Evaluation of Muscles Affected by Myositis Using Magnetic Resonance Elastography

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Abstract

Introduction—Idiopathic inflammatory myopathies (IIM or myositis), is a group of autoimmune diseases that result in decreased muscle strength and/or endurance. Non-invasive tools to assess muscle may improve our understanding of the clinical and functional consequences of myopathies and their response to treatment. This study examined Magnetic Resonance Elastography (MRE), a non-invasive technique that assesses the shear modulus (stiffness) of muscle, in IIM subjects.

Methods—Nine subjects with active myositis completed the MRE protocol. Participants lay in a positioning device, and scans of the vastus medialis (VM) were taken in the relaxed state and at two contraction levels. Manual inversion was used to estimate the stiffness.

Results—A significant reduction in muscle stiffness was seen in myositis subjects compared with healthy controls during the 'relaxed' condition.

Discussion—The use of non-invasive technologies such as MRE may provide greater understanding of the pathophysiology of IIM and improve assessment of treatment efficacy.

Keywords

Muscle; Magnetic Resonance Elastography (MRE); Myositis; Muscle Stiffness; Noninvasive

Introduction

Polymyositis (PM), dermatomyositis (DM) and juvenile dermatomyositis (JDM), are a group of autoimmune inflammatory disorders of the muscle, collectively known as idiopathic inflammatory myopathies (IIMs) [1]. While they differ in pathology, common findings include lymphocytic infiltration, edema within the muscle and myofiber necrosis on muscle biopsy. Serum levels of creatine kinase (CK), aldolase, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) are frequently elevated[2]. Proximal muscle weakness and muscle fatigue are common symptoms for all conditions. This weakness can be quantified using manual muscle testing (MMT), while changes to muscle activation are measured by electromyography (EMG). Corticosteroid therapies and immunosuppressive agents are traditionally used for disease management[1]. Exercise is often recommended and

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is effective for increasing function and activity[3]. However, the complex yet inconsistent onset and progression of myositis make diagnosis and treatment exceptionally difficult.

Knowledge of the effects of these diseases on whole muscle is currently lacking. To the authors' knowledge, no study has examined material properties of muscle in this patient population. While significant information is gained from biopsies, the inhomogeneity of the disease does not guarantee a measure of the diseased tissue. MMT and other functional indices provide an overall picture of muscle function, but they do not provide direct information on the inherent properties of the muscle. The elevation of various enzymes[4] and the proliferation of destructive cells suggest significant changes to muscle composition and mechanical aptitude. Such changes in enzymes are expected to have deleterious effects to the overall mechanical integrity of the muscle. These enzymes are known to attack the passive components of the muscle like the extra-cellular matrix[5]. This idea is further supported by the work of Krivickas et al.[6] who concluded that the functional capacities of single fibers are preserved in patients with IIM. However, altered function of the passive elements cannot be ruled out, as it has not been studied. While the aforementioned techniques have been relatively successful in disease assessment, they still do not fully assess impaired muscle function. Invasive techniques, such as muscle biopsy are not feasible on a repetitive basis. Tools and methods are needed to evaluate the mechanical integrity of significant volumes of diseased tissue. For this reason, non-invasive techniques have been developed to evaluate a muscle's material property known as shear modulus or what is termed "stiffness".

It is challenging to determine the material properties in muscle without altering the tissue and affecting measurement. Many non-invasive methods use an indirect measure of a tissue's density as a substitute for a direct measurement of its stress-strain relationship (elastic modulus). Magnetic Resonance Elastography (MRE) is a non-invasive imaging technique capable of estimating the mechanical properties of human tissue, in vivo, based on the propagation of shear waves[7]. MRE is able to image a larger area of tissue and thus provide more information than a single biopsy. Several studies have reported on the utility of MRE in evaluating muscle in different disease states, including its ability to differentiate muscle properties in subjects before and after treatment for thyroid disorders[8], and to detect differences in muscle tissue with aging [9]. The purpose of this study was to apply MRE to a group of subjects clinically diagnosed with active myositis to non-invasively assess the mechanical characteristics of muscle tissue. The combination of muscle weakness and increased enzyme levels led to the hypothesis that the shear modulus would be significantly lower in the vastus medialis muscle of subjects with IIM.

