Original article

Ultrasound and MR muscle imaging in new onset idiopathic inflammatory myopathies at diagnosis and after treatment: a comparative pilot study

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Abstract

Objectives. To prospectively compare ultrasound (US) and whole-body MRI for detection of muscle abnormalities compatible with idiopathic inflammatory myopathies (IIM).

Methods. Newly diagnosed IIM patients underwent US (14 muscles) and MRI (36 muscles) at diagnosis and after nine weeks monotherapy with intravenous immunoglobulin. Muscles were compatible with IIM when quantitative US echo-intensity (EI) z scores was ≥ 1.5, semi-quantitative US Heckmatt score was ≥ 2, qualitative US was abnormal, or when MRI showed oedema on T2-weighted images. At patient level, findings were classified as abnormal when quantitative US EI z scores was >1.5 ($n = 3$ muscles), >2.5 ($n = 2$ muscles) or >3.5 ($n = 1$ muscle), or if ≥ 3 muscles showed abnormalities as described above for the other diagnostic methods.

Results. At diagnosis, in 18 patients US of 252 muscles revealed abnormalities in 36 muscles (14%) with quantitative, in 153 (61%) with semi-quantitative and in 168 (67%) with qualitative analysis. MRI showed oedema in 476 out of 623 muscles (76%). Five patients (28%) reached abnormal classification with quantitative US, 16 (89%) with semi-quantitative and qualitative US, and all patients (100%) with MRI. Nine-week follow-up of 12 patients showed no change over time with quantitative US or MRI, and a decrease in abnormalities with semi-quantitative US ($P < 0.01$), and qualitative US ($P < 0.01$).

Conclusion. At diagnosis, MRI was more sensitive than US to detect muscle abnormalities compatible with IIM. Semi-quantitative US and qualitative US detected abnormalities in the majority of the patients while evaluating fewer muscles than MRI and showed change over time after nine weeks of treatment.

Key words: idiopathic inflammatory myopathy, myositis, magnetic resonance imaging, ultrasonography, muscle imaging

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Rheumatology key messages

- Whole-body MRI detects muscle abnormalities in treatment naive IIM patients at diagnosis better compared to muscle ultrasound.
- Semi-quantitative ultrasound detects changes over time in muscle abnormalities better than MRI.
- Echo-intensity based quantitative ultrasound is not suited to diagnose treatable IIMs.

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CLINICAL SCIENCE

Introduction

Dermatomyositis, antisynthetasesyndrome, immune-mediated necrotizing myopathy and non-specific/overlap myositis are treatable idiopathic inflammatory myopathies (IIMs) that typically present with proximal muscle weakness [1]. Muscle imaging has become an increasingly important tool in the diagnostic work-up and follow-up of IIMs. Both ultrasound (US) and MRI can demonstrate abnormalities compatible with IIMs in the muscle and subcutaneous fat and fasciitis, which is usually present in the active (early) phase of IIMs as oedema [2–4]. Oedema can be seen as a hyperintense signal on T2 MRI and may result in echo-intensity (EI) changes on US. Other detectable muscle abnormalities, such as muscle atrophy and fatty replacement, typically occurring as signs of chronic damage, may be found in later disease phases, and are less specific for IIMs [5–9].

Whereas US is easily accessible, and without claustrophobic issues, whole-body MRI (WB-MRI) provides a representation of a large number of muscles including deep muscles that are not assessable by US. US acquisition is operator dependent, MRI protocols may differ between centres, and US and MRI image analysis both require experienced evaluators.

Studies comparing the usefulness of muscle US as compared with MRI in IIMs are scarce: some studies compared US to MRI in only one muscle via grayscale analysis, muscle perfusion or strain sono-elastography at diagnosis [10, 11] and another study compared the diagnostic value of US and MRI cross-sectionally during the disease process in mainly amyopathic dermatomyositis patients [2]. To date, no studies systematically compared both techniques during follow-up. A recent expert review states that the position of US as compared with MRI in the diagnosis of IIMs is unknown and comparative longitudinal studies are needed [12].

We aimed to compare the ability of US and WB-MRI to detect muscle abnormalities in IIM patients at diagnosis and correlated these abnormalities with markers used in daily clinical practice such as muscle strength and serum creatine kinase (sCK). Additionally, we investigated changes in these parameters at follow-up after a 9-week period of treatment with IVIg.

