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Elastic properties of skeletal muscle and subcutaneous tissues in Duchenne muscular dystrophy by magnetic resonance elastography (MRE): a feasibility study

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Abstract:

Objectives: Increasing fibrosis of skeletal muscle is a hallmark of the dystrophic process in Duchenne muscular dystrophy (DMD) and is a hindrance to functional muscle regeneration. We sought to evaluate the capacity of magnetic resonance elastography (MRE) to characterize the elastic properties of the vastus medialis (VM) muscle as well as that of its adjacent subcutaneous tissue in relaxed and exercised states.

Material and Methods: Six healthy controls and six ambulant DMD boys underwent a MRE test. The shear stiffness (μ) and cartographies of stiffness were generated.

Results: At rest, the DMD stiffness of the VM was higher than the healthy control muscle, suggesting altered elastic properties of the DMD muscle, most likely due to muscle fibrosis. In a contracted state, the VM stiffness of the DMD was lower than that found in healthy muscle, due to a lack of the muscle contractile properties. The results further showed a stiffer subcutaneous adipose tissue for the DMD compared to the healthy participants at rest.

Conclusion: This is the first study to demonstrate muscle altered elastic properties of dystrophic muscle in DMD by MR elastography. Surprisingly, subcutaneous tissue in DMD also showed dramatically altered elastic properties, a new observation which will need further investigation.

Key words: Magnetic resonance elastography; Duchenne muscular dystrophy; stiffness; vastus medialis; subcutaneous adipose tissue.

Resumé:

Objectifs : La myopathie de Duchenne (DMD) se traduit par un muscle dystrophique caractérisé par une augmentation de la fibrose qui entrave sa régénération fonctionnelle. Nous avons cherché à évaluer la capacité de l'élastographie par résonance magnétique (ERM) à caractériser les propriétés élastiques du muscle vastus medialis (VM), ainsi que celles de son tissu sous-cutané adjacent, dans un état relâché et contracté.

Matériels et Méthodes : Six sujets sains et six garçons DMD ambulants ont subi un test ERM. Le module de cisaillement (μ) et la cartographie des propriétés élastiques ont été générés.

Résultats: Au repos, les propriétés élastiques du muscle VM pour les patients DMD étaient plus élevées que celles des muscles VM sains. Ce résultat révèle une altération des propriétés élastiques du muscle DMD, probablement due à la fibrose musculaire. Dans un état contracté, les propriétés élastiques du muscle VM pour les patients DMD étaient inférieures à celles obtenues pour les muscles sains, à cause de son manque de contractilité. Au repos, les résultats ont également montré un tissu sous-cutané plus rigide pour les patients DMD comparé à celui des participants sains.

Conclusion: Cette étude est la première à démontrer une modification des propriétés élastiques pour les muscles DMD dystrophiques avec l'élastographie par IRM. Étonnamment, le tissu sous-cutané des patients DMD a également montré des propriétés élastiques qui étaient considérablement modifiées. Cette nouvelle observation nécessitera des études approfondies.

Mots clés: Elastographie par résonance magnétique, dystrophie musculaire de Duchenne, élasticité, vastus medialis, tissu sous-cutané

1. INTRODUCTION

Duchenne muscular dystrophy (DMD) is caused by mutations of the dystrophin gene which lead to absence of dystrophin protein in skeletal muscle inducing repetitive cycles of muscle necrosis and regeneration. This process eventually results in loss of contractile tissue, intra- and perimyseal fibrosis, and finally regenerative failure and fibro-fatty replacement of skeletal muscle tissue. DMD is a systemic disease and absence of dystrophin and its different isoforms also variably affects other organs such as the heart, brain, eyes, and smooth muscles notably of the gastrointestinal tract. However, no qualitative alteration of the subcutaneous tissue has been described in DMD so far.

