation coefficients. 25WT, 25 foot walk test; TUG, timed up and go test; 6MW, 6 minute walk test; SA, strength asymmetry; EDSS, expanded disability status scale. * $P < 0.05$ represents statistically significant correlation.

Figure 24. Correlation Coefficients between Isometric Strength Asymmetry and Functional Performance Tests in Multiple Sclerosis (n = 13)

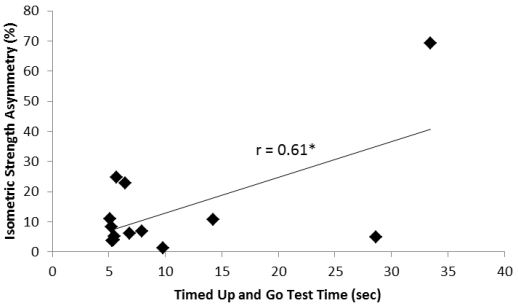
24a – 25-Foot Walk Test



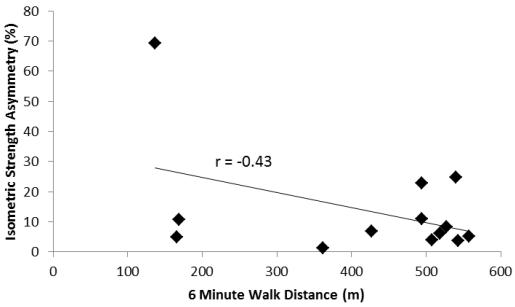
24b – Gait Speed



24a – Timed Up-and-Go Test



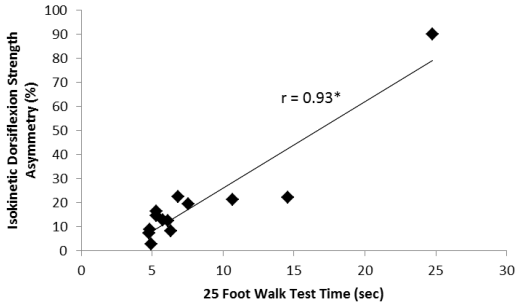
24b – 6-Minute Walk Test



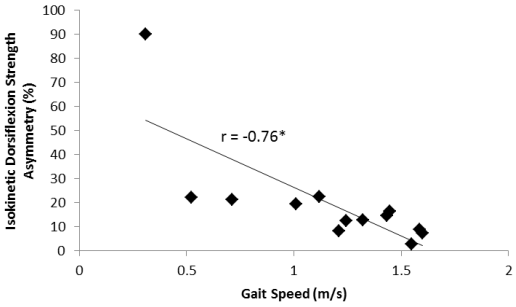
Values are means ± SD. * $p < 0.05$ represents statistically significant correlation.

Figure 25. Correlation Coefficients between Isokinetic Strength Asymmetry and Functional Performance Tests in Multiple Sclerosis (n = 13)

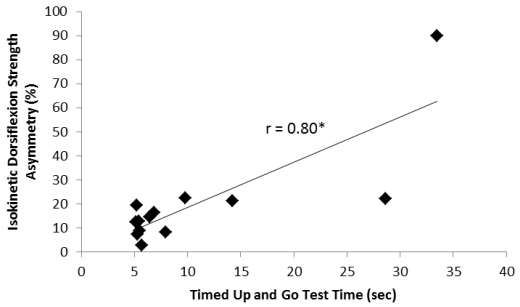
25a – 25-Foot Walk Test



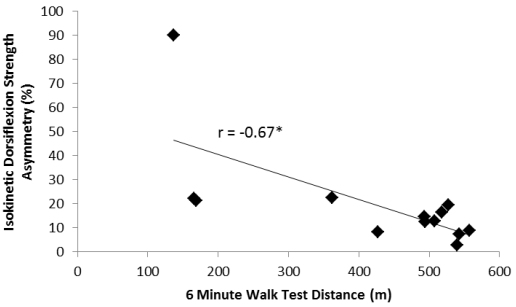
25b – Gait Speed



25a – Timed Up-and-Go Test



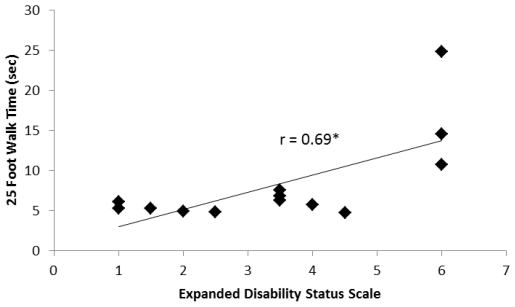
25b – 6-Minute Walk Test



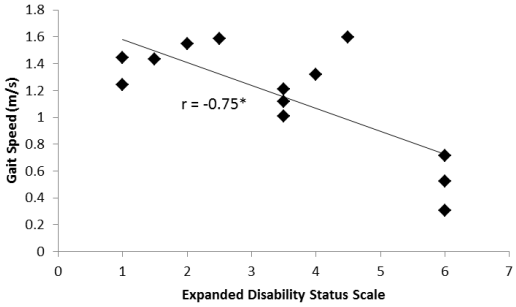
Values are means ± SD. * $p < 0.05$ represents statistically significant correlation.

Figure 26. Correlation Coefficients between Expanded Disability Status Scale and Functional Performance Tests in Multiple Sclerosis (n = 13)

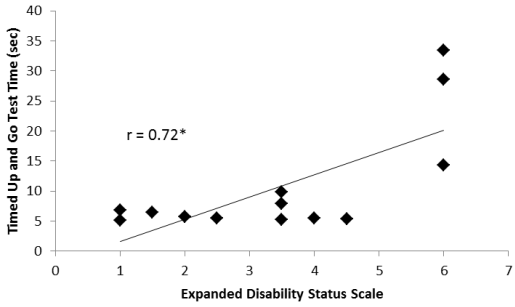
26a – 25-Foot Walk Test



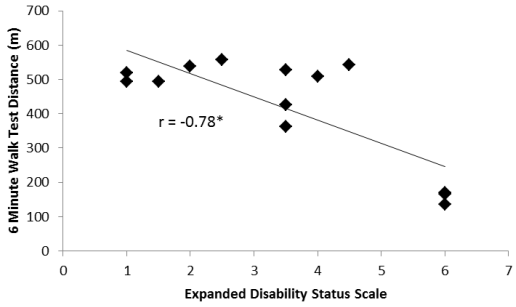
26b – Gait Speed



26a – Timed Up-and-Go Test



26b – 6-Minute Walk Test



Values are means ± SD. * $p < 0.05$ represents statistically significant correlation.

Discussion

Main Findings

The main findings of this study are as follows:

1) Individuals with MS exhibited a bilateral difference in isometric dorsiflexion strength. The asymmetry for isometric dorsiflexion strength was significantly greater in the MS group than in the NON-MS group.
2) Individuals with MS exhibited a bilateral difference in isokinetic dorsiflexion strength at all four speeds tested; 30^{o}/sec, 60^{o}/sec, 90^{o}/sec, and 120^{o}/sec. The asymmetry for isokinetic dorsiflexion strength as a group was not significantly greater in the MS group than the NON-MS group.
3) Individuals with MS exhibited bilateral differences in the muscle performance variables VCT and MTMC examined in the isometric dorsiflexion strength testing.
4) Individuals with MS did not exhibit a bilateral difference in fatigability of the dorsiflexors during isometric exercise.
5) Individuals with MS did not exhibit a bilateral difference in fatigability of the dorsiflexors during isokinetic exercise. There was no bilateral difference in fatigability between groups.
6) Individuals with MS exhibited a bilateral difference in isometric dorsiflexion strength and in muscle performance variables MTMC, TRTD, and VCT before and after fatiguing exercise.

7) Individuals with MS exhibited a bilateral difference in isokinetic dorsiflexion strength and in the muscle performance variable VCT before and after fatiguing exercise.
8) Individuals with MS exhibited a significant decrement in functional performance testing compared to the NON-MS group.
9) Individuals with MS exhibited a significant correlation between strength asymmetry and the functional performance tests. The correlation between strength asymmetry and functional performance tests were greater than correlations in the NON-MS group.

Maximal Torque Testing

The results of the isometric strength testing agree with our hypothesis, that the MS group would exhibit a significant difference between the strong and the weak limb in isometric strength. To our knowledge, this is the first study to show a significant difference in dorsiflexion isometric PT, which is in contrast with previous studies analyzing dorsiflexion strength in MS patients (15, 35). The difference between these studies results and our own may be due to the current study analyzing the limbs based on strength as opposed to the more common right-left or dominance comparisons (14, 15, 35, 45). Due to the heterogeneity of MS, we decided defining the limbs based on strength would be better for assessment of any clinical implications the results may have. This analysis is similar to previous studies that have shown bilateral differences in isometric strength of the knee flexors (40, 46, 47).

Further analysis of the bilateral strength differences by calculating isometric SA showed that the MS group exhibited significantly greater isometric SA. SA has previously been calculated in MS subjects to investigate bilateral differences in muscular strength (15, 35, 77). The results of the current study agree with previous work by Kalron et al. (2011) in clinically isolated MS patients (35). Chung et al. (2008) found a non-significant difference in isometric dorsiflexion SA (mean difference: 1.6%), while Kalron et al. (2011) found a significant difference (mean difference: 6.6%), albeit lower than the difference in the current study (mean difference: 10.4%). One unique aspect of the current study was having subjects lie in the supine position during testing as opposed to the more common testing of having subjects seated (15). We chose to test subjects in the supine position to mimic the position the body would be in during walking, which is similar to the testing position when MS patients exhibited a greater isometric dorsiflexion SA than individuals without MS in previous research (35).

The results of the isokinetic strength testing showed the strong limb to be significantly stronger than the weak limb in the MS group at all four testing speeds; 30^{o}/sec, 60^{o}/sec, 90^{o}/sec, and 120^{o}/sec. This is in agreement with our hypothesis that there would be bilateral strength differences in the MS group for isokinetic dorsiflexion PT. To our knowledge this is one of the first studies to investigate bilateral differences in isokinetic exercise testing of the dorsiflexors. Researchers have used isokinetic testing to examine limb differences for knee extension/flexion in MS patients, but they did not show any significant limb differences (45). The NON-MS group also exhibited a significant mean limb difference for isokinetic PT at each speed.

Cohen's d effect size analysis showed a weak effect size between limbs at all speeds in the NON-MS group (d = 0.27, 0.27, 0.32, and 0.43 respectively), and a moderate effect at speeds 30^{o}/sec, 60^{o}/sec, and 90^{o}/sec and a large effect size at 120^{o}/sec (d = 0.54, 0.74, 0.73, and 0.83) in the MS group.

Isokinetic SA analysis showed that MS patients did not exhibit isokinetic asymmetry that was significantly different from the NON-MS group. This disagrees with our hypothesis that the MS group would exhibit greater asymmetry than the NON-MS group. However, effect size calculations indicated a weak effect between group isokinetic SA means at 30^{o}/sec, a moderate effect at 60^{o}/sec and 90^{o}/sec, and a trivial effect at 120^{o}/sec (d = 0.39, 0.69, 0.56, and 0.16 respectively). Closer examination of the data show that both groups had increased SA with increasing contraction speed; however it seemed to plateau in the MS group after 60^{o}/sec. The difference between the two groups at the 60^{o}/sec speed was similar to that of the isometric SA which showed significant group difference (isometric SA vs isokinetic SA: 10.4 % and 10.8 % respectively). Dorsiflexion during walking in individuals with hemiparesis commonly moves between 30^{o}/sec-60^{o}/sec and that may be why isokinetic SA did not show further increases in the MS group (70). Further studies should investigate the effect of contraction speed on SA to clarify the ceiling effect observed in the current study.