Methods

After approval from our institutional review board and written informed consent, nine subjects (6 females, 3 males; age range 12-68 years) with active myositis (PM, DM, and JDM), were recruited from the Division of Rheumatology at Mayo Clinic. The diagnosis was supported by muscle biopsy and/or EMG with the diagnosis of inclusion body myositis excluded based on muscle biopsy. At the time of MRE scan, comprehensive disease activity assessments were available for myositis subjects, as created by the International Myositis Assessment and Clinical Studies (IMACS) which include manual muscle testing, muscle enzymes, health assessment questionnaires and physician global assessment [10]. Disease activity was based on previously published criteria[11,12]. Age- and gender- matched controls with no history of muscle disease were included for comparison.

A setup similar to what is described in the literature[8,13] was used here. Subjects lay supine on a custom-made non-magnetic positioning device, and their knees were placed in 30°

flexion. The entire device was placed on the scan table of a 1.5T General Electric Signa Magnetic Resonance Imaging (MRI) machine. The device contained two magnetic resonance (MR) compatible load cells (Interface, Scottsdale, AZ, USA) that measured forces generated by the subjects. Shear waves were delivered to the thigh via pneumatic driver. A large active loudspeaker was connected to a hose, which connects to a smaller silicone tube. This smaller tube wrapped around the thigh at approximately 1/3 the distance from the patellar tendon to the anterior superior iliac spine. The sound created by the loud speaker varied the standing air pressure in the hose and tube, causing the tube around the thigh to expand and contract. This created a vibration at an operating frequency of approximately 90Hz. A custom-made Helmholtz surface receiver coil was placed around the thigh and was used for data acquisition. Lastly, a mirror was placed over the head of each participant, which allowed the participant to receive visual feedback. An illustration of the complete setup can be seen in Figure 1.

For this study, the vastus medialis (VM) of the leg most affected by the disease was studied. This muscle was used because it is a proximal leg muscle, and initial tests showed good wave propagation in this muscle. If the patient was unable to determine which leg was most affected by myositis, the dominant leg was scanned, as long as no biopsy had been taken from that leg. For the healthy controls the dominant leg was scanned. Axial, coronal, and sagittal MR images or "scouts" were obtained to visualize the muscles of interest. Based on these scout images, three scan planes were placed within the muscle. These scan planes were the planes in which the MRE images would be taken. Each plane was evaluated based on the amount of muscle area present in the image. The two planes with the largest area were used for the MRE exam. A two-dimensional gradient-echo sequence was used while shear waves were passed through the thigh from the vibrating silicone tube. Typical data acquisition parameters were: repetition time (TR) of 100–350 msec, echo time (TE) of 10–60 msec, acquisition matrix size of 256 by 256, and flip angle of 45°. Four phase offsets were acquired for each acquisition or scan; these offsets are essentially four snapshots of the propagating wave. Therefore, each scan or acquisition measures the motion of the tissue in the direction of a motion sensitized gradient.

Each study participant completed the following study protocol to the best of their ability. Scans were taken at three force levels: relaxed, 10%, and 20% maximum force. This maximum force was determined by asking the participant to press as hard as possible, with the tested leg, over a course of 10 seconds. The resting leg weight as well as the maximum force was entered into the LabView (National Instruments, Austin, TX, USA) program, which automatically calculated percentage values. Visual feedback was in the form of a large bulb that turned green as the subjects generated the prescribed amount of force through the load cells. Approximately three to five minutes of recovery time between scans was given to controls, while six to seven minutes of recovery time between scans was given to myositis subjects. A slightly longer recovery time was given to myositis subjects to account for the excessive fatigability of their muscles.

Data Analysis

After collection of scans, the data was analyzed on an individual basis in MREview (mreview 6.06.08, Mayo Clinic and Foundation, Rochester, MN, USA). The first step was to "unwrap" wave data. This procedure seeks to eliminate any aliasing of the wave, and a manual inversion technique was then used to estimate stiffness in the tissue. A one-dimensional profile was drawn within the muscle in a direction that was perpendicular to the traveling wave front. It was important to place this 1D profile in the middle of the muscle, away from the vibration source and edges of the muscle. Since four offsets were taken, four graphs of the peak and trough along that 1D profile are generated. The wavelength (distance

between peaks) was measured and averaged over the four offsets. Average wavelength was then used to calculate the shear modulus according to equation 1:

$$\mu = \lambda^2 f^2 \rho$$

where μ is the shear modulus (stiffness), λ is the average wavelength, f is the frequency, and ρ is the assumed density of muscle tissue (1000 g/cm^3).

