Original Article

Assessment of Muscular Stiffness in Children with Duchenne Muscular Dystrophy using Real-Time Elastography

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Abstract

Background: Imaging modalities, such as ultrasonography (USG), can be used to evaluate and monitor the musculoskeletal system during the clinical progression of Duchenne muscular dystrophy (DMD). **Aim:** This study aimed to measure passive muscle stiffness in children with Duchenne muscular dystrophy and to compare these measurements with those of healthy children. **Methods:** Patients with DMD were evaluated clinically (age, clinical functional score, timed Gover score), serum creatine kinase level, B-mode ultrasonography, and real-time tissue elastography imaging. **Results:** A total of 64 boys were included in this study. The medial and lateral gastrocnemius muscle strain ratio in patients with DMD was significantly bigger than that in the control group (medial; 1.66 ± 1.23 vs 0.81 ± 0.16, $P < 0.001$, lateral; 1.49 ± 0.52 vs 0.85 ± 0.16, $P < 0.001$). **Conclusion:** The strain ratios of the medial and lateral gastrocnemius muscles were greater in patients with Duchenne muscular dystrophy than in the controls, indicating that ultrasound elastography may be beneficial for diagnosis and follow-up.

Keywords: *Children, Duchenne muscular dystrophy, strain ratio, ultrasound elastography*

Introduction

Duchenne muscular dystrophy (DMD) is an X-linked recessive and fatal neuromuscular condition that is among the most prevalent neuromuscular disorders encountered in childhood. DMD is characterized by the absence or mutation of dystrophin, a glycoprotein complex integral that preserves the integrity of the muscle membrane.[1,2] The early stages of the disease include muscle damage, repair, and inflammatory responses, followed by irreversible fat infiltration.[3]

Although the clinical functional score (CFS) system has been devised for evaluating muscle strength in individuals with DMD, it faces certain constraints, particularly when dealing with noncooperative children. Elevated serum creatine kinase (CK) levels are often detected in these patients but are unreliable markers of disease activity.[1] Because the sampling area is limited in muscle biopsy, information about the whole muscle cannot be obtained, and repeated muscle biopsies are impractical, particularly for children. For this reason, it is essential to have a noninvasive technique to follow the treatment response and quantify the disease status.[4,5]

Imaging modalities, such as ultrasonography (USG), are used to evaluate and monitor the musculoskeletal system during the clinical progression of DMD.[6,7] Muscle USG can be used in many patients with DMD and suspected DMD and can be a useful biological marker for intermittent assessment of disease progression.[1] Computed tomography (CT) scans only show abnormalities, such as fat infiltration, edema, and atrophy, but they cannot differentiate fibrosis from healthy muscle tissue. In cases of neuromuscular disorders, particularly when edema is present, magnetic resonance imaging (MRI) is more sensitive than CT in detecting changes.[8] Another reliable technique used to measure the amount of fat in muscle tissue, also called

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the three-point Dixon MRI technique, has been used as a follow-up tool for DMD.[9] Elastography is a quantitative USG technique, and there are two main techniques of sonoelastography: strain elastography (also known as real-time tissue elastography [RTE]) and shear wave elastography (SWE). RTE uses mild tissue compression using an ultrasound transducer. Compression is applied to form a stretch in live tissues, followed by RTE, which shows the real-time map of the strain distribution within tissues.[10]

RTE was chosen over SWE in this study due to its practicality, accessibility, and suitability for the study population. Unlike SWE, which requires more advanced equipment and may involve higher costs, RTE offers real-time visualization of strain distribution, making it particularly effective for dynamic assessments in pediatric patients. Additionally, RTE is less sensitive to motion artifacts, an important consideration when working with children who may have difficulty remaining still during imaging procedures. Its ability to provide immediate, qualitative insights into muscle stiffness aligns well with the study's objective to investigate muscle elasticity changes in DMD. These advantages make RTE a cost-effective and efficient option for the evaluation of muscle stiffness in clinical and research settings.

The objective of this study was to compare muscle stiffness using RTE between children with DMD and healthy children, and to investigate the hypothesis that gastrocnemius muscle (GCM) stiffness may be higher in children with DMD.

Methods

Written informed consent and verbal consent were obtained from all the participants and/or their parents before participation in the study. This study was approved by the university ethics committee (approval number: 25.07.18/132). This study was conducted in accordance with the principles of the Declaration of Helsinki.