As expected, when the contraction speed increased in the NON-MS group the isokinetic PT declined significantly in both limbs (73). In the MS group, the strong limb

followed a similar pattern as the NON-MS group, however in the weak limb there was not a significant decline in strength between 90^{o}/sec-120^{o}/sec. The lack of a significant decrease in PT between 90^{o}/sec-120^{o}/sec in the weak limb also was the only speed difference that did not exhibit a large effect for mean difference (d = 0.67). The inability for the weak limb to produce higher torque values at the 90^{o}/sec speed may be related to the limited ankle muscle recruitment that has been shown to occur during walking in MS patients (56). This would agree with research by Newsome et al. (2011) which showed dorsiflexion in the weak limb to be negatively related to walking speed (65). Alterations in gait kinematics may lead to an increased risk in falls, therefore future research should investigate the relationship between weak limb isokinetic strength and fall risk in MS patients.

Muscle Performance Variables

To further investigate bilateral difference in muscle function, muscle performance variables were calculated from the isometric strength testing. The results of VCT indicated a significant limb effect, and post-hoc analysis showed that the MS group exhibited slower VCT in the strong limb than the weak limb. Post-hoc analysis also showed that VCT in the strong limb was slower in the MS group compared to the NON-MS group. Slower VCT in the strong limb in MS patients may be due to a reduction in motor unit firing rates and impaired motor unit recruitment (25). MS is a centrally mediated disease, therefore MS patients may show impaired activation of the muscle translating to slower VCT. The demyelination in the CNS presumably would

reduce the spinal excitability and result in a reduction in motor unit recruitment (74). Previous work in the dorsiflexors has shown lower central activation in MS patients than individuals without MS and this inability to activate the muscle during maximal exercise may be due in part to this central impairment (15, 74). While central impairment is evident, alterations to the periphery can cause impaired excitation in the muscle. Similar to our result, Kent Braun et al. (1994) showed that MS patients exhibit prolonged twitch contraction time and tetanic force relaxation time, suggesting altered excitation-contraction coupling (38, 82). The impaired excitation-contraction coupling may be due to altered muscle metabolism as well as less muscle fibers containing type II myosin heavy chain and reduction in cross bridge numbers (25). The slowed VCT in the present study in the strong limb may suggest altered muscle characteristics in the weaker limb, and the ability to produce force at a faster rate in the weaker limb may be a compensatory mechanism due to lower strength necessary for motor gait (1).

In the present study, the MS group also exhibited a bilateral difference for MTMC. Our results indicated a significant group x limb interaction, and a limb effect for MTMC. Post-hoc analysis showed that the MS group exhibited significantly greater MTMC in the strong limb compared to the weak limb. MTMC is a measure of sustained maximal force and requires coordination of multiple muscle groups to produce smooth movements (14). Activation of the agonist muscle (anterior tibialis) and deactivation of the antagonist muscle (plantarflexors) is required to produce steady force for a given time (14). These requirements to sustain a maximal

contraction may be difficult in MS patients whom are prone to increased fatigability and muscle incoordination. Short duration of force generation and sustained force is necessary for posture and balance, and the altered posture and balance in MS patients may be due to central impairments from neural disturbances caused by demyelination. The lower MTMC in the weak limb may be a sign of increased fatigability of the weak limb, or a lack of central drive to recruit and sustain activation of motor units (74).

Researchers have previously shown a reduction in MTMC in MS patients compared to individuals without MS (14). The results of the current study did not show a group difference between the MS group and the NON-MS group. Because the calculation of MTMC uses an integral function that includes maximal torque achieved, initial strength would have a strong positive correlation with MTMC. In the current study, the MS group had higher strength values than the NON-MS group which may provide reason for the lack of group differences. Future research may look into central and peripheral causes of the reduced MTMC in the weak limb in MS patients.

There was not a significant difference between groups or limbs for TRTD. TRTD is a measure of force development, and previously MS patients have been shown to have impaired rate of force development in the anterior tibialis muscle (67). The differing results may be due to the difference in rate of force development calculations. Traditional calculations are made by finding the maximum slope of the MVC curve; however we chose to simply divide PT by the time it took to reach PT from the initiation of the contraction. We used this calculation of force development

because it is similar to previous analysis in MS patients (14). The rate of force development requires activation of motor units and the execution of adequate excitation-contraction coupling, both of which are impaired in MS patients (38, 82). Rate of force development calculated in the traditional sense has been shown to be asymmetric in the knee extensors and flexors of MS patients (40). Future research should quantify the rate of force development using the maximum slope of the MVC curve in the dorsiflexors to examine any asymmetries present.

Isometric Fatigue

We hypothesized that bilateral differences would occur during the isometric fatigue test, to which our results showed no significant bilateral difference in the MS group. The use of a relative force value (30% MVC) in the current study may be the reason for similar fatigability between the two limbs. NG et al. (2000) used a similar protocol using 30% MVC during their endurance test of the dorsiflexors and did not show a group difference between MS patients and individuals without MS. Ng et al. (2000) did have a similar effect size between groups for fatigue test time (d = 0.90) as the effect size in the weak limb of the current study (d = 0.78). It should also be noted that there was a moderate effect in the fatigue time of the strong limb between groups, although not significantly different (d = 0.63). Fatigue rates may differ in MS patients due to a suppressed mean arterial pressure response and altered metabolic (phosphate, phosphocreatine, pH, and $H_2PO^-_4$) responses during exercise (38, 66). While our results did not show a significant limb difference in the MS group, further

studies should evaluate the potential difference in limb fatigue as it relates to metabolic processes.

Isometric MVC's were conducted before exercise (PRE), immediately after exercise (POST), and after 2 minutes of recovery (REC). When investigating isometric SA at all three time points between groups, the results of the two-way repeated measures ANOVA indicated no significant group x time interaction. This is in disagreement with our hypothesis that the MS group would exhibit greater asymmetry than the NON-MS group. The NON-MS group did exhibit a significant increase in asymmetry after exercise that was still significantly higher after two minutes of recovery. The isometric PT decreased significantly PRE-POST in both limbs of the MS group and the NON-MS group and significantly increased POST-REC, although still significantly less than PRE-REC. Post-hoc analysis indicated a significant mean difference for PT between limbs in the MS group at the PRE and REC time points. As discussed above, this agrees with earlier work by Kalron et al. (2011) that there is greater isometric SA in the dorsiflexors of MS patients compared to individuals without MS. Other researchers have investigated bilateral differences over the course of fatiguing exercise but did not show asymmetrical differences between MS patients (81, 86). These studies were conducted in the hand muscles and data was analyzed based on limb dominance, as opposed to the stronger-weaker method utilized in the current study. In the current study there was a non-significant increase in isometric SA in both groups after the fatiguing exercise that did not decrease after two minutes of recovery which is expressed by the decrease in effect size over the course of the testing (d= 0.74

and 0.54 respectively). The NON-MS group did not show any mean limb differences of isometric PT at any of the time points, which agrees with previous research in the hands (87). The lack of bilateral PT difference in the MS group immediately after exercise may suggest attenuation in bilateral strength differences in a fatigued state. This may be due to independent central adaptive motor control mechanisms in the strong and weak limb to cause the decrement in force to be greater in the strong limb (87).

The isometric MVC's PRE, POST, and REC also indicated significant bilateral differences in the muscle performance variables measured. MTMC showed a significant time and limb effect in the MS group. MTMC was utilized to assess the individual's ability to maintain a maximal force, an indirect measure of central drive during the isometric task (87). The strong limb in the MS group showed a similar trend to both limbs in the NON-MS group, decreasing PRE-POST but increasing POST-REC, although still significantly less than PRE. In the weak limb, there was only a significant difference between PRE-POST and PRE-REC. This suggests that the strong limb was able to regain central drive after the two minutes of recovery, while the weak limb had still not recovered. The lack of recovery in the weak limb also elicited a significant limb difference at the REC time point. Maintaining maximal force requires the continued recruitment of motor units over a period of time. MS patients have shown lower levels of central activation during isometric exercise in the dorsiflexors when compared to individuals without MS (67). Researchers previously have shown that submaximal fatiguing exercise may lead to an enhanced central motor drive indicated

by motor evoked potential amplitude (87). The increased central drive during the submaximal fatigue test may have led to the weak limb MTMC not recovering. MS patients have also been shown to have slower rates of phosphocreatine recovery kinetics, which may lead to inadequate recovery in the weak limb (82). Future research should investigate the independent central and peripheral mechanisms that may lead to different limb responses to fatiguing exercise.

There were no significant group differences for TRTD in current study at PRE or POST time points. TRTD was assessed to measure rate of force production (14). Rate of force development would be an indication of central motor function or the ability to develop force quickly. The dorsiflexors have previously been shown to elicit similar force development from stimulated tetanic contractions between MS patients and individuals without MS; however they appear to be impaired during voluntary contractions (67). Individuals without MS have shown the rate of force development to decline after fatiguing exercise (67). The results of the current study did not show a significant decline in the NON-MS group, which may be due to the manner in which TRTD was calculated for the current study. We chose to assess TRTD similar to previous work in MS patients, which looks at the rate of force production over the course of a maximal contraction from the onset of the contraction until PT is achieved (14). This assessment allows TRTD to better describe the entire contraction as opposed to small portion of the rise. In individuals without MS the anterior tibialis muscle contains ~ 70% type I muscle fibers and ~62% in MS patients, and type I muscle fibers are fatigue resistant (36). The decrement in PT and rate of force development is

much less pronounced in muscles with a high percentage of type I muscle fibers. This would agree with work by de Ruiter et al (2001) in the adductor pollicis muscle, another muscle with a high percentage of type I fibers, which showed similar rate of force development between MS patients and NON-MS individuals.

The MS group did exhibit a significant decrease in TRTD between time points PRE-POST in the strong limb, showing a large effect (d = 0.80). The decrease of TRTD in the strong limb after fatiguing exercise agrees with previous MS research showing a greater decrement in maximal rate of force rise in the quadriceps muscles (18). Closer examination of the data showed that the p-value between time points in the weak limb also approached significance (p = 0.09), evident by the moderate effect size in the weak limb (d = 0.54). As discussed earlier, MS patients appear to have increased corticomotor excitability during submaximal exercise testing that may cause a greater reduction in central motor drive after a fatiguing test (86). The reduced central motor drive could lead to delayed force production after fatiguing exercise in MS patients.

The current study did not find any limb x time interactions in isometric VCT in either group between PRE-POST. VCT was measured to assess how quickly individuals could produce maximal torque before and after fatiguing exercise (76). These findings agree with previous work in individuals without MS showing that fatiguing exercise does not affect VCT (41).

Isokinetic Fatigue

During the isokinetic fatigue test, there were no group or limb interactions between or within the MS group and the NON-MS group. We hypothesized there to be a bilateral difference in the MS group, which was not supported by the data. The isokinetic fatiguing protocol is similar to that which has been used in individuals without MS (30). Isokinetic exercise has previously been shown to be a safe method of testing in MS patients and has been utilized as a means of inducing fatigue (5, 45, 81). Only one other study looked at dynamic fatigue of the dorsiflexors, and they conducted intermittent foot tapping bouts as opposed to using a dynamometer (86). These dynamic tasks require concentric and eccentric contractions of the agonist muscle and its antagonists, the plantarflexors in this case. The use of multiple muscle groups may attenuate any strength differences between limbs, as one muscle group may be able to make up for the impairment of the other.

