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FULL PAPER

Strain sonoelastography of inflammatory myopathies: comparison with clinical examination, magnetic resonance imaging and pathologic findings

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Objective: To evaluate strain sonoelastography (SSE) in patients with inflammatory myopathies (IM) compared with clinical examination, MRI and pathologic findings.
Methods: 18 lesions from 17 consecutive patients with IM (5 males and 12 females; mean age, 41.2 years; range, 11–67 years) were assessed with SSE after MRI. The ratio of strain in the target muscle (A) and a nearby normal muscle (B), defined as the strain index value (SR) (B/A), was calculated automatically. Elastograms were assigned an elasticity score according to the degree and distribution of strain induced by manual compression. Ultrasonography and MRI were analyzed in conjunction with clinical information, biochemical data, final clinical diagnosis and grading of pathology. Correlations between SR and qualitative analyses of MRI and ultrasonography, elasticity score, biochemical data and final clinical diagnosis were analyzed using Pearson's correlation coefficient.
Results: The SR of the target muscles was high in patients with IM (mean 3.14; range, 0.95–5.93 ± 1.42). The correlations between SR and pathologic grading and elasticity score were statistically significant ($p < 0.05$). There was no significant agreement between SR and other clinical and radiologic parameters.
Conclusion: Muscle hardness, as semi-quantitatively measured by SSE, was increased in cases of IM. The correlation between the SR and the pathologic grading suggests that SSE could be an important tool in not only the diagnosis of but also in measuring the degree of muscular inflammation.
Advances in knowledge: This work describes a correlation between tissue elasticity and pathology in IM.

INTRODUCTION

Inflammatory myopathies (IM) represent a heterogeneous group of systemic autoimmune disorders characterized by inflammation of the skeletal muscle and proximal muscle weakness. According to the most commonly used diagnostic criteria established by Bohan and Peter,[1,2] IM are divided into five subgroups: adult-onset dermatomyositis (DM), polymyositis (PM), juvenile dermatomyositis (JDM), paraneoplastic myositis and overlap syndromes. The diagnosis of IM is based on a typical clinical manifestation of muscle weakness with or without myalgia and elevated muscle enzymes, such as creatine kinase (CK), lactate dehydrogenase (LDH), serum myoglobin, aldolase, transaminases, electromyographic abnormalities and pathologic findings.[1–4] Recently, MRI, which is helpful in establishing the diagnosis of IM, has been validated as a sensitive indicator of muscle oedema and active disease, as well as assessing disease activity and treatment response.[5,6]

Compared with MRI, ultrasonography has several benefits, including relatively low cost, portability, real-time scan, short study time and a tool of guidance of muscle biopsy. Recently, sonoelastography (SE) has been used to measure the mechanical properties of tissues. SE in musculoskeletal applications has been used in assessing tendons, plantar fascia pathology and soft-tissue masses.[6–9] There are two major forms of SE for measuring tissue stiffness: one is strain SE (SSE) and the other is shear-wave sonoelastography (SWSE). SSE was the first method to measure stiffness under manual compression. Tissue strain can be calculated semi-quantitatively using strain ratios. Strain ratios have been used for the diagnosis of focal lesions in the breast,[10,11] thyroid glands[8] and muscles.[12] Currently used SWSE depends on the acoustic radiation force generated by the ultrasound beam or the measurement of shear-wave induction.[13,14] Quantitative shear-wave imaging technique has problem with the linear probe because it is affected by

target depth.[15] Shear wave does not allow sufficient elastogram in proximal thigh muscles, which are the most commonly involved site of IM.[12,16–19] Although IM have been previously studied using conventional ultrasonography and MRI, there are only a few studies in the literature that have attempted to use SSE in IM.[12,20] Furthermore, there are no published data available for the pathologic correlation of myositis including muscle stiffness.

Thus, the purposes of this study were to evaluate the clinical utility of SSE in patients with IM and to evaluate the correlation between the mean strain index value (SR), biochemical data, qualitative features of ultrasonography and MRI and pathologic findings.