Methods

Patients

We used data of patients in a phase-2 open-label cohort study on IVIg as first-line treatment [13]. The patients had newly diagnosed, biopsy-proven IIM, were assessed clinically before and during treatment and underwent US and MRI at diagnosis and after 9 weeks of treatment. All patients signed informed consent prior to inclusion. The study protocol has been approved by the medical ethics committee of the Academic Medical Centre, Amsterdam, The Netherlands, and was conducted in accordance with the declaration of Helsinki.

Clinical examination

Six core set measures of the International Myositis Assessment and Clinical Studies (IMACS) group [14] were collected at baseline and during follow-up. These were the Physician Global Activity, Patient Global Activity, Extra Muscular Activity, Muscle Enzymes (among which sCK), Health Assessment Questionnaire Disability Index and Manual Muscle Testing (MMT13). The MMT scores the individual muscle strength ranging from 0 to 10, and the total score per patient ranged from 0 to 260, with higher scores representing a better strength.

Ultrasound

The standardized US examination was done by trained neurophysiologists (C.V. and C.G.J.S.) using an US scanner with an 8–14 MHz broadband linear transducer with a 53-mm footprint and an axial resolution of around 0.2 mm (MyLabTwice, Esaote SpA, Genoa, Italy). Images were anonymized prior to scoring for patient identification and for the moment of examination (i.e. baseline or follow-up) [15, 16]. For the assessment of muscle abnormalities with quantitative, semi-quantitative and qualitative analysis, we used the same US images at standardized anatomical sites [17].

EI of 14 muscles (bilateral deltoid, biceps brachii, flexor carpi radialis, flexor digitorum profundus, rectus femoris, vastus lateralis and tibialis anterior) was scored with three methods.

Quantitative analysis

Mean EI of standardized predefined regions of interest were compared with muscle-specific reference values from a healthy control population and expressed as z-scores. Abnormal EI was defined as a z scores ≥ 1.5 for an individual muscle [17, 18]. Regions of interest were drawn manually in the muscles by A.W.W., J.L, and C.V.

Semi-quantitative analysis

EI was visually rated using the 4-point Heckmatt grading scale (1–4); a score ≥ 2 was considered abnormal [6]. Scoring was performed by C.G.J.S.

Qualitative analysis

EI was visually rated as normal or abnormal. An abnormal score was reached when there were visual changes in EI. These visual changes also included a 'shine-through' appearance or 'see-through echogenicity increase' as described for muscle oedema, which can be missed by the semi-quantitative Heckmatt grading, and/or focal changes, i.e. focal areas of increased echogenicity, loss of definition of perimysial septa and focal change in echotexture [12]. Scoring was performed by C.G.J.S.

Muscle thickness (MT) of the same 14 muscles was scored quantitatively and decreased MT was defined as a z score <-2 for an individual muscle [17, 19]. Fascial thickness was scored quantitatively for the deltoid, rectus femoris and vastus lateralis muscles and considered abnormal when showing a z score >2 compared with previous published normal values [16]. The callipers to measure the MT and thickened fascia (FT) were

positioned manually by A.W.W., J.L. and C.V. with 0.25 cm interval. In addition, fascial thickness was scored qualitatively for the fasciae of all 14 muscles.

At the patient level, quantitative US analysis was abnormal in case of an EI z scores $\geq$1.5SD in at least three muscles, a z score of $\geq$2.5 in two muscles or a z score of $\geq$3.5 in one muscle [18]. Semi-quantitative and qualitative US analysis were scored abnormal when at least three muscles showed abnormalities according to the EI criteria described above. The number of abnormal muscles per patient were calculated for quantitative, semi-quantitative and qualitative US. For semi-quantitative analysis a Heckmatt sumscore per patient was calculated ranging from 0 to 42. To calculate this sumscore, Heckmatt scores 1–4 of individual muscles were recoded to 0–3 and summed.

The number of muscles with maximal muscle strength according to manual muscle strength evaluation and with abnormal muscles according to semi-quantitative US (Heckmatt score $\geq$2) were calculated for ten muscles (or muscle groups) that were evaluated with MMT and US; i.e. the bilateral deltoid, biceps brachii, forearm flexors, quadriceps femoris and tibialis anterior muscles.

MRI

The standardized WB-MRI protocol, performed on a 3.0 Tesla Ingenia MRI scanner (Philips, Best, The Netherlands), included water and fat imaging using 2D coronal and axial T2-weighted two-point Dixon scans; an equivalent MRI scanning protocol was used by Sigmund *et al.* [20]. Sequences were anonymized for patient identification and for the moment of examination, and scored by a trained musculoskeletal radiologist (F.F.S.) according to a previously described method [3].