Isokinetic MVC's were conducted before exercise (PRE), immediately after exercise (POST), and after 2 minutes of recovery (REC). When investigating isokinetic SA at all three time points between groups, the results of the two-way repeated measures ANOVA found no significant group x time interaction. This does not support our hypothesis that the MS group would exhibit greater bilateral differences than the NON-MS group. There was a significant limb x time interaction in the MS group for isokinetic PT. The isokinetic PT decreased significantly PRE-POST in both limbs of the MS group and the NON-MS group and significantly increased POST-REC, although still

significantly less than PRE. The reduction in dorsiflexion force after dynamic exercise in the MS group and the NON-MS group agrees with the previous dynamic toe-tap exercise by Thickbroom et al. (2008). Post-hoc analysis indicated a significant mean difference between limbs in the MS group at the PRE and REC time points. This agrees with our isometric fatigue test results as well, that the PT limb difference is attenuated after exercise but returns after two minutes of recovery in MS patients. These results also agree with our hypothesis that MS patients would exhibit bilateral differences in isokinetic dorsiflexion performance. Unexpectedly, there was also a significant mean limb difference at all time points in the NON-MS group. The inability for limbs to produce symmetrical force may be the result of inadequate motor unit recruitment and motor discharge rate production; which may result in reduced exercise capacity and disturbances in gait after exercise.

There was a significant time effect in both groups for isokinetic VCT. In the NON-MS group both limbs significantly increased VCT after the fatigue test PRE-POST, and significantly decreased back after REC to levels similar to PRE. Previously Chen et al. (1988) reported that MS patients and individuals without MS have similar time to peak tension values during isokinetic exercise, albeit during knee extension and flexion (14). The VCT during isokinetic testing is determined by the inhibition of force by the antagonist muscle (plantarflexion) in order to initiate force in the agonist muscle (dorsiflexion). The speed of the isokinetic contraction dictates VCT to a certain extent once the movement is initiated, so any differences would occur in the latency period prior to activating the dorsiflexors. In the MS group the weak limb behaved similar to

the limbs in the NON-MS group, increasing in time PRE-POST, but returning to similar baseline values after REC. VCT in the strong limb however did not change over the course of the fatigue testing in the MS group at any time point. This is one of the few instances in the current study that the weak limb behaved similar to the NON-MS group and the strong limb did not. This may be due to the fact that the strong limb had a lower fatigue time and total reps than the weaker limb in the MS group. Although isokinetic PT showed similar rates of fatigue after the test, the shorter test may not have been adequate to elicit VCT changes in the strong limb. The lack of change in the strong limb may also be a central adaptive motor control mechanism to compensate for the weakness in the weaker limb.

Functional Performance Tests

We hypothesized that the MS group would exhibit decrements in functional performance compared to the NON-MS group. The results of the current study confirm our hypothesis, and there were significant decrements in all four functional performance variables in the MS group compared to the NON-MS group. The MS group exhibited significantly slower times in the 25WT and slower gait speed. The 25WT is a part of the Multiple Sclerosis Functional Composite Score, and has been shown to be a good measure of overall walking ability in clinical settings (26). The longer duration of the 25WT in the current study in the MS group agrees with previous research (7, 26, 71). Gait speed as determined by the 25WT also was significantly lower in the MS group, confirming previous results (15, 55, 62). MS patients exhibit

slower gait for a variety of reasons from decreased stride length, prolonged double support phase, limited ankle motion, altered ankle recruitment, and muscle strength and endurance among others (7, 35, 56). MS patients also self-identify attention deficits, heat sensitivity, muscle endurance, and fatigue as risk factors for falling (69). Previous research has identified the weaker limb (knee extensor) to have a negative correlation with walking performance, and ankle dorsiflexion strength to be a significant predictor of walking ability in MS patients (40, 65). Being that the ankle has shown limited motion and altered recruitment in MS patients, the dorsiflexors in the weaker limb may also be a good predictor of walking ability in MS patients. Future research should continue to investigate the relationship between dorsiflexion strength of the weak limb and walking performance and fall risk.

The TUG test took significantly longer to complete in the MS group compared to the NON-MS group, which is in agreement with previous research (2). While initial standing and sitting requires more involvement of the hip and knee extensors, the dorsiflexors are also important in the early stages of standing to stabilize the foot to the ground at the initiation of forward trunk flexion (50). A strong correlation has been shown in stroke patients with hemiparesis between ankle dorsiflexion strength of the affected limb and sit to stand time (53). Thus, the SA of the dorsiflexors and strength of the weak limb in MS patients may also show a strong relationship with the ability to stand from the seated position.

The 6MW also showed a significant difference between the two groups in the current study, with the MS group walking less distance than the NON-MS group. The 6MW has been shown to be a good indicator of muscle and walking endurance in MS patients and is considered to be a good indicator of the exercise level of activities of daily living (7). The results of the current study agree with previous studies showing decreased distance during the 6MW in MS subjects (27, 47, 79). The decrease in walking distance in the 6MW test may be due to limitations in walking ability as discussed earlier.

Walking Performance and SA Relationship

Linear correlations were examined to assess the relationship between isometric/isokinetic SA and the four variables of the functional performance tests. We examined the relationship between SA and the four functional performance variables in all subjects pooled together to increase the sample size and reduce type II error. In the linear correlations of the pooled subjects, all four performance variables were significantly correlated to isometric SA: 25W time, r = 0.78; Gait Speed, r = -0.52; TUG time, r = 0.65; 6MW distance, r = -0.47). The linear correlations indicated significant correlations between all four performance variables and isokinetic SA as well: 25W time, r = 0.89; Gait Speed, r = -0.68; TUG time, r = 0.78; 6MW distance, r = -0.62). These relationships indicate that as SA increase, walking performance decreases. One of the first studies to examine SA in MS patients also ran correlations between gait speed and isometric dorsiflexion SA; however they did not report a significant

relationship when MS patients were pooled with NON-MS individuals (15). It is difficult to determine the differing results between the current study and Chung et al. (2008) since asymmetry score was calculated in a similar fashion and walking speed was determined using a 25WT (15). One possible explanation may be due to previous researchers comparing power asymmetry to walking performance as opposed to SA (15).

To investigate if the MS group exhibited correlations between isometric/isokinetic SA of the dorsiflexors and the four functional performance variables, linear correlations were examined in each group independently. In support of our hypothesis, the MS group exhibited significant correlations between isometric SA and 25W ($r = 0.76$) and TUG ($r = 0.61$). The MS group also exhibited significant correlations between isokinetic dorsiflexion SA and all four functional performance variables: 25W time, $r = 0.93$; Gait Speed, $r = -0.76$; TUG time, $r = 0.81$; 6MW distance, $r = -0.67$. In contrast, the NON-MS group did not show any significant correlations with the four functional performance variables and isometric/isokinetic SA. This supports our hypothesis that the MS group would exhibit stronger correlations between isometric/isokinetic SA and functional performance variables than the NON-MS group.

The MS group exhibited significant positive correlations between 25WT and TUG with isometric SA, such that individuals with greater asymmetry had longer walking times in these two tests. To our knowledge, this is the first study to show a correlation between dorsiflexion SA and walking abilities in MS patients. Previously

power and strength asymmetry in knee extensors as well as the knee flexors has been shown to be strongly correlated to walking ability in MS patients (15, 40, 77). Dorsiflexion of the weak limb has been shown to be strongly correlated with sit to stand time and gait velocity in stroke patients (50, 51). MS patients that have previously fallen are known to have slower gait speed and TUG time than those that have not fallen (11). Thus, if there is a relationship between isometric dorsiflexion SA and slower walking speeds during 25WT and TUG time, there may also be a relationship between dorsiflexion SA and risks of falls. Future research should investigate the relationship between dorsiflexion SA and fall risk in MS patients.

Additionally, the MS group also exhibited significant correlations between isokinetic dorsiflexion SA and all four functional performance variables. To our knowledge this is the first study to investigate dorsiflexion SA using isokinetic contractions. Because isokinetic contractions require movement of the ankle unlike isometric contractions it may be a better predictor of walking performance. Isokinetic dorsiflexion SA in stroke patients has a strong correlation to gait speed and walking ability (51). Weak dorsiflexion strength may lead to limited ankle motion during walking, and in elderly individuals isokinetic dorsiflexion strength at 60^{o}/sec was much lower in individuals who had previously fallen (92). Also dorsiflexion strength has a non-linear relationship with walking ability, that at lower strength values a small decrease in strength may lead to a large decrement in walking speed (8). The relationship between isokinetic dorsiflexion SA and the functional variables in the

current study may suggest an increased risk of falls and decreased walking ability in MS patients.

To better understand the relationship between disease severity and functional performance variables in MS patients, we ran correlations between EDSS score and the functional performance variables. The results of the linear correlations indicated significant relationship between all four functional performance variables and EDSS: 25W time, r = 0.69; Gait Speed, r = -0.75; TUG time, r = 0.72; 6MW distance, r = -0.78. These correlations indicated that as disease severity (EDSS) increased, the performance of the four functional performance variables decreased. EDSS has previously been shown to have strong positive relationships with 25WT, TUG, and negative relationship with 6 MW distance (72, 77). Significant correlations have also been found between dorsiflexion strength in the weak limb and EDSS (64). Follow up correlations examining EDSS and SA indicated no significant relationship for isometric SA or isokinetic SA of the dorsiflexors (r= 0.29 and 0.55 respectively). This suggests that the relationship between SA and walking ability may be independent of disease severity based on EDSS. EDSS score is not solely based on walking ability, but also includes assessment of neurologic function of a variety of categories (44). Future research should investigate the prevalence of SA at different levels of EDSS.

Chapter 5: Conclusions

Purpose

The purpose of this study was to investigate bilateral differences in isometric and isokinetic dorsiflexion strength and bilateral differences in fatiguing exercise tests in multiple sclerosis patients compared to individuals without multiple sclerosis. We also investigated the relationship between strength asymmetry and various walking tests in multiple sclerosis patients and individuals without multiple sclerosis.

Hypotheses

1. Multiple sclerosis patients will exhibit bilateral differences in isokinetic/isometric strength of the dorsiflexors and these differences will be greater than those observed in individuals without multiple sclerosis.

    a. Multiple sclerosis patients did exhibit bilateral differences in isometric peak torque. Isometric strength asymmetry was greater in multiple sclerosis patients compared to individuals without multiple sclerosis. Multiple sclerosis patients also exhibited bilateral differences in the muscle performance variables measured.

    b. Multiple sclerosis patients did exhibit bilateral differences in peak torque at four isokinetic speeds; 30^{o}/sec, 60^{o}/sec, 90^{o}/sec, and 120^{o}/sec. The multiple sclerosis patients exhibited similar asymmetry as the healthy individuals at all contraction speeds.