Study design

Thirty-four children with DMD were recruited from the Department of Paediatric Neurology. Thirty-four sex- and age-matched healthy controls volunteered to participate in the study after the clinical evaluation. All participants with a history of orthopedic surgery or trauma to the lower extremities and children who could not tolerate the prone position required for USG were excluded from the study. Patients diagnosed with DMD underwent lower extremity performance tests. Each child underwent clinical evaluation conducted by a pediatric neurologist (O.G., a specialist in pediatric neurology with a decade of experience). Patient age, GCM CFS score, and timed Gover score (TGS) were evaluated. CFS was determined using the Medical Research Council scale, ranging from grade 1 (normal function) to 8 (severe dysfunction).[11] CFS of the GCM was evaluated in children older than four years (28 patients). TGS, which is the time required for the patient to stand up from a sitting position, was evaluated in seconds. TGS was measured in only 15 patients who were cooperative for clinical assessment and had mild dysfunction (CFS grade 1–3). Serum CK levels were obtained from all patients with DMD.

Imaging assessments

All participants underwent USG and RTE (Aplio 400, Toshiba Medical Systems Corporation, Otawara, Japan) with a 12 MHz linear array transducer to quantitatively measure the strain of the bilateral medial and lateral GCM with longitudinal scans. The ultrasound probe was placed in the thickest muscle belly to scan the central regions of medial and lateral GCM.

All measurements were conducted separately for various participants according to a standardized protocol by one of the two radiologists (G.G. and M.S.M.), each with 14 and 15 years of experience, respectively. The inter-rater reliability, determined by intra-class correlations between the two evaluators, was 0.915 for the five participants. In the elastogram, regions of low strain are represented in red, whereas those of high strain appear in blue. At each measurement time point, three RTE images were chosen for analysis. Measurements were performed during the decompression phase. A circular region of interest (ROI) with a diameter of 4 mm was used to measure the strain ratio (SR) within the muscle belly of interest. In every patient, the ROI within the medial or lateral GCM (A) was compared with the ROI of the nearby subcutaneous fatty tissue (B), and SR (B/A) was automatically computed. Mean values were derived from each of the three images. Subcutaneous fat is predominantly depicted as a mosaic of green and red colors, whereas areas of the affected muscle (M) appear stiffer and are denoted by blue [Figure 1].

Statistical analysis

The data underwent Statistical analysis was performed using the SPSS software (version 25.0; SPSS Inc., Chicago, IL, USA). Statistical significance was set at $P < 0.05$. Descriptive statistics are presented as numbers (n), percentages (%), and means ± standard deviation (SD). If the assumptions for parametric tests were met, an independent samples *t*-test was used to assess the differences between the independent groups. In cases where parametric test assumptions were not

met, the Mann–Whitney U test was used to compare independent group variances. Differences between categorical variables were analyzed using the Chi-square test. **Correlation analysis was conducted using Spearman's rank correlation to assess relationships between continuous variables.**

Results

This study included 68 male participants comprising 34 children diagnosed with DMD and 34 healthy children. In comparison with healthy children, no significant differences were observed in age or BMI between the two groups. Among the 34 DMD participants, 21 (61.7%) were ambulatory at the time of the study. Steroid treatment was administered to 23 participants (67.6%), with the maximum duration of therapy not exceeding one year. The steroid dosage was standardized at 0.5 mg/kg/day. Only 15 participants (44%) were receiving physical therapy, which was lower than expected due to issues such as problems with health insurance coverage, difficulties in accessing physical therapy centers, and the recent diagnosis of some patients. None of the participants were involved in clinical trials for therapeutic interventions (all $P > 0.05$). The mean CK level was 7250.31 ± 3200 IU/L.

In patients with DMD, there was an increase in the thickness of both the medial and lateral GCM compared to that in the control group. A significant difference was observed in SR between children with DMD and healthy children. Patients with DMD exhibited higher SRs in medial and lateral GCM than those in the healthy group. Table 1 presents a comparison of the demographic characteristics, thickness, and SR of the medial and lateral GCM between children with DMD and healthy children [Table 1]. There was also no association between the SR of the medial and lateral GCM and CFS [Figure 2].

