A longitudinal study using B mode ultrasound and power Doppler as monitoring imaging tools in inclusion body myositis

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Abstract

Objectives

There is growing interest in ultrasound (US) as an outcome measure in IBM. Our study aimed to determine the ability of B mode US and power Doppler (PD) to detect changes in affected muscles over time and if US domains correlate with disease progression.

Methods

Participants attended on four occasions over a median follow-up period of 26 months. All completed a patient self-reported health assessment questionnaire (HAQ), patient visual analogue scale (pVAS), manual muscle testing (MMT), and US (fascial thickness-FT, muscle bulk, echogenicity, and PD) on deltoid and vastus lateralis (VL) muscles at each visit.

Results

This longitudinal observational study had 35 participants: 21 (60%) males, median age 70 (IQR (64-76), and the majority (85.7%) not on immunosuppression. When analysed for sex differences at baseline, males had lower FT-VL ($p=0.018$) and higher muscle bulk ($p=0.002$) than females. Only FT-deltoid ($p<0.001$) increased significantly over time with follow-up. When participants were stratified into progressors and non-progressors, FT at baseline was lower in progressors (0.06 vs. 0.09, $p=0.017$), who were predominantly male. There were no significant differences in other US domains.

Conclusion

Our study highlights previously unreported sex differences in US findings in IBM. Certain US domains, such as FT, showed measurable changes over time and correlated with disease progression. However, further studies with longer follow-up periods and larger patient cohorts will need to be performed to determine whether B mode US could be a useful disease outcome measure for therapeutic trials.

Key words

inclusion body myositis, ultrasound, shear wave elastography, muscle, power Doppler

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Introduction

Inclusion body myositis (IBM) is a distinct subtype of idiopathic inflammatory myopathy (IIM) that most commonly affects individuals over 50 and is characterised by a selective pattern of involvement of proximal and distal limb muscles (1, 2). While much debate surrounds whether IBM is primarily an autoimmune muscle disease or an age-related degenerative myopathy with secondary muscle inflammation (1), its refractory nature to treatment sets it apart from the other IIM subtypes. As a result, IBM is generally not treated with conventional immunosuppression, and the natural history of the disease is of continued relentless progression over time (2). However, novel therapies are currently being explored.

Of late, there has been growing interest in identifying predictors of disease progression in IBM, which may be helpful in both the clinical trial and practice settings. A recent paper described three distinct trajectory groups that could aid with prognostication and stratification of cases in future IBM clinical trials (3). Other factors that could influence the clinical course and need to be taken into consideration, include age-at-onset and gender. For example, in one study, women were more affected by muscle unloading, resulting in reduced muscle strength (4).

In contrast to other subtypes of IIM, IBM is known to preferentially affect specific muscle groups, namely flexor digitorum profundus (FDP), quadriceps femoris, tibialis anterior and medial gastrocnemius (1). Recent research has found that the ultrasound (US) finding of increased echogenicity in the FDP relative to flexor carpi ulnaris (FCU) is specific to IBM, suggesting US may have some diagnostic utility (5, 6). To date, there have not been any prospective studies assessing US changes longitudinally in IBM.

The aims of the present follow-up study of an Australian IBM patient cohort were to determine: (i) whether US has the discriminant capacity to detect changes in clinically affected muscles over time and which US domains are most discriminating; (ii) whether there are any sex differences in US changes in affected muscles and in disease progression; and iii) which US domains correlate best with disease progression.

Materials and methods

A prospective longitudinal single-centre study was conducted from June 2019 to January 2022. Patients were recruited if they were >18 years of age and had a diagnosis of IBM in accordance with the 2013 ENMC diagnostic criteria (7). Eligible patients were followed up for a maximum of 4 visits at ~3–10-month intervals. The median follow-up period was 26 months (IQR: 21–35). Ethics approvals were obtained through South Metropolitan Health (EC00265) (RGS0000003714). Participants (>18 years) were those eligible to give written consent and fulfilled the ENMC 2013 diagnostic criteria for sporadic IBM (7).