2. Multiple sclerosis patients will exhibit bilateral differences in fatigability of the dorsiflexors and these differences will be greater than those observed in individuals without multiple sclerosis.

    a. Multiple sclerosis patients did not exhibit bilateral differences in isometric fatigue time. Peak torque did show bilateral differences before the fatigue test and after two minutes of recovery in multiple sclerosis patients, however there were no differences in strength asymmetry at any time point from the individuals without multiple sclerosis.
    b. Multiple sclerosis patients did not exhibit bilateral differences in isokinetic time and performed the isokinetic fatigue test similarly to individuals without multiple sclerosis. The multiple sclerosis patients showed a bilateral difference in peak torque before exercise and after two minutes of recovery, however there were no differences in strength asymmetry at any time points from the individuals without multiple sclerosis.

3. Multiple sclerosis patients will exhibit correlations between isometric/isokinetic strength asymmetry of the dorsiflexors and walking performance and that healthy individuals will not exhibit these correlations.

    a. Multiple sclerosis patients exhibited positive correlations between isometric strength asymmetry and the 25 foot walk and timed up-and-go tests. Individuals without multiple sclerosis did not show any

correlations between isometric strength asymmetry and functional performance.

b. Multiple sclerosis patients exhibited positive correlations between isokinetic strength asymmetry and the 25 foot walk and timed up-and-go tests. They also exhibited negative correlations between isokinetic strength asymmetry and distance during the six minute walk test and gait speed. Individuals without multiple sclerosis did not show any correlations between isokinetic strength asymmetry and functional performance.

Strengths and Limitations

The results of this study may be limited to multiple sclerosis patients with an EDSS < 6.5 and may be different in individuals with higher EDSS scores. The multiple sclerosis patients had significantly more body mass and fat mass than individuals without multiple sclerosis which may have influenced strength values observed. Another limitation may be strength asymmetry variability. Although we performed multiple trials during the strength testing, day-to-day variation in strength asymmetry levels has not been investigated in multiple sclerosis patients and it is possible that strength asymmetries and functional performance may vary day-to-day in this population. Another limitation is that we used a different method of assessing bilateral differences. Many other studies have chosen to view bilateral differences by comparing right-left limb or dominant-non-dominant limbs. In this study we chose to compare the limbs by defining a strong-weak limb for each visit. This may have biased

the data to show limb significance, however it would have done so for both groups. We also implemented the strength asymmetry score to account for this.

This is one of the first studies to examine isokinetic dorsiflexion strength asymmetry in multiple sclerosis patients. Additionally, this is the first study to examine the relationship between isokinetic dorsiflexion strength asymmetry and walking performance. The strong-weak study design allowed asymmetry to be more easily compared and allowed for unique within group comparisons.

Significance

Isometric strength asymmetry of the dorsiflexors in multiple sclerosis patients is greater than individuals without multiple sclerosis. This did not cause differences in fatigability between limbs, but did attenuate bilateral peak torque differences directly after exercise. The isometric/isokinetic strength asymmetry of the dorsiflexors was significantly correlated to walking performance during the functional performance tests. The isokinetic strength asymmetry showed greater correlations with functional performance tests than the isometric strength asymmetry in multiple sclerosis patients. The relationship between strength asymmetry and walking ability provides evidence that asymmetry may increase the risk of falls and reduce the ability to perform activities of daily living in multiple sclerosis patients.

Conclusions

The results of this study indicate that bilateral differences exist in the dorsiflexors of multiple sclerosis patients. The strength asymmetry in multiple sclerosis patients is related to functional performance of walking tests, and isokinetic strength asymmetry shows a stronger relationship with walking performance. The relationship between dorsiflexion strength asymmetry and walking ability may lead to increased fall risk and mobility issues in multiple sclerosis patients.

Future Research Directions

Future studies should examine strength asymmetries in a variety of muscle groups in multiple sclerosis patients. Additionally, further exploration of altered gait kinematics due to strength asymmetries should be investigated. Bilateral differences in multiple sclerosis patients may not be only occurring in muscular strength, therefore other physiologic variables should be measured to evaluate other asymmetries.

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Appendix A: IRB Approval Letter, Consent Form, and Research Privacy Form

The UNIVERSITY of OKLAHOMA

Institutional Review Board for the Protection of Human Subjects

Initial Submission – Board Approval

Date: July 13, 2016
To: Rebecca D Larson, PhD
Reference Number: 651533

IRB#: 6802
Meeting Date: 07/11/2016
Approval Date: 07/11/2016
Expiration Date: 06/30/2017

Study Title: Bilateral Fatigue of the Anterior Tibilals in Individuals with Multiple Sclerosis

Study Status: Active - Open
Collection/Use of PHI: Yes

At its regularly scheduled meeting the IRB reviewed the above-referenced research study. Study documents associated with this submission are listed on page 2 of this letter. To review and/or access the submission forms as well as the study documents approved for this submission, open this study from the *My Studies* option, click to open this study, look under Protocol Items to click on the current *Application, Informed Consent* and *Other Study Documents*.

If this study required routing through the Office of Research Administration (ORA), you may *not begin your study yet*, as per OUHSC institutional policy, until the contract through ORA is finalized and signed.

As principal investigator of this research study, it is your responsibility to:

- Conduct the research study in a manner consistent with the requirements of the IRB and federal regulations at 45 CFR 46 and/or 21 CFR 50 and 56.
- Request approval from the IRB prior to implementing any/all modifications.
- Promptly report to the IRB any harm experienced by a participant that is both unanticipated and related per IRB Policy.
- Maintain accurate and complete study records for evaluation by the HRPP quality improvement program and if applicable, inspection by regulatory agencies and/or the study sponsor.
- Promptly submit continuing review documents to the IRB upon notification approximately 60 days prior to the expiration date indicated above.

In addition, it is your responsibility to obtain informed consent and research privacy authorization using the currently approved, stamped forms and retain all original, signed forms, if applicable.

If you have questions about this notification or using IRIS, contact the IRB at 405-271-2045 or irb@ouhsc.edu.

Sincerely,

Karen Beckman, MD
Chairperson, Institutional Review Board

Consent Form
University of Oklahoma Health Sciences Center (OUHSC)
University of Oklahoma - Norman

Bilateral Fatigue of the Anterior Tibilais in Individuals with Multiple Sclerosis

Principal Investigator: Rebecca D. Larson, PhD

This is a research study. Research studies involve only individuals who choose to participate. Please take your time to make your decision. Discuss this with your family and friends.

Why Have I Been Asked To Participate In This Study?
You are being asked to take part in this study because you have been diagnosed as having multiple sclerosis, or you match one of the participants with multiple sclerosis involved in the study.

Why Is This Study Being Done?
The purpose of this study is to determine whether individuals with multiple sclerosis exhibit leg differences that are greater than that of healthy individuals. Multiple sclerosis may affect the body asymmetrically, and this study hopes to investigate the difference in strength and fatigue between limbs, and compare that difference to healthy controls.

How Many People Will Take Part In The Study?
About 60 people (30 individuals with multiple sclerosis and 30 healthy individuals without multiple sclerosis) will take part in this study. All testing visits will occur in the Body Composition and Human Performance Lab at the University of Oklahoma.

What Is Involved In The Study?
If you take part in this study, you will have to perform the following tests and procedures:

<u>Visit 1</u>
Prior to the first visit of the study a physician's clearance letter will need to be completed by your physician and given to the research team. During the first visit of the study we will discuss the purpose of the study and go over the details of each study visit. If you choose, you will be asked to read and sign this informed consent. You will also fill out questionnaires regarding your physical health and quality of life.

After completing the questionnaires, you will be asked to undergo a dual X-ray absorptiometry (DXA) scan which allows us to measure the amount of the fat and muscle in your body. This is a procedure that requires you to lie down and remain as still and quietly as possible for approximately 10 minutes.

After the DXA scan, you will then be fitted and familiarized to a specialized machine called an isokinetic dynamometer (Kin Com) which will be used to measure the strength of your lower legs. You will be seated in the Kin Com and adjustments will be made to

ensure comfort and proper fit using safety straps around the waist, chest, and testing leg. You will then be asked to perform submaximal efforts (contractions) until you feel comfortable with the device. Submaximal contractions require you to perform the exercise at low intensities that are less than maximal effort. Two types of contractions will be performed, an isometric contraction which is similar to pushing against a stationary object (ex. pushing against wall) and isokinetic contractions which is where you push against an object that moves at various speeds (slow-fast). You will be fitted and familiarized for both legs during this visit. All measurements of the limb and seat settings will be recorded and be used in subsequent testing visits.

Visit 1 will take approximately 60 minutes.

Visit 2

The maximal isometric and isokinetic testing will be conducted during visit 2. All testing will be performed using the Kin Com as you were familiarized with during Visit 1. You will begin by performing three maximal isometric muscle contractions (feels like you are pushing against a stationary object) after a warm up at 25%, 50%, and 75% of your maximal effort, with 120 seconds of rest in between each warm up effort. During your maximal effort contractions you will be instructed to push as hard as you can for five seconds and be given 120 seconds of rest between attempts; after the last effort you will be given 10 minutes of rest. Once you are fully recovered, you will be asked to perform maximal isokinetic contractions at different speeds with the same leg for four different speeds; 30°/sec (slow), 60°/sec (medium), 90°/sec (fast), and 120°/sec (very fast). The speed of a contraction is measured in "°/sec" which defines how much the angle of the ankle moves during the contraction. Again you will be asked to perform three maximal efforts at each speed with 120 seconds of rest between speeds.

After 15 minutes of rest, you will be set up into the Kin Com and perform the same tests that were previously described, with the opposite leg. The order of legs tested (right vs. left) will be randomized as well as the testing speeds.

Finally, during this visit you will also be familiarized with the three functional tests to be performed at Visit 5. These tests include the 25-foot walk test, 6-minute walk test, and the timed up-and-go test. During this time, instruction will be provided how to perform the tests and ample time will be given for you to perform all three tests until you feel comfortable performing them. Below is a description of each test.

The 25-foot walk test will consist of you walking in a straight line when instructed for 25 feet as quickly and as safely as possible.
The timed up-and-go test requires you to start sitting in a standard chair with your back against the chair, arms resting on the chair's arms. You will be instructed to stand, walk 3 meters, turn around and walk back to the chair, and sit down.

The 6-minute walk test consists of walking a course of 30 meters in length for 6 minutes. The goal of the test is to walk as far and as long as possible without running or jogging. You are free to speed up and slow down accordingly.

Visit 2 will take approximately 90-120 minutes.

Visit 3-4
On visits 3-4, you will perform two different types of fatiguing exercise on the Kin Com. The fatiguing exercise will consist of similar movements (isometric and isokinetic) as during visit 1and 2. You will be positioned similarly to how you were for the testing on visit 1and 2, using the same recorded marks and seat adjustments.

During the isometric fatiguing exercise on visit 3, you will be asked to press against the Kin Com machine maintaining a specific effort. This effort will be told to you before the testing, and you will be able to visually see how much effort you are producing on a computer screen. You are required to maintain this specific effort level for as long as possible, until researchers deem that you are fatigued. You will also perform maximum contractions before and after the fatiguing isometric exercise. You will then be given 15 minutes to rest before performing the exercise with the opposite leg.

The isokinetic protocol will be performed on visit 4 in a similar manner as the isometric fatiguing exercise, but at 60º/sec contractions. You will also perform maximum contractions before and after the fatiguing exercise as you did during visit 3. The order of which leg is tested (right vs. left) will be randomized for each subject.

Visits 3 and 4 will take approximately 90-120 minutes each.

