Study Title: **A Pilot Project for Multifidus Muscle Evaluation in Patients with Multiple Sclerosis and Back Pain**

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Background and Rationale

Multiple sclerosis (MS) is an inflammatory disease affecting over 400,000 Americans that causes brain, optic nerve and spinal cord demyelination culminating in neurological symptoms.[1,2] Currently, MS is the most common non-traumatic cause of disability in patients between 20 to 50 years old.[1,2] Over 80% of MS patients have pain that largely affects their physical and mental quality of life, increasing disability.[1,2] Almost one-half of patients with MS and pain report that it interferes with social activities, work, or sleep.[1] As there is no cure for MS, approaches that improve quality of life while decreasing pain are needed. Moderate physical exercise has anti-inflammatory effects and decrease the sensation of pain in patients with MS, as it brings other benefits as better bone health and improvement in fatigue and balance.[2]

Low back pain is present in 42-52% of MS patients, reaching 76% of patients in a French cohort.[3] The multifidus muscle stabilizes the lumbar spine and its atrophy is associated to chronic back pain.[4,5] Oriented rehabilitation can increase the size and control of this muscle, improving lower back pain.[6,7]

As physical exercise can increase multifidus muscle performance and it has beneficial impact in MS, we propose a pilot study to evaluate the feasibility of a home-exercise program for the diagnosis and treatment of low back pain in MS patients focused on the multifidus muscle. If shown to be feasible, this novel tool can be taught in person or in online appointments, adding to the care of MS patients.

Specific Aims

We propose a pilot study to evaluate the feasibility of a home-exercise program for the treatment of low back pain in MS patients that are not pregnant or do not have a prior diagnosis of lumbar radiculopathy or fibromyalgia. This novel tool would target the multifidus muscle and could be taught in person or in online appointments.

Aims/Objectives

- Primary aim: study the feasibility of a home-exercise program in patients with MS younger then 50 years old with expanded disability status scale (EDSS) between 1.5 to 5.5.[8] Feasibility will be evaluated by the percentage of patients that finish the study as also by the compliance measured in hours with the home-exercise program.
- Secondary aim: qualify the multifidus dysfunction in patients with MS through evaluation of the cross-section area of the multifidus muscle measured by ultrasound at the beginning and end of the study, and by physical exam maneuvers (multifidus lift and prone instability tests).

- Exploratory aim: Evaluate the relation between compliance with the home-exercise program and the change in the cross-section area of the multifidus muscle and the change in pain score using PROMIS scale.[9]

Study Design and Procedures

This is a prospective pilot project to evaluate the feasibility of a home-exercise program to improve the function of the multifidus muscle with the intention to decrease back pain in patients with Multiple Sclerosis. Figure 1 summarizes the study design and procedures.

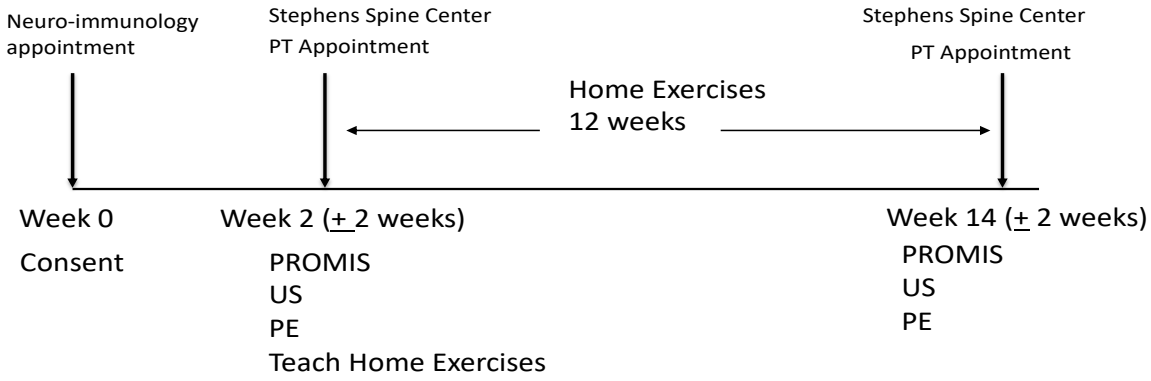

Figure 1

PROMIS: Patient-Reported Outcomes Measurement Information System, US : ultrasound, PE: Physical exam, PT: physical Therapy.

Adult patients with MS and back pain, further described in the study population section, will be asked to participate in this study during an appointment with their neuro-immunologist. It is standard of care to refer patients with back pain to the pain clinic.

After patient consent at the neuro-immunology appointment, the study participant will be contacted by UAMS Pain clinic staff for an appointment. In that appointment, the participant will fill PROMIS scale that evaluates patient's quality of life, depression symptoms and pain levels.It is standard of care to ask patients regarding pain and how pain affects their mood and their daily life. In this study, we are standardizing those questions with PROMIS scale.

Next, the participant will undergo a physical exam that will include standard of care physical exam plus physical maneuvers that evaluate multifidus muscle performance. After that, a physical therapist, who is a pain clinc staff, will teach a series of exercises focused at this muscle. This is not standard of care, and it is specific for the patients that are enrolled in this study.

On the same day, an ultrasound will measure the cross-section of the multifidus muscle. It is standard of care for patients in the pain clinic undergo ultrasound, for the participants in this clinical trial, we will include the multifidus muscle measurements.

After 3 months of home exercise, but not more than 4 months from the consent, the patient will return to repeat the same evaluations, with the same staff.