Clinical assessment

At each visit, all participants completed the patient self-reported health assessment questionnaire (HAQ) and patient visual analogue scale (pVAS). These are partially validated tools on patient-reported outcomes to assess disease activity. All patients had manual muscle testing (MMT) on the right vastus lateralis (VL) and left deltoid (maximum score 10) as well as MMT8 and MMT26, which are the sum of scores for 8 muscles (maximum: 80) and 26 muscles (maximum: 160) respectively (8). Participants were dichotomised into two groups based on whether they progressed from their baseline visit. Participants who progressed had worsening MMT-VL from baseline.

Imaging assessment

B mode ultrasound. Patients were advised to refrain from performing recreational exercise on the day or the day before these studies. This was to prevent potential influences on the US domains such as PD.

B mode US was conducted using a Siemens Acuson S3000 with 750PRF and a linear probe set at 14MHZ. All patients underwent US of the left deltoid, left flexor digitorum longus (FDP), left flexor carpi ulnaris (FCU) and right vastus lateralis (VL). The US settings and muscle studied were kept consist-

Table I. Demographics of participants at baseline visit in the whole cohort and accounting for sex differences in patients with IBM.

Demographics	Median (IQR/%) Whole cohort (n=35)	Median (IQR/%) Males (n=21)	Median (IQR/%) Females (n=14)	*p* value (Chi square) (differences between sex)
Age	70 (IQR: 64-76)	70.00 (IQR:65.00-78.00)	69.50 (IQR: 62.00-72.00)	0.241
Duration since diagnosis				
• 6-12 months	1 (2.9%)	1.00 (4.8%)	0.00 (0.00%)	0.915
• 1-5 years	8 (22.9%)	6.00 (28.6)	2.00 (14.3%)	
• >5 years	18 (51.4%)	11.00 (52.4%)	7.00 (50.0%)	
Immunosuppression				
• Yes	5 (14.3%)	4.00 (19.0%)	1.00 (7.1%)	0.339
• No	30 (85.7%)	17.00 (81.0%)	13.00 (92.9%)	
Patient VAS/cm	4.5 (IQR: 2.1-6.00)	5.00 (IQR: 2.00-6.10)	4.05 (IQR: 2.15-5.85)	0.418
HAQ	0.65 (IQR: 0.34-1.38)	0.85 (IQR: 0.40-1.45)	0.43 (IQR: 0.25-1.38)	0.247
MMT deltoid/10	10.00 (10.00-10.00)	10.00 (IQR: 10.00-10.00)	10.00 (IQR: 9.00-10.00)	0.868
MMT vastus lateralis/10	8.00 (3.00-9.00)	6.00 (IQR:3.00-8.50)	8.00 (IQR: 6.50-9.00)	0.064*

IBM: inclusion body myositis; HAQ: health care questionnaire; MMT: manual muscle testing; VAS: visual analogue scale; CK: creatine kinase. *p value <0.1: interesting result.

Table II. Demographics of US domains at baseline visit in the whole cohort and accounting for sex differences in patients with IBM.

Ultrasound domains	Median (IQR) Whole cohort (n=35)	Median (IQR) Males (n=21)	Median (IQR) Females (n=14)	Sex differences *p* value (chi square)
FT D/mm	0.07 (IQR: 0.06-0.08)	0.08 (IQR: 0.06-0.085)	0.10 (IQR: 0.07-0.12)	0.919
FT VL/mm	0.07 (0.06-0.11)	0.07 (IQR: 0.05-0.09)	0.10 (IQR: 0.07-0.12)	0.018*
Muscle bulk D/cm	1.64 (IQR: 1.43-2.06)	1.86 (IQR: 1.59-2.13)	1.44 (IQR: 1.16-1.74)	0.002*
Muscle bulk VL/cm	0.75 (IQR: 0.60-1.05)	0.78 (IQR: 0.51-1.02)	0.74 (IQR: 0.68-1.08)	0.722
Echogenicity D/1-4	2.00 (1.00-2.00)	1.50 (IQR: 1.00-2.00)	2.00 (IQR: 1.00-2.00)	0.532
Echogenicity VL/1-4	3.00 (3.00-3.00)	3.00 (IQR: 3.00-3.00)	3.00 (IQR: 3.00-3.00)	0.921
FDP/FCU ratio	1.50 (1.00-2.00)	1.50 (IQR: 1.00-2.00)	1.75 (IQR: 1.00-2.25)	0.450
PD D/0-4	0.00 (0.00-1.00)	0.00 (IQR: 0.00-1.00)	1.00 (IQR: 0.00-1.25)	0.408
PD VL/0-4	0.00 (0.00-0.00)	0.00 (IQR: 0.00-0.00)	0.00 (IQR: 0.00-0.00)	0.891