Visit 5
On visit 5, you will perform all three functional tests to assess physical function. These are the same tests you performed during visit 2 which include; the 25-foot walk test, the timed up-and-go test, and the 6-minute walk test. Each test will be performed three times except the 6 minute walk test.

Visit 5 will take approximately 60 minutes.

How Long Will I Be In The Study?
We think that you will be in the study for 3-4 weeks during which you will visit the Body Composition and Human Performance Lab on 5 occasions. Each visit will take approximately 1-2 hours.

There may be anticipated circumstances under which your participation may be terminated by the investigator without regard to your consent.

- If it is determined to be in your best medical interest.
- Your condition worsens.
- New information becomes available.
- You fail to follow study requirements.

You can stop participating in this study at any time. However, if you decide to stop participating in the study, we encourage you to talk to the researcher and your regular doctor first.

What Are The Risks of The Study?
Risks and side effects related to this study include:

Radiation Risk from DXA
During the DXA scan, you will be exposed to very low doses of radiation.

If you participate in this research, you will be exposed to radiation from a DXA scan (a type of x-ray). The amount of radiation to which you will be exposed from one DXA scan is approximately less than 1% of the amount of radiation that we are exposed to each year from natural background sources of radiation. The risk of radiation exposure is cumulative over your lifetime.
This study may be hazardous to an unborn child. If you are a pre-menopausal female participant, you will be asked to perform a simple urine test to determine possible pregnancy. There is no cost to you for this test. A negative pregnancy test is needed prior to participating in this study. For unexpected pregnancies, subjects are encouraged to speak with their family physician.

Maximal Contractions and Fatigue Exercise on the Kin-Com Dynamometer
These tests require that you exert a maximal effort. The risk for performing these tests is muscle discomfort. While rare and uncommon, you may experience faintness, nausea, and/or lightheadedness. You will be closely monitored for any possible ill effects. To further reduce your risk of discomfort you will be screened for risk factors.

This study may also include risks that are unknown at the time.

Are There Benefits to Taking Part in The Study?
There are no direct medical benefits from participating in this study. However, the information gained from this study will benefit those with multiple sclerosis in the future.

What Other Options Are There?
You may choose not to participate in the study.

What About Confidentiality?
Efforts will be made to keep your personal information confidential. You will not be identifiable by name or description in any reports or publications about this study. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law. You will be asked to sign a separate authorization form for use or sharing of your protected health information.

There are organizations outside the OUHSC that may inspect and/or copy your research records for quality assurance and data analysis. These organizations include the US Food & Drug Administration and other regulatory agencies. The OUHSC Human Research

Participant Program office, the OUHSC Institutional Review Board, and the OUHSC Office of Compliance may also inspect and/or copy your research records for these purposes.

What Are the Costs?
There will be no cost to you for participating in this study.

Will I Be Paid For Participating in This Study?
Participants will be compensated $100 for completing this study. You will be paid at the end of the study. If you do not complete the study, you will receive $10 per completed visit.

What if I am Injured or Become Ill While Participating in this Study?
In case of injury or illness resulting from this study, emergency medical treatment is available. However, you or your insurance company will be expected to pay the usual charge for this treatment. No funds have been set aside by the University of Oklahoma Health Sciences Center, the University of Oklahoma, or Oklahoma Medical Research Center to compensate you in the event of injury.

What Are My Rights As a Participant?
Taking part in this study is voluntary. You may choose not to participate. Refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled. If you agree to participate and then decide against it, you can withdraw for any reason and leave the study at any time. . You may discontinue your participation at any time without penalty or loss of benefits, to which you are otherwise entitled.

We will provide you with any significant new findings developed during the course of the research that may affect your health, welfare or willingness to continue your participation in this study.

You have the right to access the medical information that has been collected about you as a part of this research study. However, you may not have access to this medical information until the entire research study has completely finished and you consent to this temporary restriction.

Whom Do I Call If I have Questions or Problems?
If you have questions, concerns, or complaints about the study or have a research-related injury, contact Dr. Rebecca Larson at 352-359-8432 (cell) or 405-325-6325 (office).

If you cannot reach the Investigator or wish to speak to someone other than the investigator, contact the OUHSC Director, Office of Human Research Participant Protection at 405-271-2045.

For questions about your rights as a research participant, contact the OUHSC Director, Office of Human Research Participant Protection at 405-271-2045.

Signature:
By signing this form, you are agreeing to participate in this research study under the conditions described. You have not given up any of your legal rights or released any individual or entity from liability for negligence. You have been given an opportunity to ask questions. You will be given a copy of this consent document.

I agree to participate in this study:

_____	_____	_____
PARTICIPANT SIGNATURE (age ≥18) *(Or Legally Authorized Representative)*	Printed Name	Date
_____	_____	_____
SIGNATURE OF PERSON OBTAINING CONSENT	Printed Name	Date

AUTHORIZATION TO USE or SHARE
HEALTH INFORMATION[1] THAT IDENTIFIES YOU FOR RESEARCH
An Informed Consent Document for Research Participation may also be required.
Form 2 must be used for research involving psychotherapy notes.

Title of Research Project: **Bilateral Fatigue of the Anterior Tibialis in Individuals with Multiple Sclerosis.**

Leader of Research Team: **Rebecca D Larson, PhD**

Address: **Department of Health and Exercise Science, 1401 Asp Avenue., Room 117 HHC, Norman, OK 73019**

Phone Number: **405-325-6325**

If you decide to sign this document, University of Oklahoma Health Sciences Center (OUHSC) researchers may use or share information that identifies you (protected health information) for their research. Protected health information will be called PHI in this document.

PHI To Be Used or Shared. Federal law requires that researchers get your permission (authorization) to use or share your PHI. If you give permission, the researchers may use or share with the people identified in this Authorization any PHI related to this research from your medical records and from any test results. Information used or shared may include all information relating to any tests, procedures, surveys, or interviews as outlined in the consent form; medical records and charts; name, address, telephone number, date of birth, race, government-issued identification numbers, and can include physical findings from questionnaires, dual X-ray absorptiometry (DXA) scan, mitochondrial function test, isokinetic/isometric dynamometer, and physical exams and findings.

Purposes for Using or Sharing PHI. If you give permission, the researchers may use your PHI to determine whether individuals with MS exhibit limb differences in function, strength, and fatiguability at rest and during exercise.

Other Use and Sharing of PHI. If you give permission, the researchers may also use your PHI to develop new procedures or commercial products. They may share your PHI with other researchers, the research sponsor and its agents, the OUHSC Institutional Review Board, auditors and inspectors who check the research, and government agencies such as the Food and Drug Administration (FDA) and the Department of Health and Human Services (HHS), and when required by law. The researchers may also share your PHI with no one outside the research team.

[1] **Protected Health Information includes all identifiable information relating to any aspect of an individual's health whether past, present or future, created or maintained by a Covered Entity.**

Confidentiality. Although the researchers may report their findings in scientific journals or meetings, they will not identify you in their reports. The researchers will try to keep your information confidential, but confidentiality is not guaranteed. The law does not require everyone receiving the information covered by this document to keep it confidential, so they could release it to others, and federal law may no longer protect it.

YOU UNDERSTAND THAT YOUR PROTECTED HEALTH INFORMATION MAY INCLUDE INFORMATION REGARDING A COMMUNICABLE OR NONCOMMUNICABLE DISEASE.

Voluntary Choice. The choice to give OUHSC researchers permission to use or share your PHI for their research is voluntary. It is completely up to you. No one can force you to give permission. However, you must give permission for OUHSC researchers to use or share your PHI if you want to participate in the research and, if you cancel your authorization, you can no longer participate in this study.

Refusing to give permission will not affect your ability to get routine treatment or health care unrelated to this study from OUHSC.

Canceling Permission. If you give the OUHSC researchers permission to use or share your PHI, you have a right to cancel your permission whenever you want. However, canceling your permission will not apply to information that the researchers have already used, relied on, or shared or to information necessary to maintain the reliability or integrity of this research.

End of Permission. Unless you cancel it, permission for OUHSC researchers to use or share your PHI for their research will never end.

Contacting OUHSC: You may find out if your PHI has been shared, get a copy of your PHI, or cancel your permission at any time by writing to:

Privacy Official University of Oklahoma Health Sciences Center PO Box 26901 Oklahoma City, OK 73190	or	Privacy Board University of Oklahoma Health Sciences Center PO Box 26901 Oklahoma City, OK 73190
If you have questions, call: (405) 271-2511	or	(405) 271-2045.

Access to Information. You have the right to access the medical information that has been collected about you as a part of this research study. However, you may not have access to this medical information until the entire research study is completely finished. You consent to this temporary restriction.

Giving Permission. By signing this form, you give OUHSC and OUHSC's researchers led by the Research Team Leader permission to share your PHI for the research project listed at the top of this form.

Patient/Participant Name (Print): _____

_____ _____
Signature of Patient-Participant Date
or Parent if Participant is a minor

Or

_____ _____
Signature of Legal Representative** Date

**If signed by a Legal Representative of the Patient-Participant, provide a description of the relationship to the Patient-Participant and the authority to act as Legal Representative:

_____
OUHSC may ask you to produce evidence of your relationship.

A signed copy of this form must be given to the Patient-Participant or the Legal Representative at the time this signed form is provided to the researcher or his representative.

Appendix B: Medical Clearance Forms, Par-Q, Health History Questionnaires, and Kurtzke Questionnaire

The University of Oklahoma
DEPARTMENT OF HEALTH AND EXERCISE SCIENCE

Multiple Sclerosis Clearance Letter

Date_____

Dear Dr._____

A patient of yours,_____would like to participate in a study called, "Bilateral Fatigue in Individuals with Multiple Sclerosis" which will be conducted at the University of Oklahoma. The goal of this study is to investigate bilateral differences in leg performance and function. Each testing/exercise session will be performed at the University of Oklahoma. Personnel experienced at working with individuals with MS will supervise all visits.

Your support of our MS research is very much appreciated. To comply with Institutional Review Board policy, we need a letter from you clearing your MS patient for participation in this study. Attached please find a copy of the research protocol and informed consent. Your written approval letter will include the subject's diagnosis, classification of disease and level of disability at study entry, and current medications. This letter indicates that you are aware of the testing procedures and the specific activities this individual will be performing. Participants will be included if they have an expanded disability status score less than 6.5 which reflects ambulatory status.

The individual participating in this research study will be advised to contact you if they experience any clinical symptoms between study visits.

Again, we greatly appreciate your support and request, at your earliest convenience, a response to this letter indicating your approval or disapproval of subject participation.

Rebecca D. Larson, Ph.D., Principal Investigator
Department of Health and Exercise Science
College of Arts and Science
University of Oklahoma
Norman, OK

The University of Oklahoma
DEPARTMENT OF HEALTH AND EXERCISE SCIENCE

Non- MS Clearance Letter

Date_____

Dear Dr._____

A patient of yours,_____would like to participate in a study called, "Bilateral Fatigue of the Anterior Tibialis in Individuals with Multiple Sclerosis" which will be conducted at the University of Oklahoma. The goal of this study is to investigate bilateral difference in leg performance and function. Each testing/exercise session will be performed at the University of Oklahoma.

Your support of our MS research is very much appreciated. To comply with Institutional Review Board policy, we need a letter from you clearing your MS patient for participation in this study. Attached please find a copy of the research protocol and informed consent. This letter indicates that you are aware of the testing procedures and the specific activities this individual will be performing. Your written approval letter will include a list of any current medications and the reason for the medication.