The extent of muscle oedema was semi-quantitatively scored in 36 muscle groups: cervical, deltoid, supraspinatus, infraspinatus, biceps, triceps, forearm flexors, forearm extensors, gluteal, iliopsoas, sartorius, hip adductors, quadriceps, hamstring, tensor fasciae latae, tibialis anterior, peroneus and gastrocnemius. Muscles were bilaterally scored as: 0, no oedema; 1, oedema in <50% of the muscle area; and 2, oedema in $\geq$50% of the muscle area [3]. The presence of muscular fatty infiltration was noted. Four fascial areas and subcutaneous areas were scored for 0, no oedema; and 1, oedema [3].

At the patient level, MRI was considered abnormal when at least three muscles showed oedema. This criterion was chosen to enable comparison with US. The number of abnormal muscles per patient was calculated. Additionally, a MRI oedema sumscore per patient was calculated ranging from 0 to 72. To calculate this MRI oedema sumscore, the 0–2 MRI scores were added together.

The number of muscles with maximal muscle strength according to manual muscle strength evaluation and with muscle oedema on MRI (oedema score $\geq$1) were calculated for 19 muscles, i.e. neck flexors, deltoid, biceps brachii, forearm flexors, gluteus musculature, iliopsoas, quadriceps, hamstrings, tibialis anterior and gastrocnemius muscles.

Statistical analysis

Patient baseline characteristics, IMACS core set measures, scores of the different imaging modalities [quantitative US, semi-quantitative US, semi-quantitative sumscore, qualitative US, US fascia thickness, US MT, MRI oedema score, MRI oedema (average) sumscore, MRI subcutaneous oedema and MRI fascial oedema (FE)] at baseline and follow-up, and number of muscles showing maximal MMT and US or MRI abnormalities at baseline were summarized using descriptive statistics. An MRI oedema average sumscore was calculated in case of missing data: the sumscore was divided by the amount of valid muscles per patient and subsequently multiplied by the total amount of muscles.

Differences between follow-up scores and baseline scores of the IMACS core set measures, and different imaging modalities described above were expressed in median change scores with interquartile ranges. For both the MRI data and US data, differences between non-normally distributed continuous baseline and follow-up parameters were analysed using the Wilcoxon signed rank test.

Friedman analysis of varicance test (ANOVA), for three or more non-parametric variables and with an ordinal variable as the dependent variable, was used to compare the baseline scores of quantitative, semi-quantitative, qualitative US and MRI for five muscle groups that were measured with both imaging modalities; deltoid, biceps, forearm flexors (US: flexor carpi radialis and flexor digitorum profundus), quadriceps femoris (US: rectus femoris and vastus lateralis) and tibialis anterior. When Friedman ANOVA showed statistically significant differences (P <0.05) between the groups, we performed *post hoc* pairwise comparisons by Wilcoxon signed rank tests.

Correlations at baseline and follow-up
Spearman's rank correlation (r_s) was used to assess the association between the semi-quantitative US sumscore and MRI oedema sumscore on the one hand, and muscle strength (MMT13) and sCK on the other hand.

Spearman's rank correlation (r_s) was used to assess the association between the change scores (follow-up—baseline) of semi-quantitative US sumscores and MRI oedema sumscores with change scores of MMT13 and change of sCK over time. A bootstrap procedure was used to compare the correlations between the change scores.

Statistical significance was defined as a two-sided *P*-value <0.05. In view of the explorative nature of this pilot study we did not correct for multiple comparisons [21]. All analyses were performed in SPSS version 26 (IBM, Inc., Chicago, IL, USA), apart from the bootstrap procedure which was performed in RStudio 3.6.1. (www.rstudio.org).

Results

Patients

Twenty newly diagnosed, biopsy-proven IIM patients participated in the IMMEDIATE study [22]. Eighteen out of 20 patients underwent both US and MRI at diagnosis.

Due to logistical issues, one patient missed MRI and another patient missed US at baseline. Baseline characteristics are summarized in Table 1. All patients had muscle weakness. Nine had dermatomyositis (50%), four immune mediated necrotizing myopathy (22%), four non-specific/overlap myositis (22%) and one antisynthetasesyndrome (6%).

Baseline

At baseline, US and MRI were performed with a median of three days in between (range 0–21 days). In three patients, one or both examinations were performed after initiation of IVIg: US after 19 days in one patient, MRI after one day in one patient, and both US and MRI after five days in another patient. Figure 1 shows images of US and MRI in one patient.