Office visits (including physical exam, ultrasound and the PROMIS scale) and physical therapy services are considered routine care for this patient population. Data will be collected from patient medical record for research.

The study will be closed for recruitment after ten patients complete the final assessment. Data analysis will then start. Medical charts will be reviewed in all patients that gave consent. The review of the medical charts will finish after one year of study enrollment. Therefore, patient participation will be less than 2 years.

Study Population

Patients following in the two neuro-immunology clinics at UAMS will be recruited to this study. It is protocol in the neuro-immunology clinic to ask patients with MS about pain. An email to other UAMS neurologists as also neurologists that are outside of UAMS will be sent to advertise that UAMS will be providing this pilot project. If their patients want to participate to this program, a referral will be needed for those patients to be seen in the neuro-immunology clinic.

The study population will comprise of adult patients with MS who have back pain and that are following at the neuro-immunology clinic at University of Arkansas for Medical Sciences (UAMS). We anticipate including up to 10 participants in this pilot study.

Inclusion criteria:

- confirmed diagnosis by an UAMS neuro-immunologist of relapsing-remitting MS or primary progressive MS or secondary progressive MS
- Age between 18 years old and 50 years old on consent
- Complain of low back pain or severe axial back pain
- English-speaking

Exclusion Criteria:

- Patients that also have the diagnosis of thoracic or lumbar radiculopathy or history of prior thoracic or lumbar spinal surgery.
- Patients that are currently pregnant.

- EDSS over 5.5 or less than 1.0
- Patient younger than 18 years old or older than 50 years old
- Knee total extension of less than 100 degrees

Risks and Benefits

A risk to study participants is the potential for loss of confidentiality of study data. Measures to protect the confidentiality of study data will be implemented as described in the Data Handling and Recordkeeping section below.

Another potential risk is discomfort during the home-exercises. This will be low-risk. All exercises are low impact, and they will be taught by a physical therapist and can be reviewed and any moment through an app that patient will download.

Potential benefits include decrease in low back pain and improve in stabilization of the spine and in balance, as gait.

Data Handling and Recordkeeping

The Principal Investigator will carefully monitor study procedures to protect the safety of research subjects, the quality of the data and the integrity of the study.

When a participant enrolls in the study, a registration form will be completed by the physical therapist in their appointment. A study file containing the subject's name, medical record number, date of birth, sex, phone number, and address will be created. All study participant materials will kept at the Stephen's Spine Center. All questionnaires answered will be scanned into the participants' study files and electronic medical chart. Data will be collected from the patient's medical record.

A password-protected electronic file in a safe digital UAMS-maintained server will be used to store and manage data that include demographics, relevant personal information, diagnosis, current and prior treatments, and questionnaire results. The Principal Investigator, Dr. Horta, will carefully monitor study procedures to protect the safety of research subjects, the quality of the data, and the integrity of the study. Six months after the study has been completed, information will be de-identified and stored in a safe digital UMAS-maintained server.

Data Analysis

Since this is a feasibility study, power analysis was not conducted.

Specific Aim 1: Primary aim: study the feasibility of a home-exercise program in patients with MS younger then 50 years old with expanded disability status scale between 1.5 to 5.5.

Data Analysis Strategy: Analysis will be descriptive. Feasibility will be evaluated by the percentage of patients that finish the study as also by the compliance in logged hours of exercise.

Specific Aim 2: qualify the multifidus dysfunction in patients with MS through evaluation of the cross-section area of the multifidus muscle measured by ultrasound at the beginning and end of the study, and by multifidus lift test and prone instability)

Data Analysis Strategy: As there is no literature in the evaluation of multifidus muscle in patients with MS, this will be a qualitative description of cross-section area and muscle performance on physical exam.

Specific Aim 3: Evaluate the relation between compliance with the home-exercise program and the change in the cross-section area of the multifidus muscle and the change in pain score using PROMIS Scale. Variables to also be considered will be EDSS of the patient.

Data Analysis Strategy: multiple linear regression will be used to evaluate if there is an association between the change in the multifidus cross-section area with compliance with home-exercise program, EDSS and pain level. ROC curve analysis will be done evaluating average hours of exercise per week and change in the cross-section area of a muscle.

This pilot project will end after 10 patients finish the home-exercise program of after one year.

Ethical Considerations

This study will be conducted in accordance with all applicable government regulations and University of Arkansas for Medical Sciences research policies and procedures. This protocol and any amendments will be submitted and approved by the IRB as required. Patients will not be compensated.

The formal consent of each subject, using IRB-approved consent forms, will be obtained before any study procedures. All subjects for this study will be provided a paper consent form describing this study in language understandable to the study population. Consent materials will provide sufficient information for subjects to make an informed decision about their participation in this study. The person obtaining consent will thoroughly explain what the subjects need to know about the study, including study requirements, study risks and benefits, and possible alternative treatment(s).

The consent process will take place during their neuroimmunology clinic appointment. Participation privacy will be maintained and questions regarding participation will be answered. No coercion or undue influence will be used in the consent process. This consent form must be signed by the subject. The participant will receive a paper copy of

the signed consent form and the informed consent process will be documented in the research record.

Dissemination of Data

Results of this study may be used for presentations, posters, and publications. The publications will not contain any identifiable information that could be linked to a participant. The study will be listed on clinicaltrials.gov in accordance with FDA requirements. The final, anonymized dataset will be made publicly available at the clinicaltrials.gov website.

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