US: ultrasound; HAQ: health care questionnaire; MMT: manual muscle testing; D: deltoid; VL: vastus lateralis; VAS: visual analogue scale; CK: creatinine kinase. *p value < 0.05: statistically significant result.

ent throughout the study. The FDP and VL are two of IBM's most severely affected muscles (9), whereas the deltoid and FCU are less severely affected and serve as comparator muscles (1).

The deltoid was scanned at a point one-third of the distance from the acromion to the lateral epicondyle with the arm resting on a pillow, flexed in a 90° position (10). The vastus lateralis was scanned at a distance the distal three-quarters of the distance from the anterior superior iliac spine to the upper border of the patella, with the knee extended on the bed. Two images were taken in transverse and longitudinal views of the deltoid and VL. In the transverse view, an attempt was made to visualise the bone echo. The FDP and FCU were scanned 5 cm from the olecranon process, with the elbow flexed over a pillow. Two images were taken in both transverse and longitudinal views.

In B mode US, the domains scored were fascial thickness (FT), muscle bulk and echogenicity. The FT provides a measure of the connective tissue sheaths that envelop each muscle and was measured in millimetres using a calliper function in a homogenous fascia area (11). Three readings were obtained, each at least 0.25 cm apart, and averaged.

Muscle bulk was measured vertically from the superficial to the deep fascia (Fig. 1, 2). A semi-quantitative grading of echogenicity was assigned to each muscle group using the widely used Heckmatt visual grading score. Depending on the visual representation of the number of echoes displayed in the greyscale image using cortical bone as the visual anchor, a 1-4 grade is given, with one being normal and four markedly hyperechoic (12).

Power Doppler. Power Doppler (PD) was assessed at rest in both the transverse and longitudinal planes. A modified semi-quantitative PD grading scale of 0–4 (13) was used, and the highest PD score was taken as the overall score for each muscle. The higher the PD score, the higher the vascularity (10, 11).

Statistical analysis

Statistical analyses were computed through SPSS version 27. Mean (M), standard deviation (SD), median (Mdn) and interquartile ranges (IQR) were used for continuous data. Categorical data were presented using frequency and percent (%). US domains were compared at each visit (longitudinal) using the median values and reported descriptively. Due to the relatively small numbers, the data has been reported descriptively to highlight interesting trends rather than emphasising *p* values.

