Magnetic resonance measurement of muscle T2, fat-corrected T2 and fat fraction in the assessment of idiopathic inflammatory myopathies

Lawrence Yao¹, Adrienne L. Yip², Joseph A. Shrader³, Sepehr Mesdaghinia², Rita Volochayev², Anna V. Jansen², Frederick W. Miller², Lisa G. Rider²

Abstract

Objective. This study examines the utility of MRI, including T2 maps and T2 maps corrected for muscle fat content, in evaluating patients with idiopathic inflammatory myopathy.

Methods. A total of 44 patients with idiopathic inflammatory myopathy, 18 of whom were evaluated after treatment with rituximab, underwent MRI of the thighs and detailed clinical assessment. T2, fat fraction (FF) and fat corrected T2 (fc-T2) maps were generated from standardized MRI scans, and compared with semi-quantitative scoring of short tau inversion recovery (STIR) and T1-weighted sequences, as well as various myositis disease metrics, including the Physician Global Activity, the modified Childhood Myositis Assessment Scale and the muscle domain of the Myositis Disease Activity Assessment Tool-muscle (MDAAT-muscle).

Results. Mean T2 and mean fc-T2 correlated similarly with STIR scores (Spearman $r_s = 0.64$ and 0.64, $P < 0.01$), while mean FF correlated with T1 damage scores ($r_s = 0.69$, $P < 0.001$). Baseline T2, fc-T2 and STIR scores correlated significantly with the Physician Global Activity, modified Childhood Myositis Assessment Scale and MDAAT-muscle ($r_s$ range $= 0.41$–0.74, $P < 0.01$). The response of MRI measures to rituximab was variable, and did not significantly agree with a standardized clinical definition of improvement. Standardized response means for the MRI measures were similar.

Conclusion. Muscle T2, fc-T2 and FF measurements exhibit content validity with reference to semi-quantitative scoring of STIR and T1 MRI, and also exhibit construct validity with reference to several myositis activity and damage measures. T2 was as responsive as fc-T2 and STIR scoring, although progression of muscle damage was negligible during the study.

Key words: MRI, T2, fat fraction, juvenile dermatomyositis, dermatomyositis, polymyositis, idiopathic inflammatory myopathies, muscle, myositis.

Introduction

The idiopathic inflammatory myopathies (IIMs) are systemic autoimmune diseases characterized by chronic muscle weakness and inflammation. The most common IIMs include DM, PM and sporadic inclusion body myositis [1]. The patchy muscle inflammation that characterizes active disease in IIM is well depicted by MRI,
particularly with short tau inversion recovery (STIR) imaging sequences [2]. Quantification of muscle disease by MRI is challenging, however, given the diffuse extent and variable intensity of characteristic muscle signal changes. Disease severity or extent can be estimated by STIR, using semi-quantitative scoring systems, but the scoring process is subjective and potentially influenced by varying MRI scan parameters.

The measurement of muscle T2 relaxation has been advocated to more objectively gauge active muscle disease in IIM. A prior study reported elevated T2 values in areas of active muscle disease in patients with juvenile DM [3]. However, over time, atrophy and fatty involution of muscle may occur as a manifestation of muscle damage in patients with IIM. Published T2 values for fat vary widely, but are substantially greater than the T2 value of normal or even actively diseased muscle [4-6]. Fatty replacement of muscle in advanced IIM confounds the interpretation of muscle T2 measurements. The integration of a MRI estimation of fat fraction (FF) with a bi-exponential, T2 modelling procedure can yield fat-corrected T2 (fc-T2) maps, a potentially more robust indicator of active muscle disease in patients with IIM [7]. Alternatively, integration of a robust fat-water separation strategy within a T2 mapping scan procedure can streamline observation of a similar, water-specific T2 [8].

Currently, disease outcomes in IIM are based on core-set disease activity and damage measures [9], which do not include MRI. This study attempts to validate semi-automated assessment of T2, fc-T2 and FF maps of the thigh muscles against standardized scoring of conventional STIR and T1 MRI in patients with IIM. This study further evaluates these quantitative and semi-quantitative MRI measures in patients with IIM, with reference to established core-set myositis activity and damage measures, including detailed clinical muscle assessments, standardized patient-reported outcome measures and laboratory studies. The utility of these MRI measures is further examined longitudinally in a subset of patients before and after treatment with rituximab.