The individual participating in this research study will be advised to contact you if they experience any clinical symptoms between study visits.

Again, we greatly appreciate your support and request, at your earliest convenience, a response to this letter indicating your approval or disapproval of subject participation.

Rebecca D. Larson, Ph.D., Principal Investigator
Department of Health and Exercise Science
College of Arts and Science
University of Oklahoma
Norman, OK

IRB NUMBER: 6802
IRB APPROVAL DATE: 07/11/2016

Diagnosis:_____ Initials:_____

Disability Status Score:_____ Initials:_____

Current Medications: Medication rationale (e.g., blood pressure):

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

Initials:_____

Additional Comments by Physician:

Please circle as appropriate: **APPROVED**

DISAPPROVED

Name of Physician:_____

Signature of Physician:_____

Date:_____

FORM 3.1 Physical Activity Readiness Questionnaire

PAR-Q & YOU

(A Questionnaire for People Aged 15 to 69)

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly: check YES or NO.

YES	NO	
☐	☐	1. Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?
☐	☐	2. Do you feel pain in your chest when you do physical activity?
☐	☐	3. In the past month, have you had chest pain when you were not doing physical activity?
☐	☐	4. Do you lose your balance because of dizziness or do you ever lose consciousness?
☐	☐	5. Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?
☐	☐	6. Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?
☐	☐	7. Do you know of any other reason why you should not do physical activity?

If you answered

YES to one or more questions

Talk with your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want — as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- start becoming much more physically active – begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal – this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/94, talk with your doctor before you start becoming much more physically active.

DELAY BECOMING MUCH MORE ACTIVE:

- if you are not feeling well because of a temporary illness such as a cold or a fever – wait until you feel better; or
- if you are or may be pregnant – talk to your doctor before you start becoming more active.

PLEASE NOTE: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

Informed Use of the PAR-Q: The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity, and if in doubt after completing this questionnaire, consult your doctor prior to physical activity.

No changes permitted. You are encouraged to photocopy the PAR-Q but only if you use the entire form.

NOTE: If the PAR-Q is being given to a person before he or she participates in a physical activity program or a fitness appraisal, this section may be used for legal or administrative purposes.

"I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction."

NAME _____

SIGNATURE _____ DATE _____

SIGNATURE OF PARENT or GUARDIAN (for participants under the age of majority) _____ WITNESS _____

Note: This physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if your condition changes so that you would answer YES to any of the seven questions.

Supported by Health Canada Santé Canada

continued on other side...

FORM 3.2 Health Status Questionnaire

This questionnaire identifies adults for whom physical activity might be inappropriate or adults who should seek physician consultation before beginning a regular physical activity program.

Section 1 Personal and Emergency Contact Information

Name: _____ Date of birth: _____

Address: _____ Phone: _____

Physician's name: _____ Height: _____

Weight: _____

Person to contact in case of emergency

Name: _____ Phone: _____

Section 2 General Medical History

Please check the following conditions you have experienced.

Heart History

_____ Heart attack
_____ Heart surgery
_____ Cardiac catheterization
_____ Coronary angioplasty (PTCA)
_____ Cardiac pacemaker
_____ Cardiac rhythm disturbance
_____ Heart valve disease
_____ Heart failure
_____ Heart transplantation
_____ Congenital heart disease

Symptoms

_____ You experience chest discomfort with exertion.
_____ You experience unreasonable shortness of breath at any time.
_____ You experience dizziness, fainting, or blackouts.
_____ You take heart medications.

Additional Health Issues

_____ You have asthma or other lung disease (e.g., emphysema).
_____ You have burning or cramping sensations in your lower legs with minimal physical activity.

_____ You have joint problems (e.g., arthritis) that limit your physical activity.
_____ You have concerns about the safety of exercise.
_____ You take prescription medications.
_____ You are pregnant.

Section 3 Risk Factor Assessment

Risk Factors for Coronary Heart Disease

_____ You are a man older than 45 yr.
_____ You are a woman older than 55 yr, have had a hysterectomy, or are postmenopausal.
_____ You have diabetes (type 1 or type 2).
_____ You smoke or you quit smoking within the previous 6 mo.
_____ Your blood pressure is >140/90 mmHg.
_____ Your blood cholesterol is >200 mg · dl^{-1}.
_____ You have a close male blood relative (father or brother) who had a heart attack or heart surgery before the age of 55 or a close female blood relative (mother or sister) who had a heart attack or heart surgery before the age of 65.
_____ You are physically inactive (you get <30 min of physical activity at least 3 days per wk).
_____ Your waist circumference is >40 in. (101.6 cm in men) or >35 in. (88.9 cm in women).

Section 4 Medications

Are you currently taking any medication? _____ Yes _____ No

If yes, please list all of your prescribed medications and how often you take them, whether daily (D) or as needed (PRN). _____

_____

Of the medications you have listed, are there any you do not take as prescribed?

_____

Section 5 Physical Activity Patterns and Objectives

List the type, frequency, intensity (e.g., low, moderate, strenuous), and duration of your weekly exercise. _____

_____

_____

_____

List your specific goals for your exercise program. _____

_____

Please inform the fitness professional immediately of any changes that occur in your health status.

Patient Information Release Form

If you have answered yes to questions indicating that you have significant cardiac, pulmonary, metabolic, or orthopedic problems that may be exacerbated with exercise, you agree it is permissible for us to contact your physician regarding your health status.

Signature: _____ Date: _____

Fitness staff signature: _____ Date: _____

To be completed by fitness professional (circle one):

AHA/ACSM risk stratification: Low Moderate High Physician consent: Yes No

From K.S. Hanley and B.D. Fortin with G. Moore, 2022, Fitness Professional's Handbook Instructor Guide, Fifth Edition. (Champaign, IL: Human Kinetics.)

IRB NUMBER: 6802
IRB APPROVAL DATE: 07/11/2016

Date: _____

Medical History
Participation Information

Name: _____ Date of Birth: _____

Address: _____ Phone number: (w) _____

_____ (h) _____

Email: _____

Blood Pressure: _____/_____ (cell) _____

Height: _____ Weight: _____

Gender: Male Female (circle)

Ethnicity : Caucasian African American Hispanic Asian Other

Emergency contact name and number: _____

Family Physician name and number: _____

Please answer the following questions:

I. GENERAL HEALTH

1. Have you been diagnosed with diabetes? **Y** **N**
   If "yes", please explain _____
2. Have you ever had an oral glucose tolerance test? **Y** **N**
   If "yes", please explain _____
3. Have you ever been told by a physician that you have Osteoporosis/Osteopenia? **Y** **N**
4. Have you ever been told by a physician that you have a heart condition? **Y** **N**
3. Have you or anyone in your immediate family had a heart attack, stroke, or cardiovascular disease before age 50 yrs? If "yes," please explain. **Y** **N**
   _____
5. Have you ever been told by a physician that you have high blood pressure? **Y** **N**
6. Have you ever been told by a physician that you have high cholesterol? **Y** **N**
7. Have you ever been told by a physician that you have thyroid problems? **Y** **N**

If you answered yes, please define (hypothyroidism or hyperthyroidism) _____

Date: _____

8. Have you ever been told by a physician that you have kidney disease? Y N

9. Do you feel angina-like symptoms (pain or pressure in your chest, neck, shoulders, or arms) during or after physical activity? Y N

10. Do you ever lose your balance because of dizziness? Y N

11. Do you ever lose consciousness? Y N

12. Do you consider most of your days very stressful? Y N

13. Do you consider your eating habits healthy overall? Y N
(Lower in fats and fried foods, higher in fruits, veggies and grains)

14. Have you had any major surgeries, or any surgery that required incisions? Y N
If "yes", please explain: _____

15. Do you consider yourself to be generally healthy? Y N

16. Do you currently smoke cigarettes or cigars or chew tobacco? Y N
If "yes", how often and how much: _____

17. Are you a former smoker? Y N
If so, how long has it been since you quit smoking? _____

18. Has your weight changed more than 5 pounds in the last 6 months? Y N

EARS:
_____ hearing difficulty
_____ ringing
_____ pain
_____ discharge
_____ other

NOSE:
_____ bleeding
_____ difficulty smelling
_____ nasal congestion
_____ sinus problems
_____ other

Please explain _____

PULMONARY:
_____ shortness of breath
_____ wheezing
_____ asthma
_____ chronic cough
_____ allergies
_____ other

Please explain _____

19. Are there any other health-related issues we should know about? _____
Please explain _____

Date: _____

_____

II. MEDICATION/SUPPLEMENTS

1. Please list all of the **prescription medications** you are currently taking.

Medicine name	Amount taken per day	Months/years on the medication	Reason
a. _____	_____	_____	_____
b. _____	_____	_____	_____
c. _____	_____	_____	_____
d. _____	_____	_____	_____
e. _____	_____	_____	_____
f. _____	_____	_____	_____

2. Any known allergies? Explain _____

3. Have you been on steroid medication in the past? Y N
   If so, please explain in detail _____
   _____
   _____

4. Please list all of the **over-the-counter medicines or supplements** (including vitamins that you take regularly)

Item name	Amount taken per day	Months/years on medication	Reason
a. _____	_____	_____	_____
b. _____	_____	_____	_____
c. _____	_____	_____	_____
d. _____	_____	_____	_____
e. _____	_____	_____	_____
f. _____	_____	_____	_____

Date: _____

III. REPRODUCTIVE STATUS (If male, skip to section IV)

1. Have you reached menopause? (if NO skip to Section IV) Y N

2. How long has it been since you reached menopause? _____ Y N

3. Do you still have your ovaries? _____ Y N
   a. If not, how old were you when they were removed? _____.

4. Have you ever been on hormone replacement therapy? Y N

   a. If so, are you still taking hormone replacement therapy? Y N

   b. If you have previously taken hormone replacement therapy, but have since stopped, when did you stop taking hormone replacement therapy?
   _____

5. Have you ever taken osteoporosis medications? Y N

   Which ones and for how long? _____
   _____

IV. OSTEOPOROSIS/FRACTURE/BONE HEALTH SECTION

1. Have you ever had a bone scan? Y N
   If so, what year? _____
   What was the outcome?_____

2. Please provide a list of any bone fractures you have had in the past.

Bone	Cause (fall, accident, etc)	Year
_____	_____	
_____	_____	

3. Did a doctor tell you that any of these fractures were due to osteoporosis/osteopenia? Y N

4. Is your diet low in dairy products (≤ 3 servings/day)?
   Y N

5. Do you take calcium supplements? Y N
   If so, how much per day? _____

6. In a typical week, how many alcoholic drinks do you consume? _____

7. Do you drink coffee, tea, or cola products routinely? Y N
   About how much coffee, tea, or cola do you drink on an average day? _____.
   _____

Date: _____

8. Do you have a heart valve or implant device such as knee, hip etc.? Y N

FEAR OF FALLING (Falls Efficacy Scale)

On a scale from 1 to 10, with *1 being very confident and 10 being not confident at all*, how confident are you that you do the following activities without falling?