In the control muscle, one wave front was seen propagating through the tissue. Initially, multiple profiles were drawn within the control VM, however all calculated values for stiffness were equal (because of wave uniformity) and one profile was used to determine the shear modulus or stiffness. It should be noted that all the controls were able to maintain the 20% maximum force, however some wavelengths were too long to process and therefore no data point is shown in the results.

Multiple wave fronts or wave patterns were often seen in the muscles of the myositis patients. For processing, multiple 1D profiles were drawn within the muscle, which in turn, led to multiple MRE readings for the same muscle. Therefore the lowest and average measurements were used for the myositis subjects, whereas a single measurement was used for healthy controls, as a single wave front was observed.

Statistics

Paired t-tests ($\alpha = 0.05$) were used to detect differences in shear modulus between myositis subjects and controls. Both the lowest and average stiffness in myositis subjects were compared with healthy controls.

Results

The demographics of myositis subjects and their clinical measures are presented in Table 1. All subjects had either low to moderate disease activity and were on different treatment regimens. Those subjects recorded as having no current treatment at the time of study had either been newly diagnosed or had been diagnosed previously but were off treatment when their disease flared. When comparing the lowest stiffness values for a myositis subject with a healthy, matched control, a statistically significant difference was seen between the two groups during the 'relaxed' force level, while the other force levels approached statistical significance (Figure 2). When comparing the average MRE measurements of stiffness from the myositis subjects to the single MRE measurements from the healthy controls, no statistical difference was seen between the two populations; however a trend of reduced muscle stiffness in myositis subjects was noticeable. Effects from fatigue were also observed, as some of the myositis subjects had difficulty holding the 20% maximum contraction levels. This data was not included in the analysis.

Discussion

MRE, a novel non-invasive technique to evaluate tissue in vivo, was used to assess the material characteristics of muscles from subjects suffering from active myositis due to PM or DM/JDM. Of particular interest was the noticeable trend of reduced muscle stiffness in myositis subjects compared with healthy controls. There was also a noticeable difference in the forms of propagating waves, as well as the number of wave fronts within one muscle, in the myositis subjects when compared with controls.

Elastography, and more specifically MRE, is based on a concept similar to traditional palpation exams, as a tissue's abnormal response (resistance) to an external stress (pressure), is a sign of abnormality. However elastography uses this response to quantify tissue stiffness or modulus of elasticity. Manduca et al.[14], report tissue stiffness as being one of the most severely altered parameters in pathologic tissues, and therefore it is an excellent variable for examination. Such an evaluation becomes challenging in muscle because of the complexity of the tissue, including mechanical and biochemical adaptations and multiple functional components (*i.e.* force generation and transmission). The principles of elastography are also applied with other imaging modalities like ultrasound or a combination of ultrasound and MR. Ultrasound elastography is often applied in the form of transient elastography or ultrasound transient elastography (UTE). UTE transmits a vibration through a tissue while an ultrasound probe captures wave propagation or wave velocity[15]. A commercial version of this technology known as the Fibroscan (Echosens, Paris, France), has been employed in Europe to measure the material properties of the liver. Ultrasound-based elastography methods are often the choice of clinicians because of their availability and lower cost compared to MRE. An additional method known as Acoustic Radiation Force Impulse (ARFI) imaging has also be used to evaluate the material properties of soft tissues, in vivo, by creating short acoustic radiation pulses in the tissue of interest and evaluating the displacements or relaxation properties of the tissue[16-18]. Bensamoun et al.[15], compared in vivo liver stiffness results using MRE and the Fibroscan® device. Overall, the authors found no significant difference in the measurements between the two modalities. The authors also noted more variation in the measurements taken by the Fibroscan®. Oudry et al.[19], conducted a study comparing the two modalities in gel phantoms. These phantoms are solid samples that can be manufactured into various shapes with predetermined material properties. Oudry and colleagues a found a high correlation between MRE and UTE (r^2=0.93).[19] They also noted a greater difference in measurement in stiffer phantoms, however overall there were no statistically significant differences between the two techniques.