Patients and methods

Patients

This study was approved by the National Institute of Diabetes and Digestive and Kidney Diseases/National Institute of Arthritis and Musculoskeletal and Skin Diseases Institutional Review Board, and informed consent was obtained from all patients. The study included 44 patients: 30 patients had DM (8 adult DM, 22 juvenile DM with age at onset <18 years) and 14 patients had PM by probable or definite Bohan and Peter criteria [10]. The median disease duration at baseline assessment was 3.1 years [inter-quartile range (IQR) 5.1 years] and the median patient age was 19.9 years (IQR 34.4 years). Of the 44 patients, 32 (72%) were female. Thirty patients were taking prednisone at a median daily dose of 20.0 mg or 0.32 mg/kg/day. Follow-up imaging and clinical evaluations were performed in 18 of the 44 patients 10–11 months after initial assessment; these patients received rituximab therapy at weeks 0 and 1, or at weeks 8 and 9. These 18 patients were also included in the Rituximab in Myositis trial, which consisted of 195 patients [11]. Published results for this trial were based on an analysis of clinical and functional outcome measures, and did not include imaging or MRI [11].

Clinical and laboratory assessments

Patients underwent manual muscle testing (MMT) by a physical therapist, and results were tabulated for a subset of tests encompassing the thigh muscles (MMT-thigh) [12]. Quantitative muscle testing (QMT) was performed using fixed-frame isometric dynamometry [9], and the results for knee extension and hip extension were combined into a score specific for the thigh muscles (QMT-thigh). Serum creatinine (CR) and serum enzymes were measured, including creatine kinase (CK), aldolase and lactate dehydrogenase (LDH).

Additional assessments of disease activity included the Physician Global Activity (PGA) score, the Childhood-HAQ (C-HAQ) for parents of paediatric patients or the HAQ for adults, and the MDAAT [13]. This study analysed the Visual Analogue Scales from the MDAAT, and the muscular component of the MDAAT (MDAAT-muscle) was analysed separately from the MDAAT scores of six different systems (constitutional, cutaneous, skeletal, gastrointestinal, pulmonary and cardiovascular), which were combined as an indicator of Extra-Muscular Global Activity (MDAAT-EMGA) [13]. A subset of the Childhood Myositis Assessment Scale (CMAS) [9] relevant to thigh and hip girdle function (CMAS-thigh) was also analysed.

Disease damage was analysed using the physician global damage assessment and the muscle-specific portion of the Myositis Damage Index (MDI), which includes scores for both disease severity and extent [9]. The general fatigue subscale of the Paediatric Quality of Life Index Multidimensional Fatigue Scale was examined as a measure of fatigue [14, 15]. Parents of paediatric patients completed the fatigue questionnaires and C-HAQ.

The primary definition of improvement (DOI) was based on the International Myositis Assessment and Clinical Studies Group (IMACS) criterion [16]: improvement of ≥20% in at least three of six core set activity measures, and worsening in no more than two core set measures (but not muscle strength) by ≥25%. Core set activity measures include physician and patient or parent global activity, MMT, physical function by the C-HAQ or HAQ, serum muscle enzymes and extra-muscular activity by the MDAAT [17].

MRI protocol

Patients underwent a standardized MRI exam at 1.5 Tesla, which included axial 2D scans of the bilateral thighs: T1 spin echo (TR = 525 ms, TE = 11 ms, averages = 2); fast spin echo STIR (TR = 5700 ms, TI = 150 ms, effective TE = 35 ms, echo train length = 9, averages = 2); spoiled gradient echo at consecutive in-phase and out-of-phase
echo times (TR = 250 ms, TE = 2.3 and 4.6 ms, flip angle = 90, pixel bandwidth = 380 Hz, averages = 3); and multi-echo Carr-Purcell–Meiboom–Gill sequence (TR 2000/TE 15, 30, 45, 60, 75 ms, pixel bandwidth = 144 Hz, averages = 1). Slices were obtained at the same locations for all scans (field of view = 36–44 cm, slice thickness = 10 mm, interslice gap = 10 mm).