Table 1: Demographic characteristics, the thickness, and strain ratio of medial and lateral gastrocnemius muscle (GCM) of children with DMD compared to healthy children

	Patient (n=34) mean±std. dev	Control (n=34) mean±std. dev	p
Year	82.12±45.75	81.82±46.73	p>0.05
BMI	21.03±1.65	21.05±1.5	p>0.05
Lateral GCM thickness	16.11±6.48	9.73±2.15	p<0.05
Medial GCM thickness	20.25±6.34	13.88±3.33	p<0.05
Lateral GCM strain ratio	1.49±0.52	0.85±0.16	p<0.05
Medial GCM strain ratio	1.66±1.23	0.81±0.16	p<0.05

Statistical significance was (p<0.05). BMI: body mass index p for normally distributed variables (year, BMI, and GCM thickness) were calculated using independent samples t-test. p for non-normally distributed variables (GCM strain ratios) were calculated using the Mann–Whitney U test

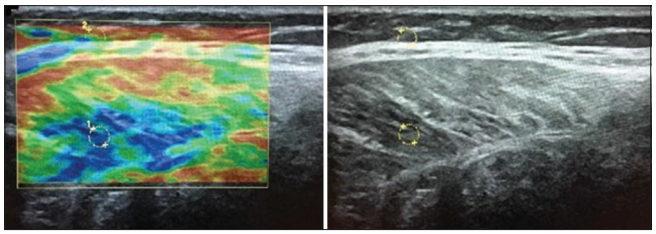

Figure 1: Real-time elastogram of gastrocnemius muscle from a seven-year-old boy with Duchenne muscular dystrophy. A real-time elastogram of the gastrocnemius muscle shows that unaffected areas (green/red) at the periphery of the muscle (m) are softer than the dystrophic muscle (blue). The subcutaneous fat (f) appears green/red

Discussion

Here, we present RTE imaging findings of the GCM in patients with DMD and compare muscle elasticity with that in healthy children. The objective of this study was to examine whether RTE, used to measure lower limb muscle (GCM) stiffness, could serve as a promising noninvasive biomarker for exploring the long-term pathophysiology of lower limb muscles and monitoring lower limb function in children with DMD. We hypothesized that employing RTE to assess lower limb muscle stiffness would distinguish between individuals with DMD and healthy individuals. Our results established that the strain rates of the medial and lateral GCM were greater in DMD patients than in controls and that muscle stiffness increased among patients with DMD. These findings indicate that ultrasound elastography may be beneficial for diagnosis and follow-up even in very young children. In addition, we detected a strong correlation between the age of DMD patients

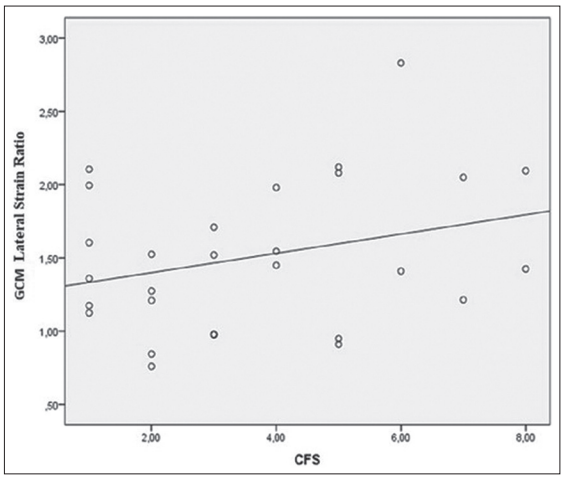

Figure 2: The graph shows the correlation between the strain ratio of the lateral gastrocnemius muscle (GCM) and the clinical functional score (CFS) in 28 patients. There was no significant correlation observed (r = 0.12, $p = 0.52$)

and GCM thickness. However, it is impossible to determine whether this result occurred as a result of the natural course and stage of the disease, or an increase in muscle thickness during growth.