METHODS AND MATERIALS

Patients

This retrospective study was approved by our institutional review board, which waived the requirement for informed consent because of the study's retrospective nature. Between June 2012 and June 2015, a total of 27 patients (19 females and 8 males) with clinically suspected IM were recruited at our institution for diagnosis and treatment. The diagnosis of IM was based on the modified criteria of Bohan and Peter.[4] Patients with evidence of neurological disease associated with muscle wasting, granulomatous and endocrinological disorders and a family history suggestive of muscular dystrophy were excluded. Other exclusion criteria were patients with extramuscular manifestation of the disease ($n = 0$), time interval between MRI and ultrasonography of more than 5 days ($n = 4$) and absence of ultrasonography-guided biopsy ($n = 6$). 18 lesions from 17 consecutive patients (12 females and 5 males) with a mean age of 41.2 ± 13.3 years (range: 11–67 years) [male age = 42.8 ± 10.6 years (range: 30–57 years); female age = 40.5 ± 14.5 years (range: 11–67 years)] were included in the analyses. All the patients underwent clinical evaluation (clinical symptoms, symptom duration and physical examination) and laboratory tests for muscular inflammatory disease: proximal muscle weakness, the presence/absence of skin rash, increased values of non-specific inflammatory markers (erythrocyte sedimentation rate and C-reactive protein) and increased levels of serum muscle enzymes (CK, LDH, aldolase and transaminase), rheumatoid factor and antinuclear antibody. The final diagnoses were categorized by a board-certified rheumatologist (DY) as DM, PM, JDM, overlap syndrome, mixed connective tissue disease (MCTD), systemic lupus erythematosus (SLE) or other.

MRI protocols and analysis

All patients underwent MRI of both thighs on the same day as their clinical examination. Imaging was performed using a 3.0-T MRI system (Achieva 3.0T TX; Philips Healthcare, Best, Netherlands) with a torso coil. The conventional MRI protocols included axial T_1 weighted spin-echo imaging [repetition time (TR)/echo time (TE) = 532–624/10–15 ms], axial and coronal T_2 weighted spin-echo imaging (TR/TE = 2584–5132/100 ms), axial short tau inversion-recovery imaging (TR/TE = 11,516–12,563/65 ms) and axial and coronal fat-suppressed T_1 weighted spin-echo imaging after the administration of a gadolinium-based contrast agent (Gadovist®; Bayer Schering, Berlin, Germany) (TR/TE = 564–631/15 ms). The number of signal averages was 1 or 2, field of view was 277–440 mm, matrix size was 249 × 350–440 × 430 pixels, echo train length was 4–16 and flip angle was 90°. The section thickness and intersection gap were set from 5 mm/0.5 mm to 8 mm/0.8 mm. All parameters for conventional imaging were variable depending on patient size.

Conventional MRI findings of IM were evaluated in consensus, according to the following criteria: the presence/absence of intermuscular fascial or subcutaneous fat involvement, muscle oedema, active inflammation, fatty atrophic changes in the muscle and grading of muscle involvement by two fellowship-trained musculoskeletal radiologists with 9 and 2 years' experience, respectively, (SL, YS), who were blinded to the radiologic reports, clinical information and results of histologic examination. Assessments of fascial and subcutaneous fat signal intensity were based on fluid-sensitive sequences. When the muscle showed high signal intensity on fluid-sensitive sequences such as T_2 weighted and short tau inversion-recovery images, it was regarded as muscle oedema. In addition, active inflammation was defined as enhancement on a fat-suppressed gadolinium-enhanced T_1 weighted sequence. Decreased volume of muscle with fatty degeneration (atrophy) was also evaluated. Muscle involvement was based on axial fluid-sensitive sequences showing high signal intensity and was determined by an estimation of the percentage of area affected. The grades were divided into five groups: Grade 0, no muscle signal abnormality; Grade 1, 1–25% muscle involvement; Grade 2, 26–50% muscle involvement; Grade 3, 51–75% muscle involvement; and Grade 4, 76–100% muscle involvement.[17] This qualitative analysis was limited to the target lesion of ultrasonography-guided biopsy.

Ultrasonography imaging protocols and analysis

All patients were examined using an ultrasonography scanner (EUB 7500; Hitachi Medical Corporation, Tokyo, Japan) with a EUP-L74M linear-array transducer (6–14-MHz image acquisition frequency). B-mode ultrasonography imaging and SSE were performed by one musculoskeletal radiologist (SL) with more than 2 years' experience in SSE. Each patient was examined in the supine position, except for one prone position used for the evaluation of the iliocostalis and longissimus muscles. The echogenicity of the target muscle was considered isoechoic if it was equal to the echogenicity of the subcutaneous fat; it was considered hyperechoic/hypoechoic if the muscle echogenicity was greater/less than that of the subcutaneous fat. SSE was performed in transverse and longitudinal scans by manual compression. The transducer was oriented perpendicular to the skin surface and was pressed by freehand manipulation. To obtain appropriate images for investigation, we used the transducer with constant pressure by monitoring the pressure indicator incorporated into the ultrasonography scanner. The pressure indicator displayed the pressure in a scale from 1 to 7, and we tried to ensure that the pressure applied to the surface remained constant between Levels 3–4. SSE is a colour-scale image for the relationship between differences in tissue deformability and its elasticity. The scale ranges from blue for the hardest components with less strain to red for the softest components with the greatest strain. A circular region of interest (ROI) with an approximate diameter of 10 mm was placed on

the target and reference muscles. Strain ratios were calculated as the average strain of the surrounding medium divided by the average strain of the target. The measurements were performed 3–5 times, and the mean value was calculated.