MRI and data analysis
Image post-processing, including T2 and FF calculation, was implemented in ImageJ (Wayne Rasband, National Institutes of Health, Bethesda, MD, USA). FFs (Fig. 1) were calculated from the in- and out-of-phase gradient echo images based on a Dixon formulation [7]. Calculated FFs were adjusted for differential fat-water relaxation using data from a pilot analysis of lean muscle and subcutaneous fat regions [7]. T2 and fc-T2 (Fig. 1) were estimated by non-linear fitting of multi-echo Carr–Purcell–Meiboom–Gill signal intensities to mono- and bi-exponential models, respectively [7]. The bi-exponential fitting procedure for fc-T2 integrates known relaxation parameters for fat, which are derived from an analysis of pilot data, assumed to remain constant, and adequately modelled by subcutaneous fat in the thigh [7]. Standardized bilateral thigh muscle regions were defined for each patient on 10 contiguous axial T1 spin echo images, matching the locations of the images used for FF and T2 maps. Muscle regions were defined using a semi-automated, adaptive, moving-window, intensity-based segmentation algorithm [18]. Quantitative FF, T2 and fc-T2 were summarized for each patient as the mean value of pixels within the standardized thigh muscle regions.

An experienced musculoskeletal radiologist applied a previously described, standardized scoring system to MRI of the bilateral thighs [7]. The sum of visual scores assigned to medial, anterior and posterior thigh compartments constituted a global score for each patient. Scores for active muscle disease and disease damage were derived from STIR and T1 spin echo images, respectively. The score for active disease reflects both the spatial extent of disease, and the intensity of signal changes [7]. MRI processing and readings were performed blinded to patient identity and clinical status.

Statistical analysis
Values for disease metrics were compared between time points using the Wilcoxon signed rank test. Differences in metrics between patients with and without visible muscle damage were tested with a Mann–Whitney test. The standardized response mean (SRM) was used to examine the responsiveness of MRI measures between time points [19]. Linear regression modelling was used to compare the responsiveness of MRI metrics [20]. Agreement for disease improvement by various metrics was examined with Cohen’s kappa [21].

Results
Semi-quantitative vs quantitative MRI measures
Table 1 summarizes the conventional T2, fc-T2 and FF values for the standardized thigh regions. Mean conventional T2 values were significantly greater than mean fc-T2 values within subjects; this difference was also significant within the subgroup of 19 patients without muscle damage (visual T1 damage scores = 0). There was no group-wise significant difference in STIR activity score or fc-T2 between patients with and without visible muscle damage, but T2 and FF were greater in patients with muscle damage, compared with those without muscle damage (P < 0.05 and P < 0.01, respectively).

Conventional T2 and fc-T2 values, as well as FF values, were significantly correlated to a similar degree with STIR visual scores for myositis (Table 1). The correlations of fc-T2 and T2 values with STIR scores in patients without visible muscle damage (r = 0.74 and 0.73, respectively) were higher than in patients with damage (r = 0.51 and 0.50, respectively), but this difference was not significant (Table 1).

As expected, FF highly correlated with T1 damage score (r = 0.69, P < 0.001). As shown in Table 1, FF also correlated with STIR disease activity score, and FF also correlated with T2 and fc-T2 (r = 0.58, P < 0.001; and r = 0.43, P < 0.01, respectively). T1 damage scores similarly correlated with T2 and fc-T2 (r = 0.46, P < 0.01; and r = 0.37, P < 0.05, respectively). Thus, muscle disease and damage tended to co-occur within patients.

MRI vs non-MRI measures of myositis
Table 2 summarizes the correlation of MRI measures with clinical and laboratory measures of myositis. The MRI measures of disease activity (STIR, T2 and fc-T2) and disease damage (T1 scores and FF) correlated similarly with a broad range of muscle and non-muscle specific metrics of myositis disease activity, including serum CK and LDH, C-HAQ/HAQ, CMAS-thigh, MDAAT-muscle and PGA scores. Significant correlations were generally in a moderate range.

Of the MRI measures, only FF and T1-damage scores significantly correlated with QMT-thigh. STIR scores and fc-T2 also did not significantly correlate with MMT-thigh (while FF and T1 damage scores did). None of the MRI measures significantly correlated with the Paediatric Quality of Life Index Multidimensional Fatigue Scale, general fatigue subscale.