Magnetic resonance imaging (MRI) techniques are currently used for the monitoring of DMD patients due to their capacity to qualitatively and quantitatively describe muscle tissue changes and patterns of skeletal muscle damage in disease [1-3]. MRI acquisitions were further improved with the application of new nuclear MR protocols previously established on dystrophin-deficient animal models, such as the *mdx* mouse [4] and the GRMD Golden Retriever dog [5], as well as for monitoring of a therapeutic response in preclinical trials [6,7]. According to MRI experiments performed on these animals, it was demonstrated that T2-weighted image analysis could be use to characterize the progression of affected DMD muscles [8-10]. Subsequently, Kim's study [11] on Duchenne patients has demonstrated the feasibility of the T2 mapping to assess gluteus behavior after steroid treatment. MRI technique was also used to quantify the DMD body composition [12] which exhibits an increase of adipose tissue with an important muscle fatty infiltration [13-14]. Thus, in addition to the muscle tissue, Gaeta et al. [15] have distinguished the fat tissue to the muscle in order to quantify the ratio muscle / fat fraction as a potential marker of the DMD disease state.

The quantification of the functional properties of DMD muscle is a key point for neurologists who need to objectively quantify the disease patterns and states of individual muscles in relation to the grade of a myopathy. Magnetic resonance elastography (MRE) is a recent clinical exam used for the diagnosis of liver fibrosis. This method was further developed to characterize the stiffness of individual muscles. MRE is composed of a pneumatic driver which generates shear waves transmitted to the tissue investigated. The velocity of the wave, or its wavelength, increases with the stiffness of the muscle and the velocity measurement allows the quantification of the muscle stiffness. Thus, healthy databases of calf [16] and thigh [17] muscles were established as a function of the age and functional state, i.e. in relaxed and contracted conditions [18, 19]. Subsequently, MRE protocols were further developed for the quantification of fibromyalgia and myofascial pain [20, 21] and for the assessment of muscles affected by myositis [22, 23]. Moreover, the MRE postprocessing was improved in order to represent a mapping of the muscle stiffness [19], thereby directly visualizing the affected muscle areas.

Thus, the purpose of this present study was to characterize the elastic properties (shear stiffness) of skeletal muscle of the upper leg as well as the subcutaneous tissue in DMD compared to healthy controls.

2. MATERIAL/PATIENTS

Twelve children composed of six healthy boys (mean age = 10 ± 0.6 yrs, range = 8-12, mean BMI = 17.5 ± 1.0 kg/m²) with no muscle abnormality or history of muscle disease, and six Duchenne Muscular Dystrophy (DMD) boys (mean age = 9.9 ± 1.4 yrs, range = 8-12, mean BMI = 17.2 ± 2.0 kg/m²) were recruited at the Polyclinique Saint-Côme and at the Institute of Myology, Groupe Hospitalier Pitié-Salpêtrière, France), respectively. Each subject underwent a magnetic resonance elastography (MRE) test and only patients satisfying the following inclusion (Duchenne myopathy validated by a genetic test, ambulant) and exclusion (corticoid treatment, pacemaker, arthrodesis, respiratory assistance) criteria were selected for a MRE exam. This study was approved by the institutional review board of Amiens' Hospital (#A00834-49) and informed consents were obtained from the patients and parents.

3. METHODS

Magnetic Resonance Elastography (MRE)

MRE is a non invasive technique which was previously applied to skeletal muscle tissue and is briefly described hereinafter [17].

Each subject lay supine inside a 1.5T MRI machine (General Electric HDxt machine) with the right leg resting on a custom MR compatible leg press, capable of measuring the applied load (Fig. 1). The knee was flexed to 30° with the right foot placed on a footplate, in which a load cell (SCAIME, Annemasse, France) was fixed to record the developed force, and a visual feedback (LABVIEW program) of the applied load is given to the study participants inside the MR room.

MRE can be summarized in three main steps in order to obtain a stiffness mapping of the muscle and of the subcutaneous adipose tissue.