Ultrasound
At the muscle level, quantitative US analysis showed EI abnormalities in 36 out of 252 muscles (14%). Semi-quantitative US showed EI changes in 153 out of 252 muscles (61%), and in qualitative US EI changes were found in in 168 out of 252 muscles (67%), among which focal changes were present in 12 muscles (5%) (Supplementary Tables S1 and S2, available at

TABLE 1 Baseline characteristics of 18 included patients in baseline analysis

Characteristic	Outcome
Age in years at diagnosis, median (IQR)	55 (36–68)
Time between first symptom and diagnosis, months; median (IQR)	4.5 (3.8–6.3)
Gender, male *n* (%)	8 (44.4)
Dysphagia, *n* (%)	13 (72.2)
Cancer, *n* (%)	1 (5.6)
Connective tissue disorder, *n* (%)	3 (16.7)
sCK, U/L median (IQR)	960 (160–4971)
MMT13 score, median (IQR)	214 (185–227)
Neck flexors	7 (4–8)
Neck extensors	9 (8–10)
Trapezius	10 (10–10)
Deltoid	9 (4–9)
Biceps brachii	9 (7.8–9)
Wrist extensors	9.5 (8–10)
Wrist flexors	10 (8–10)
Iliopsoas	6 (6–7.3)
Quadriceps	9 (9–9)
Gluteus maximus	8 (3–8)
Gluteus medius	8 (4–8.3)
Hamstrings	8 (7–8)
Tibialis anterior	10 (10–10)
Gastrocnemius	10 (10–10)

MMT, manual muscle testing according to Kendall; sCK, serum creatine kinase. Score is based on MMT13, MMT scores of the right muscles are displayed for the limb muscles (no statistically significant difference between right and left muscle MMT score).

Rheumatology online). Quantitative US showed that MT was reduced in 47 out of 252 muscles (19%). Increased fascia thickness was found in 17 out of 170 fasciae (10%). Qualitative US showed increased thickness in 8 out of 252 fasciae (3%).

At the patient level, abnormality criteria based on EI were fulfilled in five patients (28%) based on quantitative US, and in 16 patients (89%) based on both semi-quantitative US and qualitative US.

Table 2 shows the median number of abnormal muscles per patient per US method, and the semi-quantitative US sumscore.

Semi-quantitative US showed EI abnormalities in 59 out of 72 muscles (82%) with a maximal MMT, predominantly in forearm flexors and tibialis anterior.

MRI
At the muscle level, oedema was present in 476 out of 623 muscle groups (76%); 206 muscles (33%) showed ≤50% oedema, 270 muscles (43%) showed >50% oedema (Supplementary Table S3, available at *Rheumatology* online).

At the patient level, all 18 patients (100%) fulfilled our predefined criteria for muscle MRI abnormality. Two patients (11%) showed some fatty infiltration: one in the gluteus medius and another in quadriceps and hamstring muscles.

FE was present in 47 out of 132 regions (36%) and subcutaneous oedema in 44 out of 136 regions (32%), both were present among all IIM subtypes (Table 2).

MRI showed oedema in 45 out of 98 muscles (46%) with a maximum MMT, predominantly in tibialis anterior and gastrocnemius muscles.

Comparison of five muscle groups between US and MRI
Analysis of five muscle groups that were measured with both modalities showed abnormal muscles in 33 out of 180 (18%) by quantitative US, in 129 out of 180 (72%) by semi-quantitative US, in 129 out of 180 (72%) in qualitative US, and in 134 out of 180 (74%) by MRI (Friedman ANOVA = 35.8, $P < 0.001$), respectively. Quantitative US showed significantly less abnormal muscles as compared with qualitative US, semi quantitative US and MRI (Wilcoxon signed rank test; $P < 0.001$). *Post hoc* Wilcoxon signed rank tests showed no statistically significant difference in numbers of abnormal muscles between semi-quantitative US, qualitative US and MRI for these five muscle groups.

All muscle groups showing focal changes on qualitative US showed oedema on MRI. Table 3 shows the number of abnormally scored muscles of quantitative, semi-quantitative and qualitative US compared with MRI grading.