The T1 damage score and FF, as MRI indicators of muscle damage, correlated (as expected) with the physician global damage score and the MDI scores, both for the severity and extent of muscle damage. However, STIR scores, T2 and fc-T2, indicators of active muscle disease, also correlated similarly with these clinical metrics of disease damage. Only FF correlated significantly with serum creatinine.
Longitudinal changes in semi-quantitative vs quantitative MRI measures of active disease

In the follow-up evaluation of 18 patients treated with rituximab, the interval group-wise percentage change in fc-T2 was significant (median change = −5.3%, IQR = 3.8%, P < 0.05), while the group-wise interval percentage changes in STIR scores and T2 values were not significant (median change = −13.3%, IQR = 22.7%, P > 0.05 and median change = −3.4%, IQR = 8.4%, P > 0.10, respectively). However, interval intrasubject changes in T2 and fc-T2 were both significantly correlated with interval intrasubject changes in STIR scores (r_s = 0.49, P < 0.05 and r_s = 0.63, P < 0.05, respectively).

In the 18 patients treated with rituximab, 10, 14 and 13 patients showed improvement by T2, fc-T2 and STIR measures, respectively. A case of concordant improvement by these three MR measures is shown in Fig. 2. Four of 18 patients were discordant for interval improvement by T2 and fc-T2 measures; three of these four patients showed improvement by fc-T2, but not by T2. Improvement in T2 or in fc-T2 was concordant with improvement in STIR scores in 13/18 and 15/18 patients, respectively.

For the nine patients who showed improvement by STIR, T2 and fc-T2, responsiveness of STIR, T2 and fc-T2 as expressed by the SRM were −1.27, −1.43 and −1.38, respectively. Pair-wise differences in these SRM values were not significant.

Only one of the 18 patients exhibited a progression in muscle damage based on the visual T1 score, while 16/18 were unchanged. The interval group-wise percentage change in muscle FF was not significant (median change = 6.5%, IQR = 16.3%, P > 0.05). Interval intrasubject change in FF did not significantly correlate with interval intrasubject changes in T2, fc-T2 or STIR scores (P > 0.05, P > 0.20 and P > 0.20, respectively).
**TABLE 1** Summary of baseline MRI measures

<table>
<thead>
<tr>
<th>Metric</th>
<th>All cases (n = 44)</th>
<th>No damage present (n = 19)</th>
<th>Damage present (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (s.d.)</td>
<td>Mean (s.d.)</td>
<td>Mean (s.d.)</td>
</tr>
<tr>
<td>T2</td>
<td>59.6 (10.1)</td>
<td>55.9 (9.7)</td>
<td>62.4 (9.8)</td>
</tr>
<tr>
<td>fc-T2</td>
<td>54.1 (10.0)</td>
<td>51.0 (9.2)</td>
<td>56.4 (10.1)</td>
</tr>
<tr>
<td>FF</td>
<td>7.8 (3.7)</td>
<td>5.8 (1.25)</td>
<td>9.4 (4.19)</td>
</tr>
</tbody>
</table>

Intrasubject differences between mean fc-T2 and mean T2 were significant for the entire group, and for subgroups with and without visible muscle damage. **P < 0.01, Wilcoxon test.** T2 and fc-T2 are similarly and moderately correlated with STIR activity scores. Damage refers to standardized visual scores of muscle damage based on T1-weighted MRI. T2 and fc-T2 are in milliseconds. **P < 0.01; *P < 0.05.** STIR: visual scoring of short tau-inversion recovery MRI; fc-T2: fat corrected T2; FF: fat fraction; r_s: Spearman correlation.