The first step is based on the generation of shear waves inside the muscle by using a pneumatic driver represented by a silicone tube wrapped and clamped around the subject's thigh one third of the distance from the patellar tendon to the greater trochanter. The pneumatic driver had a long hose connected to a large active loudspeaker. This system created time-varying pressure waves propagating shear waves within the muscle at 90 Hz which is the optimal frequency (f) to characterize muscle elasticity with the present tube driver [24].

The second step aims to visualize the propagation of the shear waves within the muscle tissue. Thus, magnetic resonance phase images (Fig. 2), revealing the wave displacement within the vastus medialis (VM) and the subcutaneous adipose tissue, were recorded with four offsets, a motion sensitizing gradient echo sequence, a flip angle of 45°, a 24 cm field of view, a 5mm slice thickness, a 256 x 64 acquisition matrix, and a TE/TR for healthy and DMD children equal to 23/100 ms and 23.2/44ms, respectively.

The third step analyzes the displacement of the waves through a quantification of the wavelength (λ) along a white profile manually prescribed in the direction of the shear wave propagation (Fig. 2a and b) inside the vastus medialis and the subcutaneous adipose tissue. Subsequently, assuming that the muscle and adipose tissues were linear elastic, isotropic, homogeneous and incompressible, the local shear stiffness (μ) was calculated using the following equation $\mu = \rho \cdot (f \cdot \lambda)^2$, where ρ is the muscle and adipose densities fixed to 1000 kg/m^3 . Moreover, an inversion algorithm (LFE: local frequency estimate) [25] was applied to the phase image providing a cartography of the global tendency of the tissue elasticity (Fig. 3).

Statistical analysis

Unpaired student's t-tests were performed with the software Statgraphics 5.0 (Sigma Plus, Maryland, USA) to compare the shear stiffness values between healthy and DMD children for the vastus medialis at different conditions, and for the subcutaneous adipose tissue. In addition paired student's t-tests were used to compare the shear stiffness values between the muscle and the subcutaneous adipose tissue for healthy and DMD children. The level of significance was set at $P < 0.1$.

4. RESULTS

Comparison of the stiffness measurements between the VM and the subcutaneous adipose tissue for each cohort

In normal subjects, the measurement of the wavelength (Fig. 2a), along the white profiles, within the healthy (H) soft tissues showed a higher significant ($P < 0.1$) shear stiffness ($\mu_{H_VM} = 3.06 \pm 0.21$ kPa) for the vastus medialis (VM) muscle at rest compared to the subcutaneous adipose tissue ($\mu_{H_Fat} = 2.21 \pm 0.20$ kPa) (Fig. 4).

In contrast, DMD patients showed similar shear stiffnesses measured within the VM and within the subcutaneous adipose tissues ($\mu_{DMD_VM} = 4.75 \pm 0.50$ kPa vs $\mu_{DMD_Fat} = 4.19 \pm 0.39$ kPa) (Fig. 4). This result is well represented by the cartography of stiffness of Duchenne muscle tissue (Fig. 3b) where the vastus medialis and the subcutaneous adipose tissues have the same color distribution in contrast to normal controls where the muscle stiffness exceeds that of the subcutaneous tissue. Quantification of the stiffness values revealed that the subcutaneous adipose tissue ($\mu_{DMD_Fat} = 4.19 \pm 0.39$ kPa) of the DMD children had a significant ($P < 0.1$) higher stiffness (about 2 kPa) than the healthy ($\mu_{H_Fat} = 2.21 \pm 0.20$ kPa) ones (Fig. 2 and 4).

Comparison of the muscle tissue stiffness at different states of contraction between healthy and DMD children

The behavior of the shear waves within the healthy muscle showed a uniform propagation pattern (Fig. 2a) while irregular propagation, indicative of tissue heterogeneity and visible as gaps of wave displacement appears within the DMD muscle (Fig. 2b).