Activity	Score 1 very confident 10 not confident at all
Take a bath or shower	
Reach into cabinets or closets	
Walk around the house	
Prepare meals not requiring carrying heavy or hot objects	
Get in and out of bed	
Answer the door or telephone	
Get in and out of a chair	
Getting dressed and undressed	
Personal grooming (e.g., washing your face)	
Getting on and off of the toilet	
Total Score	

V. SUN EXPOSURE

1. How many times a week do you spend more than 10 minutes outside? _____
2. How much time do you spend outdoors (minutes) per week?_____
3. How much of your outdoor time is spent without sunscreen on (minutes)?_____
4. How much of your outdoor time is spent "fully exposed" (minutes)?_____
   ("fully exposed" is defined as uncovered face, arms, and hands)

VI. EXERCISE HABITS

1. How many times per week do you generally exercise? _____

   a. What type(s) of exercise do you generally perform? (circle all that apply)
   Walking Running Bicycling Swimming

Date: _____

Weight Lifting Aerobics Spinning Tennis

Other _____

b. In a typical week, how many days do you exercise? (circle)

0-1 time/week 2-3 times/week 4-6 times/week daily

c. How many minutes do you typically exercise per session (circle)

<15 min 15-30 min 30-45 >45
Other_____

d. What is the typical level of exertion during your exercise?

Light Moderate Moderate/Heavy Heavy

e. When you are exercising do you ever feel limited by the following?

	Yes	No	Activity
Breathing	___	___	_____
Chest arm neck pain	___	___	_____
Low back pain	___	___	_____
Side ache	___	___	_____
Leg pain	___	___	_____
Foot drop	___	___	_____

Other? Please explain _____
_____

VII. MULTIPLE SCLEROSIS STATUS

1. How long have you been diagnosed with Multiple Sclerosis? _____
2. When did you have your first MS symptom? _____
3. Has your physician ever discussed what type of MS you have? **YES NO**

Relapsing remitting Primary progressive Secondary progressive Progressive relapsing

4. Briefly described your current MS symptoms _____
_____

Date: _____

5. Does MS affect your legs? **YES** **NO** Does MS affect your arms? **YES** **NO**

If yes, which leg is more involved? Right Left Both same
If yes, which arm is more involved? Right Left Both same

6. Do you feel numbness in your legs? **YES** **NO**

If yes, which leg is more involved? Right Left Both same

7. Do you feel numbness in your arms? **Yes** **No**

If yes, which arm is more involved? Right Left Both same

8. Do you feel tingling in your legs? **YES** **NO**

If yes, which leg is more involved? Right Left Both same

9. Do you feel tingling in your arms? **YES** **NO**

If yes, which arm is more involved Right Left Both same

10. Do you fatigue easily? **YES** **NO**
If yes, what causes it to be worse? _____
_____

11. Do you ever experience worsening of symptoms? **YES** **NO**

	Describe	**YES**	**NO**	**How often?**
Bath/shower	_____	___	___	_____
Physical activity	_____	___	___	_____
Hot outside	_____	___	___	_____
Other	_____	___	___	_____
Other	_____	___	___	

12. Do you drive yourself independently? **YES** **NO**

13. Do you walk (circle) without aid with cane walker wheelchair

14. Has your physician ever recommended that you get a bone scan?_____

15. Has your physician ever recommended that you exercise? _____

Family Practice Physician _____ Phone _____

Neurologist _____ Phone _____

Date: _____

Other _____ Phone _____

VIII. EMPLOYMENT STATUS

1. Full-time employed ____
2. Part-time employed ____
3. Retired ____
4. Not working ____

Please describe employment status _____
_____

IX. EDUCATION

1. None ____
2. High School ____
3. College ____
4. Masters ____
5. Ph.D. ____
6. Other ____

I certify that these answers are accurate and complete

_____ _____
YOUR SIGNATURE DATE

Date: _____

Medical History – Non MS
Participation Information

Name: _____ Date of Birth: _____

Address: _____ Phone number: (w) _____

_____ (h) _____

Email: _____

Blood Pressure: ____/____ (cell) _____

Height: _____ Weight: _____

Gender: Male Female (circle)

Ethnicity: Caucasian African American Hispanic Asian Other

Emergency contact name and number: _____

Family Physician name and number: _____

Please answer the following questions:

I. GENERAL HEALTH

1. Have you been diagnosed with diabetes? Y N
   If "yes", please give date_____
2. Have you ever had an oral glucose tolerance test? Y N
   If "yes", please give date_____
3. Have you ever been told by a physician that you have Osteoporosis/Osteopenia? Y N
4. Have you ever been told by a physician that you have any heart condition/problems? Y N
   If "yes", please list_____
5. Have you or anyone in your immediate family had a heart attack, stroke, or cardiovascular disease before age 50 yrs? If "yes," please list relatives (e.g. father, mother). Y N
   _____
6. Have you ever been told by a physician that you have high blood pressure? Y N
7. Have you ever been told by a physician that you have high cholesterol? Y N
8. Have you ever been told by a physician that you have thyroid problems? Y N
9. If you answered yes, please specify (hyperthyroidism or hypothyroidism) _____

Date: _____

10. Have you ever been told by a physician that you have kidney disease? Y N

11. Do you feel angina-like symptoms (pain or pressure in your chest, neck, shoulders, or arms) during or after physical activity? Y N

12. Do you ever lose your balance because of dizziness? Y N

13. Do you ever lose consciousness? Y N

14. Do you consider most of your days very stressful? Y N

15. Do you consider your eating habits healthy overall? Y N
(Lower in fats and fried foods, higher in fruits, veggies and grains)

16. Have you had any major surgeries, or any surgery requiring an incision? Y N
If "yes", please list: _____

17. Do you consider yourself to be generally healthy? Y N

18. Do you currently smoke cigarettes or cigars or chew tobacco? Y N
If "yes", how often and how much: _____

19. Are you a former smoker? Y N
If so, how long has it been since you quit smoking? _____

20. Has your weight changed more than 5 pounds in the last 6 months? Y N

EARS:

_____ hearing difficulty
_____ ringing
_____ pain
_____ discharge
_____ other

NOSE:

_____ bleeding
_____ difficulty smelling
_____ nasal congestion
_____ sinus problems
_____ other

Please Explain _____

PULMONARY:

_____ shortness of breath
_____ wheezing
_____ asthma
_____ chronic cough
_____ allergies
_____ other

Please Explain _____

21. Are there any other health-related issues we should know about?
Please list any of these conditions_____

Date: _____

II. MEDICATION/SUPPLEMENTS

1. Please list all of the **prescription medications** you are currently taking.

Medicine name	Amount taken per day	Months/years on the medication	Reason
a. _____	_____	_____	_____
b. _____	_____	_____	_____
c. _____	_____	_____	_____
d. _____	_____	_____	_____
e. _____	_____	_____	_____
f. _____	_____	_____	_____

2. Any known allergies? Y N
   Please list _____

3. Have you been on steroid medication in the past? Y N
   If so, please list and provide dates _____
   _____
   _____

3. Please list all of the **over-the-counter medicines or supplements** (including vitamins that you take regularly).

Med./supplement name	Amount taken per day	Months/years on the medication	Reason
a. _____	_____	_____	_____
b. _____	_____	_____	_____
c. _____	_____	_____	_____
d. _____	_____	_____	_____
e. _____	_____	_____	_____
f. _____	_____	_____	_____

Date: _____

III. REPRODUCTIVE STATUS (If male, skip to section IV)

1. Have you reached menopause? (if NO skip to Section IV) Y N

2. How long has it been since you reached menopause? _____ Y N

3. Do you still have your ovaries? Y N
   a. If not, how old were you when they were removed? _____.

4. Have you ever been on hormone replacement therapy? Y N

   a. If so, are you still taking hormone replacement therapy? Y N
   If "yes", please list medication:_____

   b. If you have previously taken hormone replacement therapy, but have since stopped, when did you stop taking hormone replacement therapy?
   _____

5. Have you ever taken osteoporosis medications? Y N

   Which ones and for how long? _____
   _____

IV. OSTEOPOROSIS/FRACTURE/BONE HEALTH SECTION

1. Have you ever had a bone scan? Y N
   If so, what year? _____
   What was the outcome?_____

2. Please provide a list of any bone fractures you have had in the past.

Which bone	Cause (fall, accident, etc)	Year
_____	_____	_____
_____	_____	_____

3. Did a doctor tell you that any of these fractures were due to osteoporosis/osteopenia? Y N

4. Is your diet low in dairy products (< 3 servings)? Y N

5. Do you take calcium supplements? Y N
   If so, how much per day? _____

6. In a typical week, how many alcoholic drinks do you consume? _____

7. Do you drink coffee, tea, or cola products routinely? Y N
   About how much coffee, tea, or cola do you drink on an average day?
   _____

8. Do you have a heart valve or implant device such as knee, hip etc.? Y N

Date: _____

FEAR OF FALLING (Falls Efficacy Scale)

On a scale from 1 to 10, with *1 being very confident and 10 being not confident at all*, how confident are you that you do the following activities without falling?

Activity	Score 1 very confident 10 not confident at all
Take a bath or shower	
Reach into cabinets or closets	
Walk around the house	
Prepare meals not requiring carrying heavy or hot objects	
Get in and out of bed	
Answer the door or telephone	
Get in and out of a chair	
Getting dressed and undressed	
Personal grooming (e.g., washing your face)	
Getting on and off of the toilet	
Total Score	

V. SUN EXPOSURE

1. How many times a week do you spend more than 10 minutes outside? _____
2. How much time do you spend outdoors (minutes) per week? _____
3. How much of your outdoor time is spent without sunscreen on (minutes)? _____
4. How much of your outdoor time is spent "fully exposed" (minutes)? _____
("fully exposed" is defined as uncovered face, arms, and hands)

VI. EXERCISE HABITS

1. Do you perform any voluntary exercise? Y N

   a. What type(s) of exercise do you generally perform? (circle all that apply)
   Walking Running Bicycling Swimming

   Weight Lifting Aerobics Spinning Tennis

   Other _____

   b. In a typical week, how many days do you exercise? (circle)

   0-1 time/week 2-3 times/week 4-6 times/week daily

Date: _____

c. How many minutes do you typically exercise per session (circle)

<15 min 15-30 min 30-45 >45
Other_____

d. What is the typical level of exertion during your exercise?

Light Moderate Moderate/Heavy Heavy

e. When you are exercising do you ever feel limited by the following?

	Yes	No	Activity
Breathing	___	___	_____
Chest arm neck pain	___	___	_____
Low back pain	___	___	_____
Side ache	___	___	_____
Leg pain	___	___	_____
Foot drop	___	___	_____

Other? Please explain _____

_____

VII. EMPLOYMENT STATUS

1. Full-time employed ____
2. Part-time employed ____
3. Retired ____
4. Not working ____

Please describe employment status _____
_____

VIII. EDUCATION

1. None ____
2. High School ____
3. College ____
4. Masters ____

Date: _____

5. Ph.D. ____
6. Other ____

I certify that these answers are accurate and complete

_____ _____
YOUR SIGNATURE DATE

TABLE 13-3

Self-Administered Kurtzke

Instructions: Individuals with MS may experience difficulty in a number of different areas. For each of the 8 neurological categories below, please indicate the degree of difficulty (none, minimal, moderate, or severe) that you are experiencing at the present time.