We hypothesized that the increased stiffness identified in the GCM of children with DMD is likely a consequence of increased fibrosis within the muscle. Previous muscle biopsy studies have demonstrated that increased fibrosis has been detected in the muscles of children with DMD.[12] Lacourpaille *et al*.[13] utilized SWE and identified that patients with DMD showed increased stiffness in the upper limb muscles compared to healthy controls of a similar age. On the flip side, Lin *et al*.[5] observed a reduction in biceps muscle stiffness among adolescent DMD patients in comparison with their healthy counterparts. This may be explained by increased intramuscular fat infiltration in the later stages of DMD.[14,15] This idea is supported by previous quantitative MRI and MR spectroscopy investigations showing increased fat fraction in the upper limb muscles of DMD patients compared to healthy children of a similar age.[14,16,17] Pichiecchio *et al*.[18] explored SWE and MRI abnormalities in untreated preschoolers with DMD. Their research, utilizing SWE on specific lower limb muscles, uncovered increased muscle stiffness in DMD patients compared to healthy controls. However, because of the exceedingly limited sample size (consisting of only five patients), they refrained from establishing correlations between elastography and MRI findings.

Muscle USG imaging for the diagnosis of neuromuscular disorders in children can also characterize the pattern of involvement of the affected muscles, which may suggest or confirm the diagnosis. The usefulness of these patterns in distinguishing specific neuromuscular disorders remains controversial. However, it should be noted that these patterns depend on the observer's visual evaluation.[19] Assessing passive muscle stiffness using ultrasound elastography may be the most straightforward technique; however, it is essential to conduct this procedure in a standardized fashion. In this technique, the reliability of the measurements may be influenced by the movement of the transducer probe.[20]

Our findings must also be interpreted in the context of potential confounding factors. For instance, while steroid therapy was standardized at 0.5 mg/kg/day with a maximum duration of one year, its impact on muscle stiffness and elasticity could not be fully disentangled from the observed results. Similarly, fewer participants receiving physical therapy than anticipated—due to logistical and insurance issues—may have influenced the overall muscle elasticity findings. Age and the timing of disease onset are additional variables that were known but were not included in the analysis due to the limited sample size, which made subgrouping challenging. However, these factors could play a role in the progression of muscle stiffness and warrant further investigation in studies with larger cohorts. Future studies should incorporate these factors into their design and analyses to better understand their contributions.

Muscle weakness is a common trait observed in DMD patients. However, the sensitivity of identifying the degenerative effects of DMD varies among the different muscle groups. This could be partially attributed to the progression from proximal to distal regions, which is characteristic of the natural evolution of the disease.[17] Concordantly, various biomechanical factors affect muscle strength in a different manner than DMD, including the muscle size, structure, type, and efficiency of force transmission.

Further studies are needed to investigate RTE's specificity and clinical value of RTE for the diagnosis and follow-up of neuromuscular diseases. Future long-term studies on children with DMD should focus on imaging various muscle groups and on age-dependent assessments of strength and function. In addition, these studies should include larger sample sizes and assess interobserver reliability according to USG and SE experience. This assessment may help clinicians to detect changes in muscle stiffness earlier, thus preventing joint deformities and extending autonomy.

This study has certain limitations. First, the number of patients with DMD and healthy subjects included in the study was relatively small, and our small sample size may have limited the statistical power. Second, only one muscle group was included in the study. Third, although we assessed the muscle stiffness and injury to the GCM core, the degree of change in these parameters may vary by region within a single muscle. Fourth, elastography is influenced by user proficiency, entails a learning curve to some extent, and is susceptible to technical issues arising from variations in the pressure applied during the freehand technique that can affect image reproduction. In order to reduce the impact of this difficulty, one physician carried out all USG and strain elastography scans. Furthermore, standardizing the USG protocol and preserving all system settings fixed may negate the effect of system settings. We standardized the window depth and width for medial and lateral GCM. These efforts may provide a better inter-class correlation coefficient in repeat elastography and strain ratio measurements. Another limitation is the lack of comparison of our findings with the parameters of the reference standards, such as histological and electromyographic findings.

In conclusion, ultrasound elastography may soon evolve as a tool that complements conventional imaging techniques rather than replacing anything that is currently a standard procedure. In general, our results indicate that strain elastography is a sensitive and noninvasive technique for the quantification of muscle stiffness increase in patients with DMD. Ultrasound elastography may alert physicians to the imminent functional decline in progressive muscle disorders. Therefore, it appears to be a valuable approach for assessing DMD.

Ethical compliance

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institution. Ethical approval (25.07.18/132) was obtained from the Clinical Research Ethics Committee. The 1964 Declaration of Helsinki and its later amendments or comparable ethical standards were observed.

Data access statement

Research data supporting this publication are available from the drgulaygungor@gmail.com

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Conflicts of interest

There are no conflicts of interest.

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