Correlations between imaging modalities muscle strength and sCK
At baseline, semi-quantative US sumscore ($r_s = -0.674$, $P = 0.002$), and MRI oedema sumscore ($r_s = -0.583$; $P = 0.009$) correlated with MMT13. No statistically

Fɪɢ. 1 Images of the right rectus femoris of the same patient using different imaging modalities
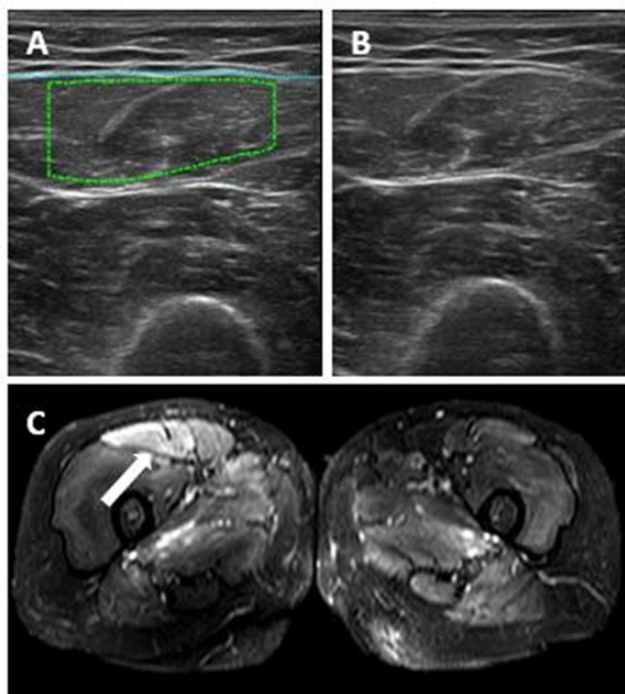
Scoring for right rectus femoris muscle showed in figure: (**A**) quantitative US z-score 0.44; (**B**) qualitative US visually abnormal, Heckmatt score 2; (**C**) MRI score 2 (white arrow).

significant correlation was found between the US sumscore or MRI oedema sumscore and sCK ($r_s = 0.207$; $P = 0.41$ and $r_s = 0.067$; $P = 0.786$, respectively).

Follow-up

Twelve patients underwent both US and MRI at follow-up after a nine-week period of IVIg, with a median of 0 days in between (range 0–15 days). Median age, sCK and MMT score at baseline did not differ according to Mann–Whitney U test (all P-values >0.3) between these 12 patients and the group of six patients that was excluded at follow-up because either US or MRI were not performed, which occurred mostly due to logistical issues.

Table 2 shows the median number of abnormal muscles of these 12 patients, the change score and the P-value of change over time. Figure 2 shows a comparison of quantitative, semi-quantitative US analysis and MRI analysis at baseline and follow-up in a heatmap.

Ultrasound
EI was assessed in 168 muscles at follow-up and compared with baseline. Quantitative US analysis showed a non-significant decrease in the number of abnormal muscles over time from 20 (12%) to 13 (8%), $P = 0.22$ (Supplementary Table S1, available at *Rheumatology* online). Semi-quantitative and qualitative US analysis showed a statistically significant decrease in the number of abnormal muscles over time; from 111 (66%) to 68 (40%), $P = 0.01$, and from 111 (66%) to 76 (55%),

$P = 0.01$, respectively. The number of focal abnormalities ($n = 7$; 4%) did not change over time, $P = 1.0$. Semi-quantitative sumscore decreased from 124 to 72 over time, $P = 0.01$.

The number of muscles with decreased thickness as assessed quantitatively for 168 muscles did not statistically significantly change over time from 36 (19%) at baseline to 45 (23%) at follow-up ($P = 0.17$). The number of fasciae with increased thickness as assessed for 120 fasciae did not statistically significantly change over time; for quantitative analysis from 12 (10%) at baseline to 10 (8%) at follow-up ($P = 0.60$) and for qualitative analysis from two (2%) at baseline to five (4%) at follow-up ($P = 0.41$).

MRI
The total number of oedematous muscles as assessed in 432 muscles decreased non-significantly over time from 295 out of 420 (70%) to 240 out of 412 (58%), Wilcoxon signed rank test; $P = 0.14$ (Supplementary Table S3, available at *Rheumatology* online). The total MRI oedema average sumscore decreased from 455 to 362 over time; $P = 0.09$.

The number of regions with FE as assessed in 96 muscle regions did not statistically significant change over time from 33 (36%) at baseline to 25 (28%) at follow-up, $P = 0.23$. The number of regions with subcutaneous oedema did not statistically significant change over time from 30 (31%) at baseline to 28 (29%) at follow-up, $P = 0.92$, Table 2. Missing values are shown in

TABLE 2 Clinical measures and abnormalities found by US and MRI in 12 patients at baseline, at follow-up and changes over time