At rest, the DMD stiffness value of the VM was higher ($\mu_{DMD_VM} = 4.75 \pm 0.50$ kPa) than the healthy control muscle ($\mu_{H_VM} = 3.06 \pm 0.21$ kPa). Moreover, the cartography of the

stiffness revealed that the VM of the DMD is composed of different elasticities represented by a mapping of various colors (Fig. 3b). This result indicates a less homogeneous composition of the DMD muscle tissue. On the contrary, the healthy VM muscle showed a more uniform cartography of stiffness (Fig. 3a).

In a contracted state, lower stiffness values were measured for the VM of the DMD compared to healthy control muscle at 10% MVC ($\mu_{\text{DMD}_{10\%}\text{MVC}} = 7.50 \pm 0.62$ kPa vs $\mu_{\text{H}_{10\%}\text{MVC}} = 15.89 \pm 2.38$ kPa) and 20% MVC ($\mu_{\text{DMD}_{20\%}\text{MVC}} = 10.96 \pm 0.60$ kPa vs $\mu_{\text{H}_{20\%}\text{MVC}} = 15.13 \pm 2.96$ kPa). It was expected that the vastus medialis of the DMD children would contract less and therefore develop a significantly ($P < 0.05$) lower increase of stiffness compared to control muscles (Fig. 5).

5. DISCUSSION

The capacity of MRE technique to assess the muscle stiffness of healthy children was recently demonstrated in a study characterizing the age-related changes of the functional properties [26]. This age-dependent data can be used as a baseline for the evaluation of age or disease related changes of elastic properties of skeletal muscle. Thus, the stiffness data base established for healthy pediatric muscles and subcutaneous tissue will be a valuable instrument to evaluate the grade of tissue alteration or the progress of the disease, as well as the effect of treatments such as the ongoing pharmaco-gene therapeutic trials for Duchenne muscular dystrophy. In the present study, we determined the feasibility of the MRE technique to detect and to quantify the stiffness of affected muscle and subcutaneous adipose tissue for DMD children as compared to normal controls.

In a previous MRE study performed on hyperthyroid patients, Bensamoun et al. [23] have showed different behaviors of the propagation of the wave (superficial and deep displacement, variation of the wavelength) before and after treatment. In the present study, the phase image of the DMD (Fig. 2b) muscle showed no discontinuity of the wave's propagation between the subcutaneous adipose tissue and the vastus medialis (Fig. 2b). This unusual propagation indicates a pathological muscle characterized by a degenerated membrane surrounding the muscle tissue. Indeed, distinct displacements of the waves were always identified within the different healthy tissues. Moreover, the presence of gaps during the propagation of the wave within the DMD muscle may be explained by the local changes of the muscle composition. The present analysis of the DMD wave behavior may be a quantifiable means of tissue heterogeneity.

MRE tests performed on DMD children revealed abnormal muscle stiffnesses as well in passive as in active conditions. Indeed, DMD muscle, characterized as a degeneration of the muscle, was expected to display lower muscle stiffness at rest compared to the healthy

one. Interestingly, the opposite result was obtained suggesting a modification of the DMD muscle composition. Upon voluntary contraction the vastus medialis of the DMD children had a lower stiffness than that found in healthy control may be due to the degradation of the DMD muscle fibers providing a lack of the muscle contractile properties.

To our knowledge, the present study is the first to demonstrate a stiffer subcutaneous adipose tissue for the DMD children compared to the healthy ones. The present paradoxical result obtained for the DMD muscle at rest may be due to a muscle fatty infiltration within the vastus medialis leading to an increase of the VM stiffness.