The trend of decreased stiffness as seen in this study further validates the negative effects of myositis on muscle tissue. We conclude that muscle of active myositis subjects is significantly less stiff than healthy controls in a relaxed state. However no conclusion regarding gender or age effects can be made based on the data presented here. To our knowledge this is the first study to use MRE to look at stiffness in IIMs, however it was not the first to use MRE to study a population with diseased muscle. Bensamoun et al.[8], used MRE to study muscle in hyperthyroid subjects compared to controls.

An increase in stiffness during contraction was expected and seen in this study. The large variation in stiffness within both groups during force generation highlights the complexities of muscle, as it appears that force generation alters the inherent material properties of the tissue. As previously mentioned, data points are not presented for some participants at the 10% and 20% maximum force levels. Unfortunately, some of the myositis subjects were unable to maintain these contraction levels during the allotted scan time which was approximately one minute and thirty seconds. This was somewhat expected, as it is recognized that increased muscle fatigue occurs in myositis patients. Though the number of participants prevented correlation analysis, it is interesting to note that two myositis subjects with the lowest strength test score and highest M.D. Global Score (*i.e.* the most active disease) did not have the lowest average stiffness. The effects of altered muscle stiffness or integrity are also seen in the complicated wave patterns or wave forms, as well as the multiple wave fronts seen within one muscle in myositis subjects. A detailed analysis of complicated waveforms in biological tissue by Papazoglou et al.[20], concluded that the material properties of the tissue caused significant changes to propagating waveforms. Therefore, the existence of multiple waveforms, as seen in this study, provides insight into

the isotropy and homogeneity or lack thereof, within diseased muscle. We recently conducted an analysis of the amplitude of mechanical waves traveling through the vastus medialis in myositis and hyperthyroid subjects as well as healthy controls[13]. A statistically significant difference was seen in a "decay constant", a single value related to the dissipation of the wave's energy, between the subjects with disease and control groups. This suggests that the underlying pathophysiology in these conditions affects muscle viscoelasticity.

The cause of the reduced stiffness, complex waveforms, and excessive fatigability warrant further study. However it could be conjectured that these are the result of a significant destruction of passive structures or elements like collagens within the muscle. Fatigue has been shown to be related to altered extracellular matrix in congestive heart failure[21]. A delicate balance exists between the destruction and repair or remodeling of muscle tissue by proteins, proteases, and protease inhibitors. The disruptions to this balance from myopathies would impact the passive elements of the muscle and ultimately impact muscle stiffness and force transmission. The hypothesized disruption of the passive components of muscle, fiber necrosis, and scarring could contribute to the difficulty in maintaining contractions. The functional consequences of reduced muscle stiffness include reduced force transmission from the active components (*i.e.* actin and myosin) to the tendon, which in turn forces the healthy fibers to generate more force.

Given the current understanding of the normalcy of the fibers or contractile components[6] and the notable difference in muscle stiffness during a "relaxed" state, treatments geared towards passive components should be explored. The success of specific exercise regimens for the treatment of myositis should also be considered. Exercise increases the percentage of type I fibers, which in turn improves endurance, and neuromuscular adaptation. In addition, exercise has been shown to downregulate many genes that cause inflammation in PM and DM[22].

One of the limitations of this study was the small number of subjects, which limited statistical power. In spite of this, differences in muscle stiffness in the relaxed state between the healthy controls and myositis subjects were great enough to show statistical significance. Another limitation of this study is that effects of treatment regimen were not considered. Therefore, stiffness values of myositis subjects on medications may not reflect the actual stiffness, as it is presumed that medications like prednisone would influence the inflammation of the muscle and its material properties. Even with these medications, all myositis subjects were still considered to have active disease; therefore, the measures presented here do in fact speak to change in the muscle. Further study is needed to determine the effects of various levels of myositis disease activity on stiffness in order to define a clinically significant change in muscle stiffness. Further work is also needed to determine whether MRE would be a useful tool in differentiating the types of inflammatory myopathies. Other material properties of muscle require additional study, as reduced stiffness is seen in both hyperthyroidism and inflammatory myopathies. Therefore, in order to differentiate between the different myopathies, viscoelastic properties or wave attenuation may provide helpful information. Finally, the placement of the MRE scanning plane was heavily dependent upon the operator. However, for our study, all of the scans were done by the same two researchers, therefore this effect was likely minimized.