**TABLE 2** Correlation of clinical and laboratory myositis measures with MRI measures

<table>
<thead>
<tr>
<th>Metric</th>
<th>Range</th>
<th>n</th>
<th>Median</th>
<th>IQR</th>
<th>STIR, r_s</th>
<th>fc-T2, r_s</th>
<th>T2, r_s</th>
<th>T1-Dam, r_s</th>
<th>FF, r_s</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGA</td>
<td>0–10</td>
<td>44</td>
<td>2.7</td>
<td>2.6</td>
<td>0.67**</td>
<td>0.41**</td>
<td>0.46**</td>
<td>0.35*</td>
<td>0.50**</td>
</tr>
<tr>
<td>MMT-thigh</td>
<td>0–40</td>
<td>44</td>
<td>34.5</td>
<td>12.3</td>
<td>−0.25</td>
<td>−0.27</td>
<td>−0.31</td>
<td>−0.49**</td>
<td>−0.45**</td>
</tr>
<tr>
<td>QMT</td>
<td>0–undefined (kg)</td>
<td>21</td>
<td>34.7</td>
<td>21.6</td>
<td>−0.30</td>
<td>−0.20</td>
<td>−0.37</td>
<td>−0.54*</td>
<td>−0.61**</td>
</tr>
<tr>
<td>CMAS-thigh</td>
<td>0–28</td>
<td>36</td>
<td>19.0</td>
<td>13.3</td>
<td>−0.48**</td>
<td>−0.48**</td>
<td>−0.61**</td>
<td>−0.62**</td>
<td>−0.74**</td>
</tr>
<tr>
<td>C-HAQ/HAQ</td>
<td>0–3</td>
<td>37</td>
<td>1.4</td>
<td>1.3</td>
<td>0.39*</td>
<td>0.42**</td>
<td>0.54*</td>
<td>0.34*</td>
<td>0.46**</td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>38–252 U/l</td>
<td>42</td>
<td>201.0</td>
<td>723.3</td>
<td>0.52**</td>
<td>0.33**</td>
<td>0.42**</td>
<td>0.50**</td>
<td>0.42**</td>
</tr>
<tr>
<td>Aldolase</td>
<td>1–6 U/l</td>
<td>40</td>
<td>8.2</td>
<td>18.1</td>
<td>0.32*</td>
<td>0.10</td>
<td>0.21</td>
<td>0.32*</td>
<td>0.38*</td>
</tr>
<tr>
<td>LDH</td>
<td>113–226 U/l</td>
<td>42</td>
<td>225.0</td>
<td>111.0</td>
<td>0.48**</td>
<td>0.32**</td>
<td>0.35*</td>
<td>0.24</td>
<td>0.28</td>
</tr>
<tr>
<td>MDAAT-muscle</td>
<td>0–10</td>
<td>36</td>
<td>3.0</td>
<td>2.8</td>
<td>0.74**</td>
<td>0.49**</td>
<td>0.58**</td>
<td>0.44**</td>
<td>0.58**</td>
</tr>
<tr>
<td>MDAAT-EMGA</td>
<td>0–10</td>
<td>36</td>
<td>2.5</td>
<td>1.8</td>
<td>0.51**</td>
<td>0.27</td>
<td>0.34*</td>
<td>0.11</td>
<td>0.26</td>
</tr>
<tr>
<td>PedsQL-MDFS</td>
<td>0–100</td>
<td>34</td>
<td>39.6</td>
<td>40.2</td>
<td>−0.21</td>
<td>0.02</td>
<td>−0.03</td>
<td>0.12</td>
<td>−0.08</td>
</tr>
<tr>
<td>MDI-Muscle Severity</td>
<td>0–10</td>
<td>43</td>
<td>2.5</td>
<td>2.7</td>
<td>0.48**</td>
<td>0.48**</td>
<td>0.57**</td>
<td>0.70**</td>
<td>0.68**</td>
</tr>
<tr>
<td>MDI-Muscle Extent</td>
<td>0–5</td>
<td>43</td>
<td>3.0</td>
<td>1.0</td>
<td>0.38*</td>
<td>0.33*</td>
<td>0.36*</td>
<td>0.44**</td>
<td>0.34*</td>
</tr>
<tr>
<td>PGD</td>
<td>0–10</td>
<td>43</td>
<td>2.3</td>
<td>2.3</td>
<td>0.34*</td>
<td>0.40**</td>
<td>0.42**</td>
<td>0.53**</td>
<td>0.58**</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.9–1.4 mg/dl</td>
<td>41</td>
<td>0.5</td>
<td>0.3</td>
<td>−0.20</td>
<td>−0.17</td>
<td>−0.24</td>
<td>−0.25</td>
<td>−0.33*</td>
</tr>
</tbody>
</table>

Spearman correlation (r_s) of selected laboratory and clinical myositis metrics and baseline semi-quantitative and quantitative magnetic resonance measures. Significant correlations are marked by asterisks (**P < 0.01; *P < 0.05). Range refers to normal values for laboratory studies, and range of possible scores for clinical measures (QMT has no defined upper limit). STIR: visual scoring of short tau-inversion recovery MRI; fc-T2: fat corrected T2; FF: fat fraction; r_s: Spearman correlation.