Recent finding of the muscle secretome indicate that skeletal muscle signals via over 900 different proteins, as well as via microRNAs, freely secreted or transported as exosomes or microparticules to neighboring cells and tissues [27]. Furthermore, other recent studies of the Duchenne muscle secretome indicate that its composition is strongly altered as compared to the normal secretome [28]. It is therefore conceivable that altered muscle signaling in the long term alters the tissues properties of the neighboring subcutaneous tissue, although this hypothesis needs further confirmation. An alternative or complementary explanation might be that the altered perfusion properties of DMD muscle tissue lead to repetitive, exercise-induced hypoxia which induces concomitant metabolic changes in the neighboring subcutaneous tissue. In addition, we have only characterized the subcutaneous tissue properties in one anatomical location, and it remains to be shown if this phenomenon is ubiquitous, and also if it is progressive with disease progression. Therefore, the time course of both skeletal muscle and subcutaneous changes in DMD warrant further study notably regarding the perspectives of magnetic resonance elastography as a diagnostic and follow-up non-invasive tool to characterize functional properties of dystrophic tissue and to assess treatment effects in DMD.

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FIGURE LEGENDS

Figure 1: MR compatible leg press used to measure the passive and active function properties of the vastus medialis muscle.

Figure 2: Phase images representing the propagation of the shear waves within the subcutaneous adipose tissue and the vastus medialis (VM) muscle of healthy (A) and DMD (B) children. The shear stiffness (μ) was measured from the wavelength (λ) along the white profiles. (Sr: Sartorius, Gr: gracilis).

Figure 3: Cartography of stiffness for healthy and DMD children.

Figure 4: Representation of the Vastus Medialis (VM) muscle shear stiffness in relaxed and contracted (10% and 20% Maximum Voluntary Contraction) conditions for healthy and Duchenne Muscular Dystrophy (DMD) children (** $P < 0.05$ and * $P < 0.1$).

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CONFLICT OF INTEREST

The authors have not declared any conflicts of interest

ACKNOWLEDGEMENT

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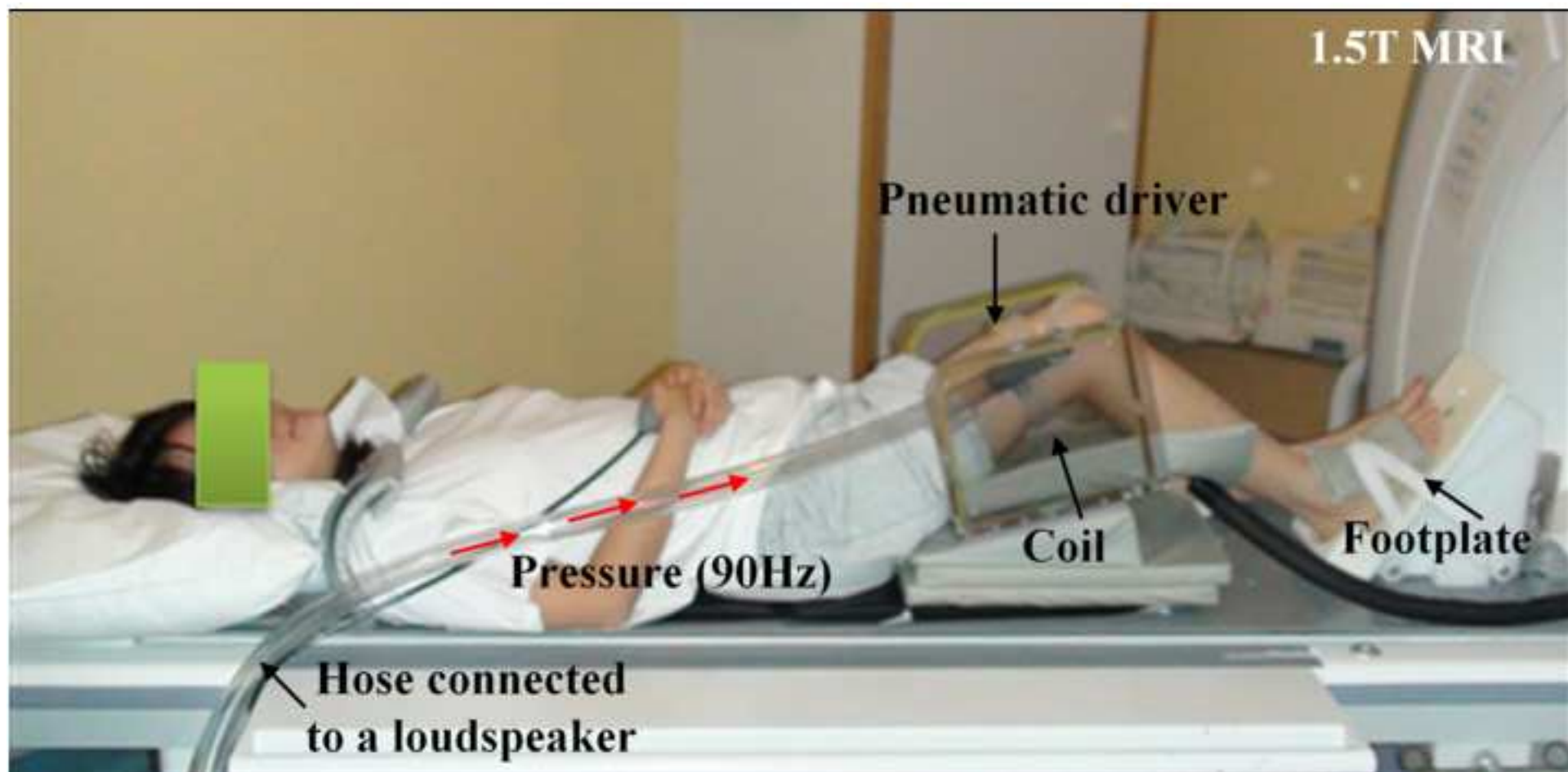