	Score range	Baseline $n = 12$, median; IQR	Follow-up $n = 12$, median; IQR	Change score, follow-up–baseline, median; IQR	P-value[a]
IMACS core set measures					
PhGA	0 – 10	3.6; 3.3 – 4.0	2.1; 1.0 – 3.7	−1.5; −2.2 – −0.2	<0.01
PaGA	0 – 10	6.0; 5.0 – 7.6	3.4; 1.6 – 6.5	−2.8; −3.9 – 0.6	0.07
MMT	0 – 260	213; 189.0 – 234.0	229; 209.0 – 240.0	11.0; −6.0 – 29	0.09
EMA	0 – 10	2.1; 0.8 – 2.9	1.4; 0.3 – 2.7	−0.4; −0.8 – 0.0	0.20
HAQ	0 – 3	2.0; 1.4 – 2.5	1.1; 0.3 – 2.0	−0.7; −1.1 – −0.2	<0.01
sCK (U/L)		960; 102.0 – 8559.0	490; 84.0 – 4733.0	−61.0; −2722.0 – −13.0	0.08
Ultrasound					
Muscle echo-intensity					
Quantitative[b]	0 – 14	2; 0 – 3	1; 0 – 2	−1; −1 – 0	0.22
Semi-quantitative[c]					
Score ≥ 2[d]	0 – 14	11; 6 – 14	5; 4 – 8	−4; −7 – −1	<0.01
Sumscore[e]	0 – 42	13; 6 – 14	5; 4 – 9	−4; −8 – −2	<0.01
Qualitative					
Visual[f]	0 – 14	11; 6 – 14	5; 4 – 10	−4; −4 – −1	<0.01
Focal abnormalities	0 – 14	0; 0 – 1	0; 0 – 1	0	1.0
Fascia thickness					
Quantitative[g]	0 – 10	1; 0 – 2	1; 0 – 1	0; −1 – 1	0.60
Qualitative	0 – 10	0; 0 – 0	0; 0 – 0	0	0.41
Muscle thickness[h]					
Quantitative	0 – 10	3; 1 – 4	4; 1 – 7	1; −1 – 2	0.17
MRI					
Muscle oedema					
Score ≥ 1[i]	0 – 36	26; 16 – 34	23; 7.5 – 31	−3; −14 – 0	0.14
Sumscore[j]	0 – 72	33; 20 – 60	29; 11 – 46	−6; −19 – 1	0.08
Average sumscore	0 – 72	35; 20 – 60	31; 12 – 46	−6; −19 – 1	0.09
Subcutaneous oedema					
Subcutaneous score	0 – 8	3; 0 – 4	1.5; 0 – 5	0; −2 – 0	0.92
Fascial oedema					
Fascial score	0 – 8	2; 0 – 4	2; 1 – 4	0; −1 – 2	0.23

EMA: Extramuscular Assessment; HAQ: health assessment questionnaire; IMACS: International Myositis Assessment and Clinical Studies Group; IQR: interquartile range; MMT: manual muscle testing; PaGA: patient global activity; PhGA: physician global activity; sCK: serum creatine kinase. [a]Wilcoxon signed rank test, $P < 0.05$ considered significant. [b]Echo-intensity z scores >1.5. [c]Heckmatt grading. [d]Numbers of abnormal muscles per patient. [e]Sum of recoded Heckmatt scores (1–4–0–3). [f]Based on visually increased echo-intensity. [g]Based on fascia thickness $>2SD$. [h]Based on muscle thickness $<2SD$. [i]Numbers of abnormal muscles per patient. [j]Sum of MRI scores of individual muscles.

TABLE 3 Comparison between US and MRI in 5 muscle groups

|	MRI no oedema	MRI <50% oedema	MRI $\geq 50\%$ oedema
MRI	35	53	81
Quantitative US, n (%)	5 (14%)	8 (15%)	20 (25%)
Semi-quantitative US, n (%)	23 (66%)	40 (75%)	66 (81%)
Qualitative US, n (%)	23 (66%)	40 (75%)	66 (81%)

Supplementary Table S3 (available at *Rheumatology* online).

Correlations over time
The change score of the semi-quantitative US sumscore correlated with change MMT13 score ($r_s = -0.624$;

$P = 0.03$). The change MRI oedema sumscore showed no statistically significant correlation with change MMT13 score ($r_s = -0.489$; $P = 0.11$). The observed difference between these correlations was −0.15 (bootstrap 95% CI −0.70–0.36), showing no statistically significant difference.