To classify elasticity images, we evaluated the colour pattern using Itoh et al's[21] elasticity score after modification. On the basis of the overall pattern, we assigned each image an elasticity score on a five-point scale. The elasticity score system is summarized in Table 1. Scoring of target and reference muscles was performed by one musculoskeletal radiologist (YS), who were blinded to histologic results, clinical diagnosis and SR. Elasticity score of each muscle and delta value, which is thought of as the difference between a reference and target, was used for statistical analyses. After SSE, ultrasonography-guided biopsy was performed in all our patients not only when active inflammation was noticed on pre-procedural MRI, but also when the highest SR on SSE was noted. All lesions were superficially located, with the most common biopsy sites being the vastus lateralis ($n = 14$) and vastus intermedius ($n = 11$). Other biopsy sites were as follows: rectus femoris ($n = 1$), gracilis ($n = 1$), iliocostalis and longissimus ($n = 1$) and deltoid ($n = 1$) muscles.

Pathologic findings and grading

A total of 18 muscle biopsy specimens were submitted for routine standard histological and immunohistochemical testing techniques. Sequential frozen sections were stained with haematoxylin and eosin and several immunohistochemistry markers of IM, such as CD4, CD8, CD68 and CD138. Each muscle biopsy specimen was coded and analyzed separately by one expert pathologist who was blinded to diagnosis, clinical status and therapy when the biopsies were evaluated. Pathologic grading was categorized by the degree of inflammation and necrosis/degeneration of muscle fibre. Inflammatory cell infiltration was assessed semi-quantitatively and categorized into four groups:[10] Grade 0, 0–10% muscle involvement in low- and high-power fields; Grade 1, 10–33.3% muscle involvement; Grade 2, 33.3–66.7% muscle involvement; and Grade 3, 66.7–100% muscle involvement. Muscular necrosis/degeneration, including vacuolization, pale or basophilic myofibrils, internal nuclei, fibre fragmentation and necrosis, were assessed semi-quantitatively as Grade 0, none/minimal; Grade 1, <25% muscle involvement; Grade 2, 26–50% muscle involvement; and Grade 3, >50% muscle involvement.

Table 1. Elasticity score for evaluating inflammatory myositis

Score	
1	Entire lesion was evenly shaded red
2	A mosaic pattern of green and red (>50% portion of red)
3	A mosaic pattern of green and red (<50% portion of red)
4	A mosaic pattern of green and blue
5	Entire lesion was evenly shaded blue

Statistical analysis

Data were descriptively reviewed and statistically tested for normality with the Shapiro–Wilk test. Data were expressed as mean ± standard deviation. p-values <0.05 were considered statistically significant. Quantitative continuous variables were summarized using descriptive statistic parameters, while qualitative variables were summarized using relative degrees. The Pearson's correlation coefficient method was used for correlations between SR and qualitative analyses of ultrasonography and MRI, elasticity score, pathologic grading, biochemical data and clinical diagnosis. All statistical analyses were performed using commercially available software (SPSS® v. 21.0; IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL).