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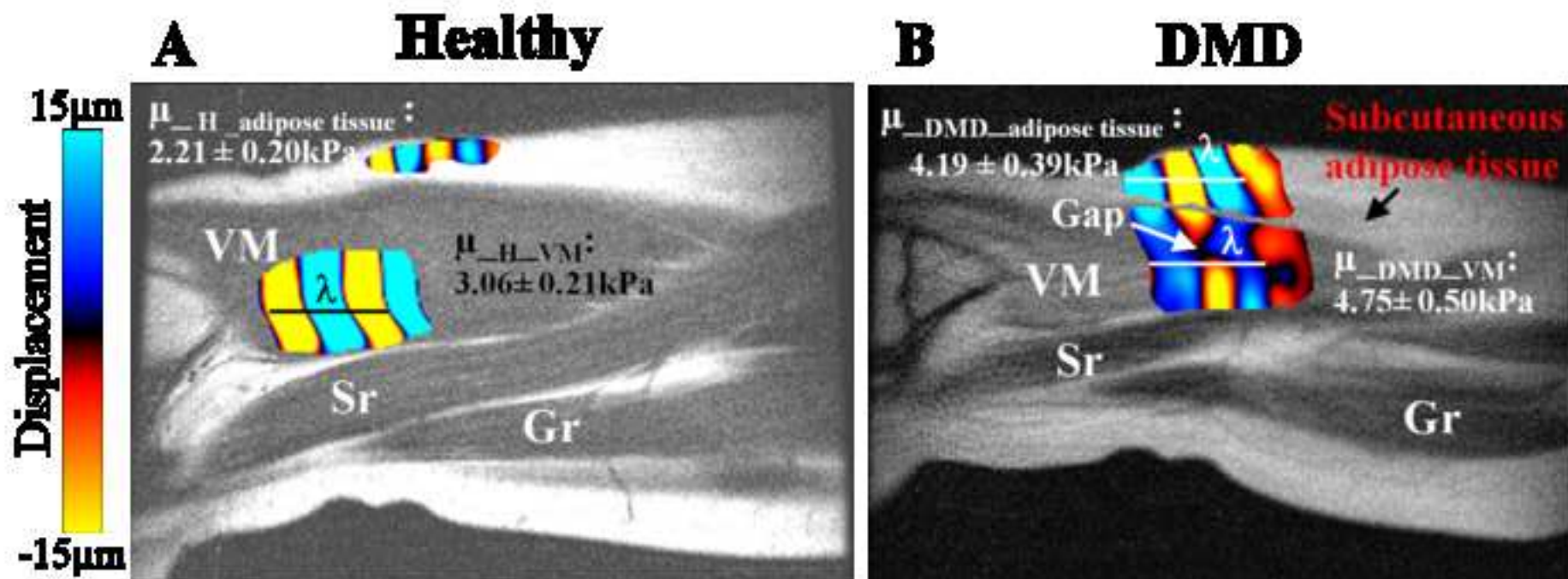