Longitudinal changes in MRI measures vs other measures of active disease

Table 3 summarizes the correlation of interval changes in STIR, T2, fc-T2 and FF and interval change in other clinical and laboratory measures. Changes in T1 damage scores are not analysed, given that 16 of 18 patients showed no change in T1 damage scores. Changes in T2 and fc-T2, but not changes in STIR scores, correlated with changes in serum enzymes. Changes in the MRI measures, including FF, did not correlate with changes in the QMT-thigh or MMT-thigh. Changes in STIR scores and fc-T2, but not changes in T2, correlated significantly with changes in PGA scores and the MDAAT-muscle.

Fifteen of 18 patients were improved by the IMACS DOI. There was no significant agreement for improvement as determined by the IMACS DOI vs by fc-T2, T2 and STIR measures (κ = 0.12, P > 0.61; κ = 0.16, P > 0.39; and κ = 0.37, P > 0.09, respectively).

**Discussion**

Signal alterations on oedema-sensitive MRI sequences such as STIR are useful signs of active muscle disease in IIM, while fatty infiltration of muscle and diminished muscle bulk or mass as depicted on T1-weighted MRI are useful indicators of muscle damage in these patients.
This study supports the potential utility of T2 and fc-T2 measurement as quantitative MRI markers of muscle disease in IIM, with reference to semi-quantitative scoring of active muscle disease on STIR images. Likewise, this study also supports the utility of FF measurement as a quantitative marker of muscle damage, with reference to semi-quantitative scoring of muscle damage on T1-weighted images.

The separation of active muscle disease from irreversible disease damage may be problematic by routine clinical assessment. In this study, STIR scores, T2 and fc-T2 (markers of disease activity), as well as FF measurements and T1 scores (markers of muscle damage), were found to correlate with the MDI and physician global damage. Likewise, MRI markers of disease damage, as well as MRI markers of disease activity, all correlated with standardized clinical and laboratory assessments of disease activity (PGA, MDAAT, C-HAQ, CMAS-thigh). However, these observations may largely reflect that muscle disease activity and damage, at least as defined by MRI measures, are correlated; patients with more severe muscle disease tended to have more severe muscle damage.

Muscle damage and concomitant fatty replacement of muscle in IIM could confound the use of T2 mapping as a metric of active muscle disease, because the T2 of fat greatly exceeds that of healthy muscle. The same confounding could occur to some degree with STIR MRI, if the inversion time is not optimized for each patient, which is typically not done in clinical settings [23]. T2 measurement may be a useful marker of disease in neuromuscular disorders such as Duchenne’s muscular dystrophy [24], exactly because T2 prolongation in affected muscles primarily reflects increases in muscle fat. In evaluating

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**Fig. 2** Baseline and post-treatment MR evaluations of the thigh in a 52-year-old female with PM

STIR image (A) shows fairly diffuse inflammation in the thigh muscles, more prominent in the adductor magnus muscles. The conventional T2 map (B) shows extensive, corresponding elevations in muscle T2, which are generally higher and also more homogeneous than those seen in the corresponding fc-T2 map (C) (calibration scale in B and C are identical; units for calibration bar are milliseconds). Forty-four weeks later, after interval rituximab treatment, the STIR image (D) shows a generalized improvement of the oedema-like muscle signal, with subtle residual signal alterations. The conventional T2 map (E) shows a heterogeneous pattern of moderate residual T2 elevation, in part reflecting concomitant muscle damage and fatty involution of muscle. The fc-T2 map (F) reveals much milder and more limited residual elevations in muscle T2 (calibration scale in E and F are identical; units for calibration bar are milliseconds).
TABLE 3 Correlation of interval changes in MRI measures and clinical and laboratory myositis measures