RESULTS

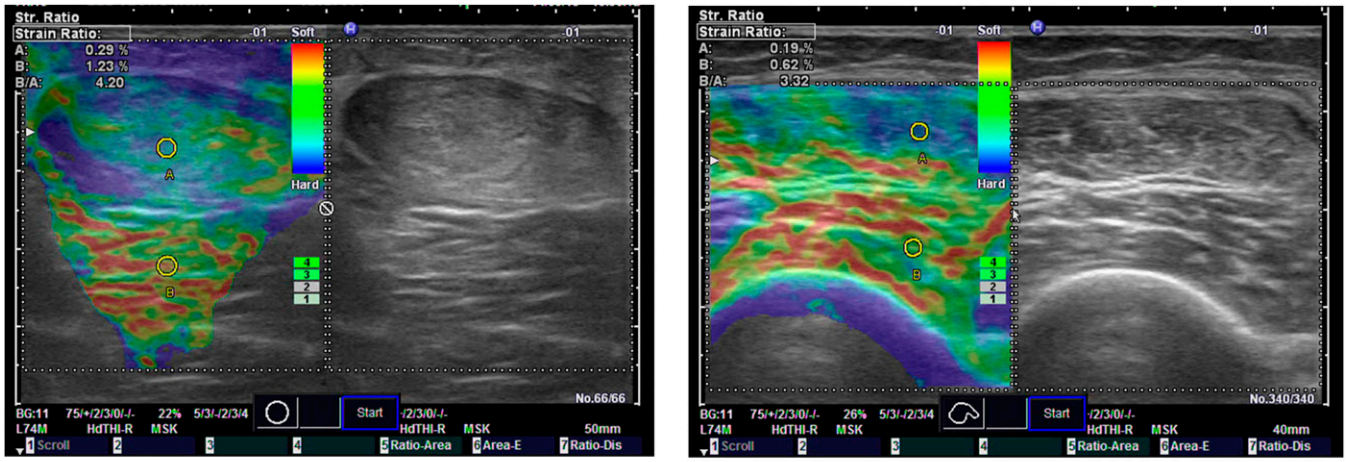
The final clinical diagnoses were as follows: DM ($n = 7$), PM ($n = 5$), SLE with overlap myositis ($n = 2$), JDM ($n = 1$), MCTD ($n = 1$) and rheumatoid arthritis with overlap myositis ($n = 1$). The clinical symptom duration ranged from 3 days to 1 year (mean, 70.9 days; median, 1 month). Active myositis was present on MRI in all cases with muscle oedema. Two cases demonstrated muscle atrophy with fat infiltration. The demographic data of all enrolled patients are summarized in Table 2. The majority of patients were diagnosed with DM (Figures 1 and 2) or PM (Figures 3 and 4). Patient clinical data, laboratory findings and mean SR are presented in Table 3. The images obtained from SSE were processed using dedicated software from Hitachi. In all affected muscles, the mean SR was high (mean 3.14; range, 0.95–5.93). The following mean SR was obtained for the various aetiologies: DM = 3.37, PM = 3.72, SLE with overlap myositis = 3.06, JDM = 1.7 (Figures 5 and 6), MCTD = 2.04 and rheumatoid arthritis with overlap myositis = 1.22. Although not statistically significant, the mean SR of DM and PM were higher than those of other causes. On SSE of the target muscle, Score 1 was found in two cases; Score 2 in seven cases; Score 3 in four cases; Score 4 in three cases; and Score 5 in two cases. The mean elasticity score of the target muscle was 2.78 ± 1.22. The

Table 2. Patient demographics

Total number enrolled	17
Total number of studies	18
Age in years (mean, range)	41.2, 11–67
Female sex	12 (70.6%)
Diagnosis	
DM	7 (41.2%)
PM	6 (29.4%)
SLE overlap	2 (11.8%)
JDM	1 (5.9%)
MCTD	1 (5.9%)
RA overlap	1 (5.9%)
Disease duration in days (mean, range)	70.9, 3–365

DM, dermatomyositis; JDM, juvenile dermatomyositis; MCTD, mixed connective tissue disease; PM, polymyositis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

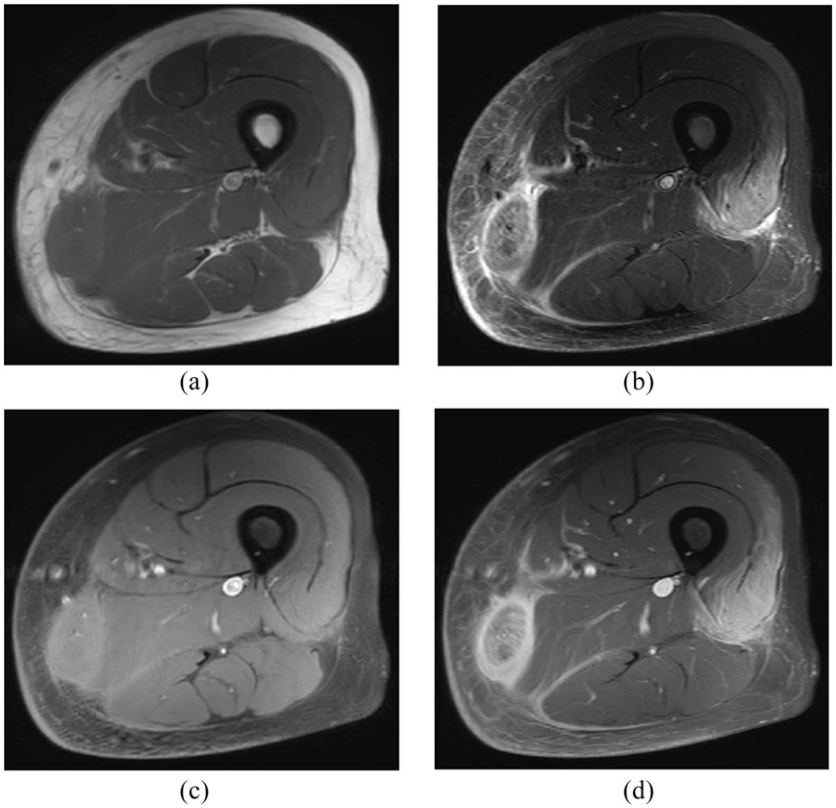
Figure 1. A 43-year-old female with dermatomyositis: (a) B-mode ultrasound (right) revealed hyperechoic gracilis and subcutaneous fat with thickening of the adjacent skin. Simultaneous sonoelastography (left) showed a green-to-blue-colour lesion. The strain ratio was 4.20. (b) The same patient had similar features in the vastus lateralis. The strain ratio was 3.32, which indicates that the tissue was harder than the reference muscle. For colour see online.