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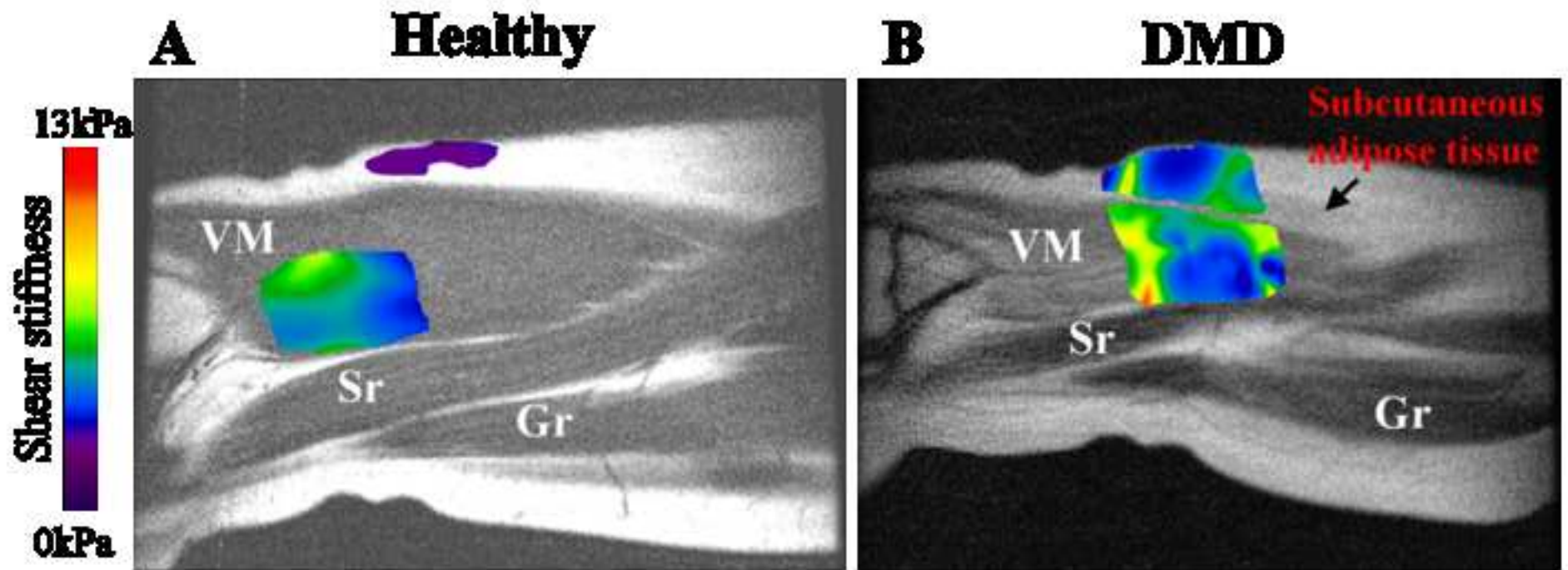