<table>
<thead>
<tr>
<th>Metric</th>
<th>Median change (%)</th>
<th>IQR (%)</th>
<th>STIR $r_s$</th>
<th>fc-T2 $r_s$</th>
<th>T2 $r_s$</th>
<th>FF $r_s$</th>
</tr>
</thead>
<tbody>
<tr>
<td>PGA</td>
<td>−45.5</td>
<td>12.2</td>
<td>0.87**</td>
<td>0.67**</td>
<td>0.37</td>
<td>0.11</td>
</tr>
<tr>
<td>MMT-thigh</td>
<td>17.6</td>
<td>12.8</td>
<td>−0.14</td>
<td>−0.28</td>
<td>0.00</td>
<td>−0.23</td>
</tr>
<tr>
<td>QMT-thigh</td>
<td>63.6</td>
<td>14.0</td>
<td>0.16</td>
<td>0.28</td>
<td>0.48</td>
<td>0.01</td>
</tr>
<tr>
<td>CMAS-thigh</td>
<td>15.5</td>
<td>65.6</td>
<td>−0.45</td>
<td>−0.12</td>
<td>−0.21</td>
<td>−0.39</td>
</tr>
<tr>
<td>C-HAQ/HAQ</td>
<td>−36.1</td>
<td>19.1</td>
<td>0.60**</td>
<td>0.31</td>
<td>0.05</td>
<td>0.22</td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>−51.6</td>
<td>54.5</td>
<td>0.20</td>
<td>0.63**</td>
<td>0.58*</td>
<td>0.12</td>
</tr>
<tr>
<td>Aldolase</td>
<td>−40.6</td>
<td>38.9</td>
<td>0.33</td>
<td>0.68**</td>
<td>0.70**</td>
<td>0.39</td>
</tr>
<tr>
<td>LDH</td>
<td>−17.3</td>
<td>19.7</td>
<td>0.36</td>
<td>0.71**</td>
<td>0.56*</td>
<td>0.19</td>
</tr>
<tr>
<td>MDAAT-EMGA</td>
<td>−56.7</td>
<td>22.3</td>
<td>0.62**</td>
<td>0.43</td>
<td>0.20</td>
<td>0.02</td>
</tr>
<tr>
<td>MDAAT-muscle</td>
<td>−47.8</td>
<td>19.4</td>
<td>0.70**</td>
<td>0.57*</td>
<td>0.23</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Spearman correlation ($r_s$) of 10–11 month interval changes in selected laboratory and clinical metrics, and interval changes in MRI measures, before and after treatment with rituximab in 18 patients. Significant correlations are marked by asterisks ($^*P<0.01$; $^*P<0.05$). STIR: visual scoring of short tau-inversion recovery MRI; fc-T2: fat corrected T2; FF: fat fraction; IQR: interquartile range; PGA: Physician Global Assessment of disease activity; MMT: manual muscle testing; QMT: quantitative muscle testing; CMAS: Childhood Myositis Assessment Scale; C-HAQ: Childhood HAQ; LDH: lactate dehydrogenase; MDAAT: Myositis Disease Activity Assessment Tool; EMGA: Extra-Muscular Global Activity.

patients with IIM, however, a MRI marker for inflammation or active disease, independent of the degree or presence of fatty replacement of muscle, would be preferable, and could better detect longitudinal changes in muscle disease, particularly in the setting of pre-existing muscle damage.

In this study and a prior report, we have demonstrated the feasibility of measuring the T2 relaxation of muscle while correcting for T2 alteration secondary to fatty replacement of muscle, using commercially available scan acquisition software in a clinical environment [7]. Our method requires a contemporaneous MRI estimation of muscle fat content [7]. Various chemical shift-sensitive MRI strategies exist to quantify tissue fat content [25], and such measures may be independently useful for evaluating muscle damage in IIM or other diseases [26, 27]. Newer T2 measurement strategies have been developed that can estimate both water-specific T2 relaxation and fat-water content in a single MRI scan acquisition [8].

As expected, observed muscle fc-T2 values were consistently lower than corresponding conventional T2 values, although this was true even in cases without evidence of muscle damage by visual scoring. The fc-T2 and conventional muscle T2 values, as expressed by the global mean, correlated to a similar degree with muscle disease activity as reflected by STIR visual scores. Baseline T2 and fc-T2 also similarly correlated with a range of muscle and non-muscle specific metrics of disease activity (PGA, CMAS-thigh, C-HAQ/HAQ and MDAAT-muscle) as well as serum CK and LDH levels. While offering construct validity for quantitative MRI as metrics of muscle disease activity, these baseline comparisons did not corroborate a theoretical advantage of fc-T2 measurement. Again, this result may simply reflect the correlation or relative co-occurrence of myositis activity and damage in our patients.