(a) (b)

mean delta value was -0.17 ± 1.82. A significant difference showed between SR and elasticity score of the target muscle ($p = 0.031$, Pearson's correlation coefficient = 0.510) and between SR and delta value ($p = 0.045$, Pearson's correlation coefficient = -0.478). There was no significant agreement between the mean SR and the biochemical data (*e.g.* CK, LDH, erythrocyte sedimentation

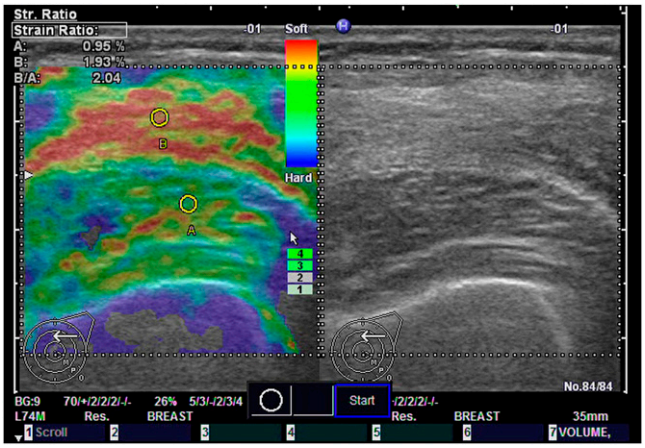
Figure 2. Corresponding MR images through the mid-thigh level in the same patient as in Figure 1 with dermatomyositis: (a, b) axial T_1 weighted [repetition time (TR)/echo time (TE) = 640/20 ms in (a)] and short tau inversion-recovery [TR/TE = 8638/70 ms in (b)] MR images are demonstrating swelling and high-signal-intensity infiltration of the gracilis, vastus lateralis and intermuscular fascia. There is thickening of the subcutaneous fat and skin of the medial thigh. (c, d) The axial fat-suppressed, pre-contrast-enhanced and contrast-enhanced T_1 weighted images (TR/TE = 650/15 ms) are showing patchy enhancement.



(a) (b)

(c) (d)

Figure 3. A 43-year-old female with polymyositis: B-mode ultrasound (right) revealed a hyperechoic vastus lateralis. Simultaneous sonoelastography (left) showed green-to-red colour of the lesion. The strain ratio was 2.04, which indicates that the tissue was harder than the reference muscle. For colour see online.



rate, C-reactive protein, aldolase, aspartate transaminase and alanine transaminase). Histologically, 16 (94.1%) of the 17 specimens were confirmed as IM. 1 (5.9%) lesion showed a well-preserved muscle fibre with little lymphocyte infiltration. With respect to pathologic grading, the sum of the pathologic grading was statistically significant ($p = 0.036$, Pearson's correlation coefficient = 0.497).

DISCUSSION

To our knowledge, no previously published study has reported the multimodality correlation of myositis using SSE to characterize IM. Only the study of Botar-Jid et al[9] briefly mentions a correlation between colour parameters and biochemical data. Our study showed that the mean SR of IM is about three times higher than that of reference muscle. A high SR denotes that the affected muscle is stiffer than the reference one. Histologically, IM shows perivascular and/or perimysial and/or endomysial infiltration of inflammatory cells, often associated with perifascicular atrophy or microinfarcts.[22] The results of our study are in agreement with those of previous studies, which have shown that inflammatory lesions of the pancreas, bowel and uterus have relatively high SR.[20,23,24] Although the target organs were different in our study, there were similar histologic features. Chronic pancreatitis is characterized by pancreatic infiltration of inflammatory cells. The presence of these inflammatory cells is consistent with the altered mechanical properties and structural changes of the muscle. In addition, we demonstrated the correlation between sonographic stiffness and inflammatory changes in this study using a multimodal approach. However, it was not possible to detect any statistical