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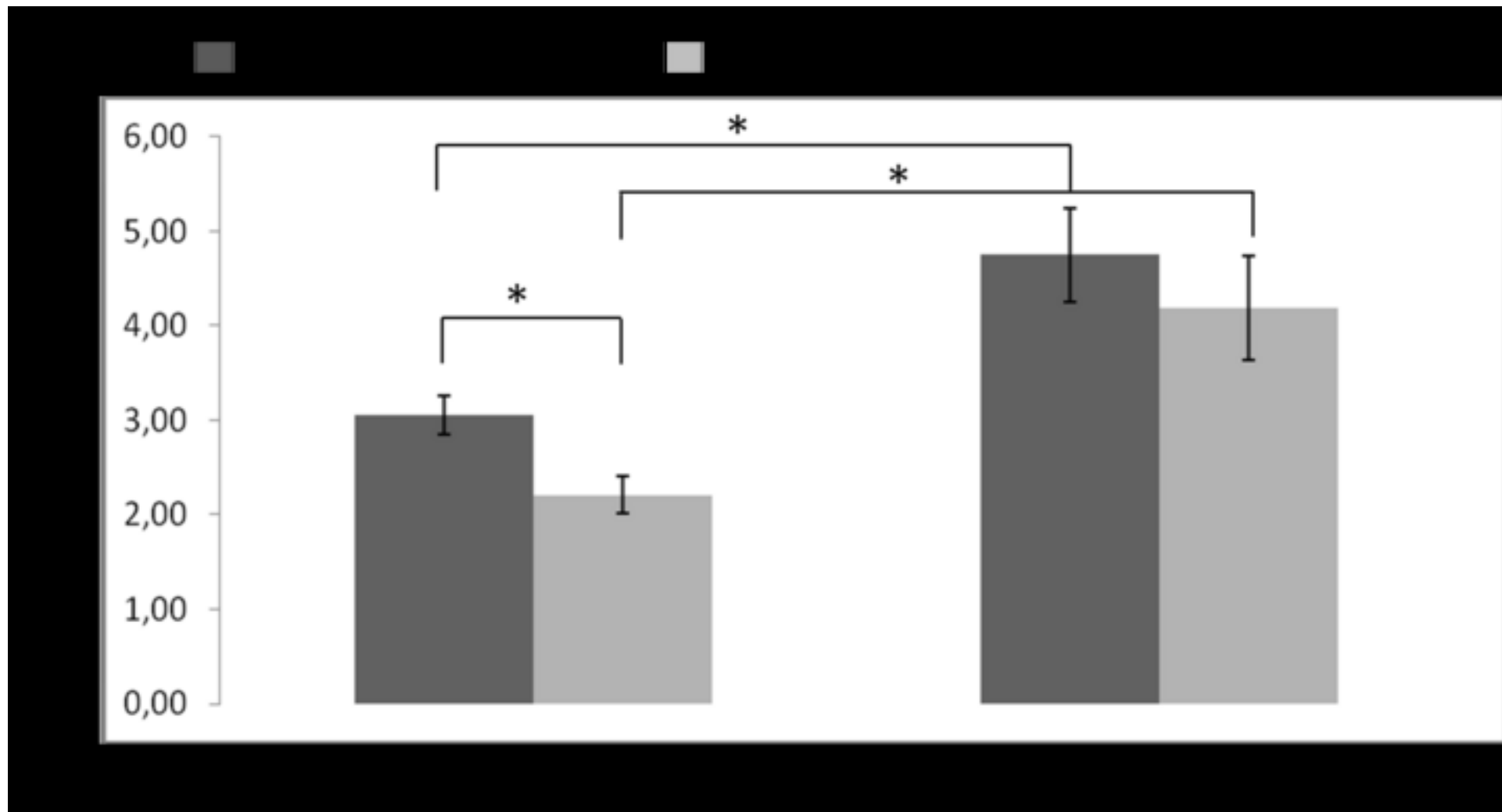


Figure 5
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