The longitudinal portion of our study suggested a variable MRI response of muscle disease to rituximab; 13 of 18 patients improved, based on STIR scores. There was no significant agreement for improvement by any of the MRI metrics and the IMACS DOI, which may suggest that MRI contributes added information to the multidimensional assessment of outcomes in patients with IIM. In the nine patients who improved by all MRI metrics of disease activity, a greater, expected responsiveness of fc-T2 as compared with conventional T2 was not observed. This may largely reflect the lack of muscle damage progression during the study period. However, four patients did show improvement by fc-T2 and not by conventional T2, and longitudinal changes in the PGA and MDAAT-muscle correlated with changes in fc-T2, but not changes in conventional T2. Interestingly, interval changes in serum enzymes (CK, aldolase, LDH) correlated significantly with changes in fc-T2 and T2, but not with changes in STIR scores.

While baseline MMT-thigh and QMT did correlate with MRI measures of muscle damage (T1 scores and FF), the lack of correlation between baseline MRI measures of disease activity and the QMT was surprising, and only T2 correlated with the MMT-thigh, while fc-T2 and STIR did not. Muscle strength may reflect both active muscle disease and chronic muscle damage. Because interval changes in MRI markers of muscle damage were minimal, a correlation between longitudinal changes in QMT-thigh and MMT-thigh and interval changes in the MRI metrics of disease activity might be expected, but was surprisingly not observed. The MMT is a validated core set measure in myosit [12], and a recent study of JDM patients did report a significant correlation between semi-quantitative scoring of whole body STIR MRI and the MMT [28]. However, a lack of correlation between muscle weakness and inflammatory infiltrates seen on muscle biopsy has
been previously described in patients with IIM [29]. Muscle strength in IIM may be influenced via disease mechanisms independent from those that manifest oedema-like MR signal changes in muscle, including non-immune mechanisms [30].

Application of quantitative T2 and fc-T2 measurements to the MRI evaluation of IIM disease activity may improve study precision, by eliminating the subjectivity of visual scoring. A quantitative imaging method is efficient and amenable to automation, and may preclude the need for specialized expertise in MRI interpretation. However, quantitative T2 and fc-T2 measurements do introduce other sources of variance. T2 varies with field strength, and systematic and substantial variances in observed T2 may arise from variations in pulse sequence design, imperfections in radiofrequency refocusing pulses and incidental magnetization transfer effects [31, 32]. Hence, reliable application of T2 and fc-T2 measurement to clinical studies requires rigorous uniformity in scan protocols, and may benefit from uniformity in MRI scan platforms as well. Methodological refinements in fc-T2 measurement, or muscle-specific T2 measurement have emerged [8] and will no doubt continue. In addition to simultaneous fat–water separation and T2 measurement, techniques that more fully incorporate the multispectral features and associated multi-exponential relaxometry of fat may improve the validity of both FF and fc-T2 measurements [33].

In summary, our study demonstrates the clinical feasibility of fc-T2 mapping, and lends content validity to T2 and fc-T2 MRI mapping as measures of myositis activity, and to FF mapping as a measure of muscle damage. Our study also presents construct validity for quantitative muscle T2 and fc-T2 measurements with reference to several standard, core set clinical and laboratory measures of myositis activity and damage. The relationship of MRI metrics and muscle strength in the setting of IIM warrants further study. T2 and fc-T2 measurements appear to be as responsive as conventional STIR imaging. A theoretical advantage of fc-T2 over conventional T2 measurement as a longitudinal metric of active muscle disease in IIM awaits definitive confirmation. These quantitative MRI metrics do offer the practical advantages of being non-invasive, objective and amenable to automation. As such, quantitative MRI methods could enhance the utility and effectiveness of MRI, and deserve further study in the assessment of muscle disease in patients with IIM.

Acknowledgements

We thank the following individuals: Dr Ashkan Shademan for assistance with data management and image processing; Laura James-Newton, Yan Li and Kathleen Gorman for assistance with patient coordination; Mina Jain for manual muscle testing; Ellen Levy for quantitative muscle testing; Dr James Katz for careful review of the manuscript; and Dr Neville Gai for helpful comments on the manuscript and important discussions on the MRI methodology.

Funding: This study was supported in part by the Intramural Research Program of the National Institute of Environmental Health Sciences, National Institutes of Health.

Disclosure statement: The authors have declared no conflicts of interest.

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