Figure 4. Corresponding MR images through the mid-thigh level in the same patient as in Figure 3 with polymyositis: (a, b) axial T_1 weighted [repetition time (TR)/echo time (TE) = 485/15 ms in (a)] and short tau inversion-recovery [TR/TE = 10,469/65 ms in (b)] MR images are demonstrating multifocal feathery high-signal-intensity infiltration of the entire compartments of the thigh muscles. There is thickening of the subcutaneous fat and skin of posteromedial thigh. (c, d) The axial fat-suppressed, pre-contrast-enhanced and contrast-enhanced T_1 weighted images (TR/TE = 632/15 ms) are showing patchy enhancement.

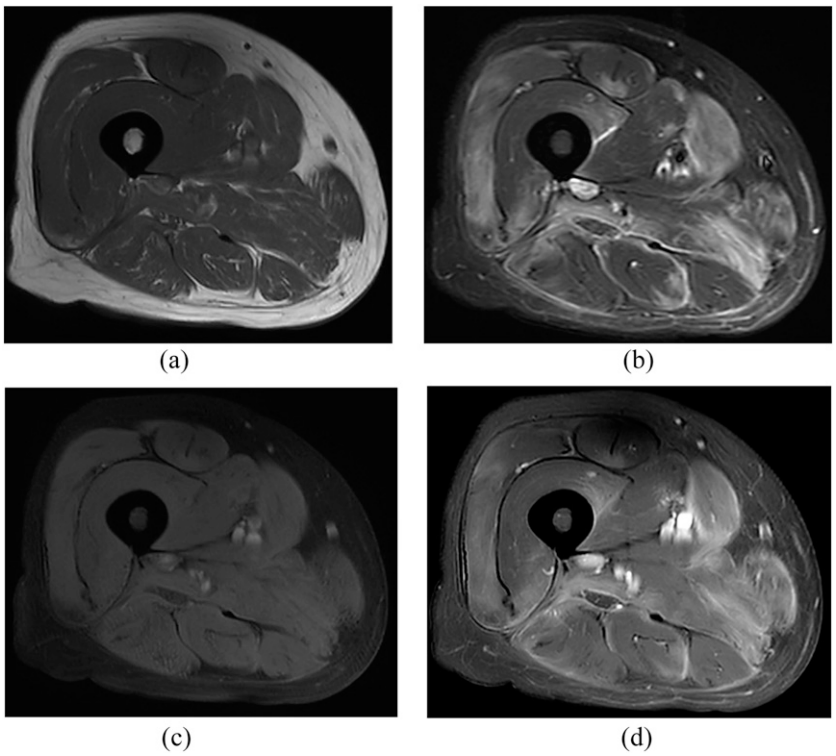


Table 3. Patient clinical diagnosis, laboratory data and mean strain index value (SR)