FIG. 2 Heatmap of muscle abnormalities with quantitative US, semi-quantitative US and MRI in 12 patients at baseline and at follow-up.
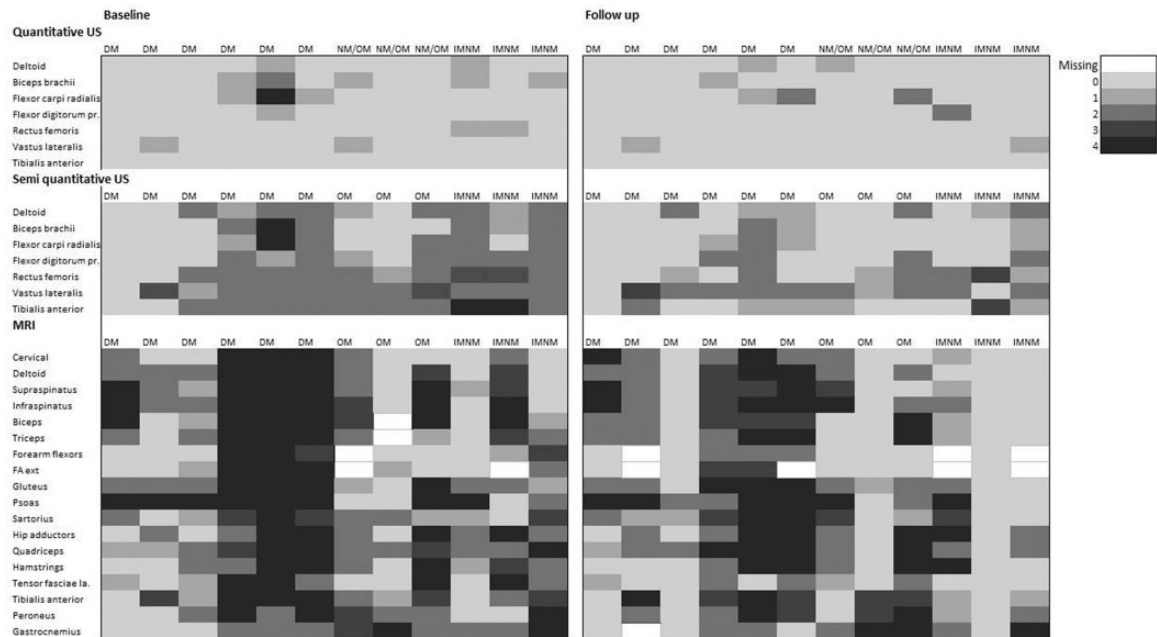
Patients: DM, dermatomyositis; NM/OM, non-specific/overlap myositis; IMNM, immune-mediated necrotizing myopathy.Colours: a darker shade of grey up to black represents a more abnormal muscle. Scores of the muscles of the left and right side are summed; Quantitative US: z-score <1.4=0; 1.5–2.4=1; 2.5–3.4=2; ≥3.5=3.Semi quantitative: Heckmatt 1–4 scores were recoded to 0–3. For quantitative US and semi quantitative US the maximum score obtained was 4 (5 and 6 were not reached).MRI: 0–2 score.

The change scores of the semi-quantitative US sumscore and MRI oedema sumscore showed a correlation ($r_s = 0.661$; $P = 0.02$). The change scores of the imaging modalities showed no statistically significant correlation with the sCK change over time; change semi-quantitative US sumscore $r_s = -0.114$; $P = 0.723$ and change MRI oedema sumscore $r_s = -0.070$; $P = 0.829$. The observed difference between these correlations was -0.04 (bootstrap 95% CI -0.56–0.49), showing no statistically significant difference.

Discussion

In this prospective, longitudinal study in patients with biopsy-proven IIM we showed that semi-quantitative, qualitative US and MRI often revealed muscle abnormalities in the acute phase of IIM, while this was not the case for quantitative US. Semi-quantitative and qualitative US were able to detect changes over nine weeks of follow-up, while MRI detected no significant change over this relatively short follow-up period. MRI detected abnormalities in all patients at diagnosis, while semi-quantitative and qualitative US detected abnormalities in most patients and quantitative US detected abnormalities in a minority of the patients. Our results for MRI are

in line with previous results that showed that WB-MRI is a sensitive modality in the early phases of IIM [23–25]. From our data we can derive that semi-quantitative or qualitative muscle US analysis are a reasonable alternative to identify muscle abnormalities at diagnosis, if muscle MRI is not routinely available in clinical practice.