	None	Minimal Difficulty Interferes only Slightly With Function	Moderate Difficulty Interferes Significantly With Function	Severe Difficulty Little or No Function Is Possible
1. Weakness in arm(s) and/or leg(s)	0	1	2	3
2. Tremor, clumsiness, or loss of balance	0	1	2	3
3. Double vision or slurred speech, or difficulty swallowing	0	1	2	3
4. Numbness or difficulty in feeling heat, pain or vibration in any part of the body	0	1	2	3
5. Frequency or urgent urination, awakening to urinate, not emptying the bladder completely, loss of bladder or bowel control, or constipation	0	1	2	3
6. Blurred vision in one or both eyes (even with glasses)	0	1	2	3
7. Difficulty with memory, calculation or reasoning	0	1	2	3
8. Stiffness or jerking of the muscles	0	1	2	3

OVERALL FUNCTION

On the following two pages are a number of statements that might be used to describe the overall function of MS subjects. These statements are arranged in order from least severe (0) to most severe (9.0).

Instructions:

1. First, locate the item that best describes your ability to walk.
   - If you are able to walk without limitations, please choose a statement under the section called "Able to Walk."
   - If you are able to walk only a limited distance, please choose a statement under the section called "Able to Walk Only a Limited Distance."
   - If you require aid(s) or assistance to walk or are unable to walk, please choose a statement under the section called "Aid(s) Required or Unable to Walk."
2. Circle the number of the one statement which best describes your overall condition at the present time.
3. In selecting your answer, refer back to your rating of the 8 neurologic categories listed.

Remember: Choose on *one* of the statements (0-9.0) which follow.

ABLE TO WALK

0.0 Essentially normal

1.0 Abnormality in *one* of the neurological categories but with no difficulty in function

1.5 Abnormality in *more* than one of the neurological categories but with no difficulty in function

2.0 Minimal difficulty in one of the neurological categories

2.5 Minimal difficulty in two of the neurological categories

3.0 Moderate difficulty in one of the neurological categories, able to walk

3.5 Moderate difficulty in one of the neurological categories and minimal difficulty in *one or more* of the neurological categories, able to walk

ABLE TO WALK ONLY A LIMITED DISTANCE

4.0 Able to walk without aid or rest at least 7 city blocks (500 meters or 1,625 feet)
Self-sufficient, up and about some 12 hours a day (Relatively severe difficulty in one neurological category or moderate difficulty in several of the neurological categories)

4.5 Able to walk without aid or rest at least 4 city blocks (300 meters or 975 feet)
May need minimal assistance, able to work a full day but may have some limitation of full activity (Relatively severe difficulty in one neurological category or moderate difficulty in several of the neurological categories)

5.0 Able to walk without aid or rest at least 2 ½ city blocks (200 meters or 650 feet)
Disability is severe enough to limit full daily activities—for example: to work a full day without job modifications
(Very severe difficulty in one of the neurological categories)

5.5 Able to walk without aid or rest at least 1 city block (200 meters or 325 feet)
Disability is severe enough to prevent full daily activities
(Very severe difficulty in one of the neurological categories or moderate difficulty in several of the neurological categories)

AID(S) REQUIRED OR UNABLE TO WALK

6.0 Assistance on *one* side (cane, crutch, brace) is required to walk approximately 1 city block (approximately 100 meters or 325 feet), with or without resting

6.5 Constant assistance on both sides (canes, crutches, braces, walker) is required to walk about 20 meters (65 feet)
(Moderate difficulty in more than two neurological categories)

7.0 Unable to walk more than about 5 meters (16 feet) even with aid
Essentially restricted to wheelchair
Can wheel self in standard wheelchair and can transfer alone
Up and about in wheelchair some 12 hours a day
(Severe difficulty in more than one neurological category or severe weakness only)

7.5 Unable to take more than a few steps, restricted to wheelchair
Can wheel self in standard wheelchair and may need aid to transfer
Cannot remain in wheelchair for a full day
May require motorized wheelchair
(Severe difficulty in more than one neurological category)

8.0 Essentially restricted to bed or chair
Propelled by others in wheelchair
May be out of bed part of the day
Can use arms and able to care for self
(Severe difficulty in several neurological categories)

8.5 Essentially restricted to bed much of the day
Has limited use of arms
Retains some self-care functions
(Severe difficulty in several neurological categories)

9.0 Restricted to bed
Cannot use arms
Can speak, can eat if fed by others
(Severe difficulty in several neurological categories)

Source: Scheinberg, L.C. Medical Rehabilitation Research and Training Center for MS, Department of Neurology, Albert Einstein College of Medical, Bronx, New York.

TABLE 13-4
Self-Administered Kurtzke (French Version)

Symptoms	NONE	MILD	MODERATE	SEVERE
1. Weakness of right arm	0	1	2	3
2. Weakness of left arm	0	1	2	3
3. Weakness of right leg	0	1	2	3
4. Weakness of left leg	0	1	2	3
5. Leg stiffness or deficit at walk	0	1	2	3
6. Tremor	0	1	2	3
7. Clumsiness of arms	0	1	2	3
8. Lose of balance	0	1	2	3
9. Double vision	0	1	2	3
10. Difficulty in speaking and/or swallowing	0	1	2	3
11. Uncontrolled urinary urgency	0	1	2	3
12. Difficulty in urination, incomplete micturition Or bladder emptying	0	1	2	3
13. Constipation	0	1	2	3
14. Loss of control of bladder	0	1	2	3
15. Loss of control of bowel	0	1	2	3
16. Difficulty in feeling a contact	0	1	2	3
17. Difficulty in feeling heat	0	1	2	3
18. Difficulty in feeling pain	0	1	2	3
19. Pain or burning sensation in any part of the body	0	1	2	3
20. Bizarre feeling (pins or needles, constriction) in any part of the body	0	1	2	3
21. Difficulty with memory	0	1	2	3
22. Difficulty with calculations	0	1	2	3
23. Difficulty with reasoning or thinking	0	1	2	3
Level of vision (with glasses)	>7/10 (reading possible)	6/10-4/10 (recognition possible)	3/10 or 2/10 (distinction of forms)	<1/10 (loss of vision)
24. Right eye	0	1	2	3
25. Left eye	0	1	2	3

Source: Verdier-Taillefer MH, Rouiiet E. Cesaro P. Alperovitch A. Validation of self-reported neurological disability in multiple sclerosis. *International Journal of Epidemiology* 1994; 23: 148-154.

Appendix C: Modified Fatigue Impact Scale and Rochester Fatigue Diary

Patient's Code: _____ Date: _____/_____/_____
month day year

Test#: 1 2 3 4 5 6

MODIFIED FATIGUE IMPACT SCALE (MFIS)

INSTRUCTIONS

Following is a list of statements that describe how fatigue may affect a person. Fatigue is a feeling of physical tiredness and lack of energy that many people experience from time to time. In medical conditions like MS, feelings of fatigue can occur more often and have a greater impact than usual. Please read each statement carefully, and then circle the one number that best indicates how often fatigue has affected you in this way during the past 4 weeks. (If you need help in marking your responses, tell the interviewer the number of the best response.) Please answer every question. You may ask for clarification to explain any words or phrases that you do not understand.

Because of my fatigue during the past 4 weeks…

	Never	Rarely	Sometimes	Often	Almost Always
1. I have been less alert.	0	1	2	3	4
2. I have had difficulty paying attention for long periods of time.	0	1	2	3	4
3. I have been unable to think clearly.	0	1	2	3	4
4. I have been clumsy and uncoordinated.	0	1	2	3	4
5. I have been forgetful.	0	1	2	3	4
6. I have had to pace myself in my physical activities.	0	1	2	3	4
7. I have been less motivated to do anything that requires physical effort.	0	1	2	3	4
8. I have been less motivated to participate in social activities.	0	1	2	3	4
9. I have been less motivated to do things away from home.	0	1	2	3	4

Date:___/___/___
Initials:_____

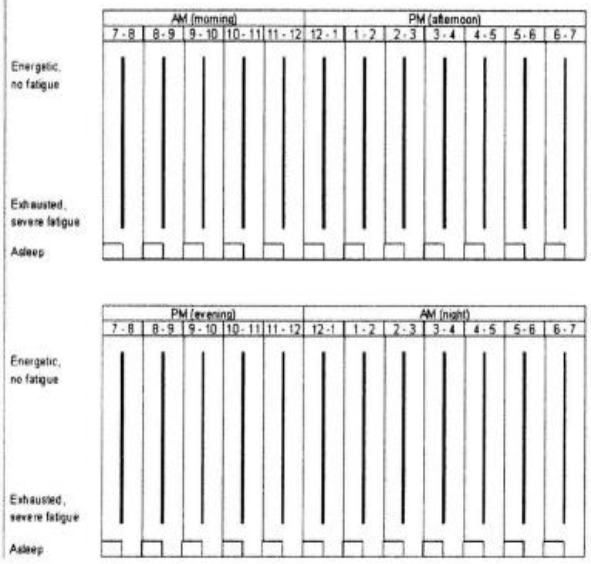
	Never	Rarely	Sometimes	Often	Almost Always
10. I have had trouble maintaining physical effort for long periods.	0	1	2	3	4
11. I have had difficulty making decisions.	0	1	2	3	4
12. I have been less motivated to do anything that requires thinking.	0	1	2	3	4
13. my muscles have felt weak.	0	1	2	3	4
14. I have been physically uncomfortable.	0	1	2	3	4
15. I have had trouble finishing tasks that require thinking.	0	1	2	3	4
16. I have had difficulty organizing my thoughts when doing things at home or at work.	0	1	2	3	4
17. I have been less able to complete tasks that require physical effort.	0	1	2	3	4
18. my thinking has been slowed down.	0	1	2	3	4
19. I have had trouble concentrating.	0	1	2	3	4
20. I have limited my physical activities.	0	1	2	3	4
21. I have needed to rest more often or for longer periods.	0	1	2	3	4

Date:___/___/___
Initials:_____

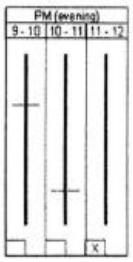
ROCHESTER FATIGUE DIARY

NAME: _____ DATE: _____

Instructions: Please mark a line each hour to rate your average energy level from energetic (high energy no fatigue) to exhausted (low energy, severe fatigue) during a 24 hour period (7 am to 7 am).



EXAMPLE



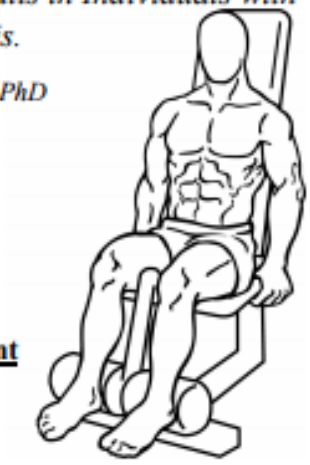
The patient has recorded mild fatigue from 9 - 10 pm, substantial fatigue from 10 - 11 pm, and asleep from 11 - 12 pm.

Appendix D: Recruitment Flyer

Subjects Needed!!!

Bilateral Fatigue of the Anterior Tibialis in Individuals with Multiple Sclerosis.

PI: Rebecca D Larson, PhD



To Participate

- Men and women, age 20-65
- Any activity level
- Interested in learning your body fat percentage
- Interested in testing leg strength

Time Commitment

- 5 Visits
- 3-4 Weeks of testing
- 1-2 Hours each Visit

Required Testing (5 visits)

- Body composition scan/body fat percentage testing (Visit 1)
- Strength testing (Visit 2)
- Fatiguing exercise (Visit 3 & 4)
- Functional performance testing (Visit 5)

If you would like more information please contact:

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The University of Oklahoma is an equal opportunity institution. Approved by the IRB for study #6802

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