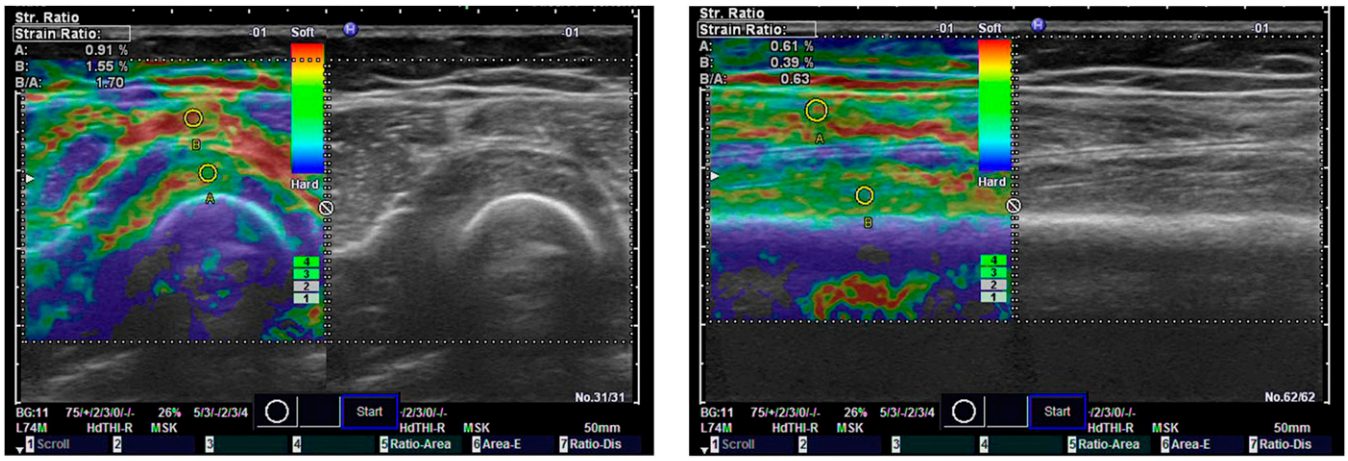
Case	Age (years)	Sex	Clinical Diagnosis	SR	CK	LDH	ESR	CRP	Aldolase	AST	ALT
1	57	M	DM	2.80	1990	410	110	3.2	21.1	69	39
2	41	F	SLE + myositis	2.63	49	366	47	2.6	18.0	42	25
3	67	F	PM	2.23	2669	693	42	5.4	58.6	125	84
4	43	F	MCTD	2.04	1283	502	117	<0.8	13.7	123	84
5	43	F	DM	5.38/3.32	677	318	14	0.9	27.6	47	21
6	59	F	PM	3.99	2590	707	23	1.1	47.2	90	109
7	11	F	JDM	1.70	552	693	13	<0.8	17.0	76	26
8	46	M	DM	0.95	311	326	20	<0.8	35.1	34	78
9	43	F	DM	5.93	92	185	14	<0.8	9.3	49	55
10	27	F	DM	1.49	126	303	51	<0.8	10.1	46	36
11	34	F	DM	3.73	2465	342	123	7.4	31.3	94	42
12	25	F	SLE + myositis	3.49	577	934	33	<0.8	8.2	100	34
13	46	M	RA + myositis	1.22	204	219	15	<0.8	6.1	29	26
14	52	F	DM	4.53	1406	486	3	<0.8	26.2	64	58
15	30	M	DM	4.73	6083	457	3	<0.8	59.6	137	160
16	35	M	PM	3.14	1078	290	2	<0.8	15.3	50	65
17	39	F	DM	2.89	2227	329	7	<0.8	18.5	48	60

ALT, alanine transaminase; AST, aspartate transaminase; CK, creatine kinase; CRP, C-reactive protein; DM, dermatomyositis; ESR, erythrocyte sedimentation rate; F, female; JDM, juvenile dermatomyositis; LDH, lactate dehydrogenase; M, male; MCTD, mixed connective tissue disease; PM, polymyositis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

significance between SR and biochemical data. Moreover, the range of SE was limited and only reflected regional resilience, whereas the biochemical data reflected the general condition of the muscle. There are no published data that have measured a wide range of elasticity using ultrasonography and MRI. To determine its clinical relationship with serum muscle enzyme levels, SR must be performed in a larger population with IM.

In Botar-Jid et al,[9] the quantitative hue histogram was obtained using institutionally developed software. However,

Figure 5. An 11-year-old female with juvenile dermatomyositis: (a) the transverse scan of B-mode ultrasound (right) revealed hyperechoic vastus intermedius and vastus lateralis. Simultaneous sonoelastography (left) showed a mixed colour of the lesion. The strain ratio was 1.70. (b) The same patient had similar features in the longitudinal scan of B-mode ultrasound. The strain ratio was 0.63.