In conclusion, we have used MRE to non-invasively quantify the material properties of muscles affected by active myositis. Overall, shear modulus or stiffness of in vivo muscle tissue has shown a general trend of decreased stiffness in these subjects when compared to matched controls. We hypothesize that this decreased stiffness creates difficulty in force transmission and is responsible for the lack of endurance seen in many myositis patients. Future work should include further exploration of the effects of myositis on passive

elements like structural proteins, which may help improve assessment of treatment strategies, as well as assist with early differentiation between types of myopathies. In addition, the use of non-invasive technologies such as MRE to understand muscle in its contracted state may provide greater insight into muscle fatigue and altered endurance.

Acknowledgments

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Abbreviations

|	
ALT	Alanine Aminotransferase
ARFI	Acoustic Radiation Force Impulse
AST	Aspartate Aminotransferase
CK	Creatine Kinase
DM	Dermatomyositis
EMG	Electromyography
IIM	Idiopathic Inflammatory Myopathies
JDM	Juvenile Dermatomyositis
MRE	Magnetic Resonance Elastography
MMT	Manual Muscle Testing
PM	Polymyositis
TE	Echo time
TR	Repetition time
UTE	Ultrasound transient elastography
VM	Vastus Medialis
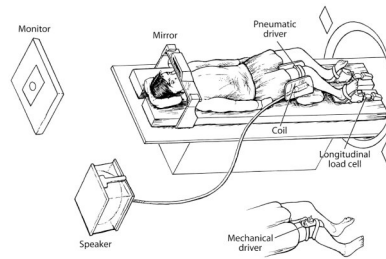
Figure 1.
The test setup for each MRE scan. Participants lie supine on a custom built jig that contained MRI compatible load cells. A pneumatic drive comprised of a loudspeaker, 6m hose, and a smaller silicone tube is used to generate vibrations in the thigh muscles. Displacements were imaged and inverted into an estimate of stiffness. **FROM: Determination of Thigh Muscle Stiffness Using Magnetic Resonance Elastography 23:242-247. Copyright (Bensamoun 2006); reprinted with permission of John Wiley & Sons, Inc.**
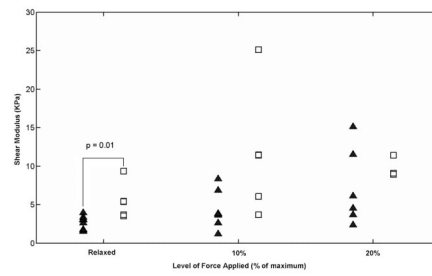
Figure 2.
Shear modulus (stiffness) of the vastus medialis muscle in myositis subjects (blue, solid triangles) versus age and gender matched controls (red, hollow squares). A statistically significant difference was seen in the relaxed condition.

Table 1

A description of the patient demographics and clinical scores at the time of MRE examination.

Patient	Diagnosis	Age	Gender	Disease Duration (months)	Treatment	MMT[*]	MD Global Score[†]	CHAQ/HAQ[‡]
1	JDM	12	female	12	prednisone and methotrexate	80	1	0
2	JDM	16	male	6	prednisone and methotrexate	80	1	0
3	DM	33	female	3	prednisone and imuran	68	4	0.5
4	DM	68	female	12	prednisone	65	4	0.5
5	PM	53	female	72	none	70	3	1
6	DM	55	male	12	prednisone	76	1	0.5
7	DM	48	male	1	prednisone	76	3	0.5
8	DM	63	female	12	none	70	1	1
9	PM	67	female	36	prednisone/methotrexate	78	1	1

[*] Manual Muscle Test (MMT) is a measure of muscle strength (0-80).

[†] MD Global score is a clinical assessment score from 0 to 10, where the higher the score the more severe the disease in the physician's opinion.

[‡] CHAQ/HAQ is a functional assessment based on the patient's impressions. It ranges from 0 to 3, the higher the score, the worse the perceived impairment.