In our study, quantitative US only detected abnormalities in a minority of adult IIM patients at diagnosis. Apparently, muscle oedema in acute myositis in adult patients may be accompanied by subtle changes in EI, which are not yet be detectable with quantitative US, while these are detectable with semi-quantitative and qualitative analysis. In a previous study quantitative US did not show an increase in EI in any of eight acute dermatomyositis patients [26], another study on juvenile dermatomyositis found increased muscle EI in >2 muscles per patient in only 28% of the patients using quantitative US at diagnosis [19]. Thus, current quantitative US methods alone may not be the best way forward to standardize outcome assessment in clinical trials in IIM, as was stated before [27]. The presence of mostly subtle changes in EI in our patient group was also reflected in semi-quantitative analysis: the higher end of the scale, reflecting a more abnormal muscle, was not reached. A study on 11 treatment-naive IIM patients showed similar results compared with our cohort; semi-

quantitative grading at baseline showed an increased Heckmatt score in 9 out of 11 patients, and none of the patients reached the most abnormal score [28].

Our study showed that muscle US and MRI abnormalities were not limited to clinically weak muscles, as was shown before in juvenile dermatomyositis [3] and in adult patients [29]. In addition to previous studies in adults, our study describes which muscles with normal strength show abnormalities on imaging: predominantly forearm flexors, tibialis anterior and gastrocnemius muscles. This finding underlines the importance of imaging as an add-on to clinical examination in the diagnosis of IIMs, as it may reveal subclinical muscle abnormalities, and as such could facilitate the selection of a muscle for biopsy.

Semi-quantitative and qualitative US were able to detect changes over time during follow-up. Previous longitudinal studies on imaging in IIM are scarce. For semi-quantitative analysis, our findings are in line with the above-mentioned study [28], which showed normalisation of semi-quantitative US scores in six out of seven patients after six months.

Data on follow-up MRI in IIMs is limited, and the timing of follow-up MRI in previous literature was not standardized as in our cohort. A significant decrease in MRI intensity and MRI oedema sumscore over time during treatment was reported in a follow-up MRI after an average of 9.4 months in one study and after 2–6 months in another study [3, 30], as compared with the relatively short follow-up (nine weeks) in our study which may have precluded the detection of changes over time. Another report, in which follow-up MRI was only performed in patients who clinically did not respond to therapy, found no decrease in oedema score [31]. Currently, there is no literature that defines a clinically important difference over time; neither for US, nor for MRI. Future studies are needed to investigate this clinical important difference so that it can be used in longitudinal studies.

Regarding fascia, it was shown before that FT on muscle US, and circumferential increased signal surrounding muscles on MRI, scored as FE, can indicate the presence of a fasciitis [32, 33]. Increased FT was found in around 10% of assessed fasciae with quantitative US, in 3% with qualitative US, and about one-third of the fasciae showed FE on MRI. Changes over time were not detected for FT of FE. Previous reports described FE as an early abnormality in IIM patients, even in the absence of muscle inflammation [4, 34, 35]. Myofascial oedema has been reported as a risk factor for rapid onset interstitial lung disease in myositis [36]. Thus, FE may have clinical relevance and is better detected by MRI as compared with US in our cohort.

Both semi-quantitative US sumscore and MRI oedema sumscore correlated with muscle strength at baseline, which was described before for semi-quantitative US [26] and MRI [3, 31, 36]. A new finding of our study is a correlation between change scores of semi-quantitative US and changes scores of muscle strength. This strengthens the suggestion that muscle imaging could serve as a biomarker in IIM in treatment evaluation [31].

Strengths of our study were the prospective, longitudinal design including a standardized intervention, the inclusion of newly diagnosed treatment-naive patients, the exploration of multiple standardised protocols for both imaging methods, the standardized time between baseline and follow-up and the blinded evaluation of baseline and follow-up. Limitations were the small sample size, the fact that only patients with biopsy-proven myositis were included which may have led to an over-estimation of muscle abnormalities, the relatively short follow-up duration, and no evaluation of intra-rater or inter-rater reliability. However, previous studies have shown a good inter-observer reliability (inter-rater intra-class correlation coefficient 0.76, CI 0.67–0.82) for semi-quantitative muscle US when performed by experienced staff physicians, which was the case in our study [37]. In addition, for MRI, a substantial to excellent inter-observer agreement (Cohen's Kappa 0.7–0.9) was described in the used protocol for the muscles we analysed [3].

A direct comparison of the imaging modalities was challenged by the higher number of muscles that were evaluated with MRI as compared with US and differences in scoring systems of muscles for both modalities, among which a difference in analysed muscle volume which was higher for MRI than for US.

In conclusion, this pilot study favours WB-MRI as diagnostic imaging modality in IIM patients. Semi-quantitative and qualitative US may be a reasonable alternative to WB-MRI at diagnosis and showed changes over time. Quantitative US was insensitive at diagnosis and follow-up in IIM patients.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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