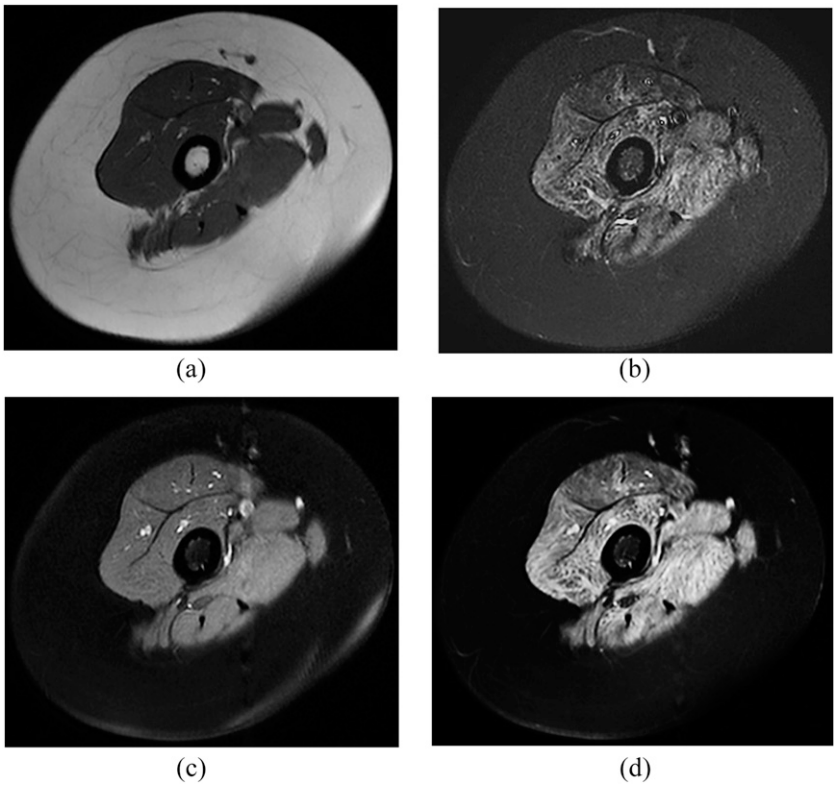
there was a reproducibility problem in the case of the absence of such software. Our simple method is intuitive and it might have an impact on guidance before an ultrasonography-guided procedure to help improve the accuracy of the biopsy. Havre et al[25] studied four phantoms and concluded that lower strain ratios were obtained in the cases where the reference areas were deep and superficial to the lesions. Zhi et al[26] demonstrated that positioning of the reference tissue influenced the strain ratio in breast lesions. In our study, the reference areas were superficial to the lesions but maintained the same size of the ROI. Thus, the SR may be lower than in the ROI placed in the same level. Because by applying light pressure to the superficial to the lesions, the superior part of the lesion has more displacement than the inferior part of the lesion. However, the mean SR is a relative measurement and it may be helpful when no difference of echogenicity is found between the target and reference tissues.

DM and PM patients showed higher mean SR rather than JDM or other causes. In JDM, major histocompatibility complex Class I protein was expressed from a young age, resulting in a more severe disease phenotype with rapid onset of weakness. Histological analysis did not suggest a different inflammatory process, rather more rapid kinetics.[27] Our case (Figures 5 and 6) indicated a diffuse involvement of the thigh muscle; it may influence low SR because of increasing stiffness of the reference muscle.

Elasticity scoring system has been used to distinguish benignity and malignancy in breast and thyroid nodules.[8,21,28] Rago et al[29] demonstrated that the highest elasticity scores were invariably associated with malignancy with minimal loss of sensitivity. They demonstrated that it can help identify nodules that are likely to be malignant. Nodules have a clear margin, but muscles do not; thus, we modified the Rago criteria.[21] A significant correlation between strain ratio and elasticity score reflects that an inflamed muscle may be stiffer than a reference muscle.

Our study had several limitations. First, this was a retrospective study and there was absence of a control group. Although we included consecutive patients, a selection bias may still have been introduced. However, it was inevitable because of the retrospective nature. Second, the sample size was small. However, the overall IM incidence was estimated at 7.98 cases/million/year and the incidence of IM as a whole ranged from 1.16 to 19 cases/million/year.[30] Third, our SR measuring method for IM was semi-quantitative compared with SWSE. Recently, Carlsen et al[15] mentioned that target depth has an influence on shear-wave velocity measurements of hard targets. Furthermore, in this

Figure 6. Corresponding MR images through proximal one-third thigh level in the same patient as in Figure 5 with juvenile dermatomyositis: (a) axial T_1 weighted [repetition time (TR)/echo time (TE) = 741/20 ms in (a)] and short tau inversion-recovery [TR/TE = 8433/70 ms in (b)] MR images are demonstrating diffuse patchy high-signal-intensity infiltration of the entire thigh muscles. (c, d) The axial fat-suppressed, pre-contrast-enhanced and contrast-enhanced T_1 weighted images (TR/TE = 734/15 ms) are showing patchy enhancement.



study, the linear probe did not allow shear-wave velocity measurements of the deeper phantoms. On paediatric population, thickness of the muscle and fat of the thigh is reported to be up to 45 mm.[11] In adults, it may be thicker than that. Thus, the SSE may be more appropriate than SWSE, especially in thigh muscles. Fourth, SR refers to the relative ratio between the target and the reference. If almost muscles have inflammation (Figures 5 and 6), SR will be closed to 1, and that is a problem to express actual tissue stiffness. Fourth, our SR measurement was performed by one radiologist. Although we tried to be standardized by elastogram applied to the surface remaining constant between Levels 3 and 4, a selection bias may still exist.

In conclusion, the correlation between the mean SR and the pathologic grade suggests that SE could be an important tool in not only the diagnosis of but also measuring the degree of muscular inflammation.

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