Nevertheless, the comparisons between groups were made using Pearson's chi-

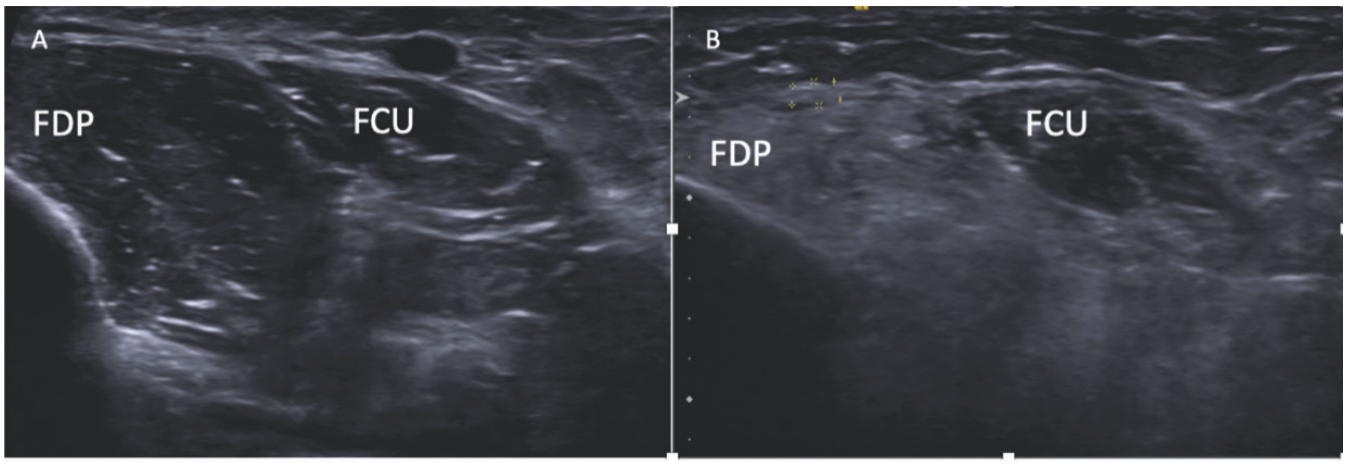

Fig. 1. Contrasting echogenicity in the FDP to FCU muscle in a patient with inclusion body myositis.
(**A**) Normal FDP and FCU muscle in cross section. (**B**) Hyperechoic FDP compared to the FCU muscle in a patient with inclusion body myositis. The callipers (yellow) in image (B) denotes the superficial fascia measurement of the FDP muscle.
FDP: flexor digitorum profundus; FCU: flexor carpi ulnaris.

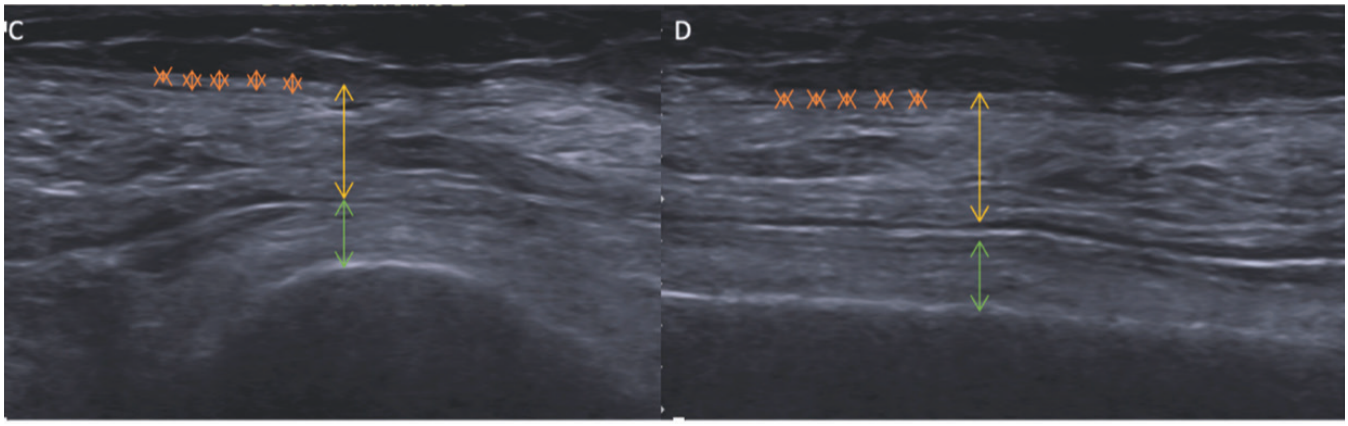

Fig. 2. Hyperechoeic vastus lateralis and vastus intermedius in a patient with inclusion body myositis.
(**C**) The vastus lateralis and vastus intermedius in cross section. (**D**) The vastus lateralis and vastus intermedius in longitudinal view. The arrowheads (orange) show the measurement of the superficial fascia. The arrow (yellow) outlines the vastus lateralis and arrow (green) the vastus intermedius with partial loss of bone echo, which would be in keeping with grade 3 in accordance with the Heckmatt visual grading scale.

square. Pearson's correlation coefficient (r) was used to show the relationship between US domains at baseline and clinical outcome measures at the final examination. One-way ANOVA was used to determine changes over time.

Results

Clinical parameters at baseline

Baseline clinical parameters data are presented in Table I. This observational study involved 35 participants, 21(60%) males and 14 (40%) females. The majority (n=30, 85.7%) were not on immunosuppression.

At the baseline visit, participants had a median age of 70 (IQR: 64–76), median patient VAS score of 4.5 (IQR: 2.1–6.00), median HAQ of 0.65 (IQR: 0.34-1.38), median MMT deltoid of 10.00 (IQR: 10.00–10.00) and MMT VL of 8.00 (IQR:3.00–9.00).

When data was analysed for sex differences at the baseline visit, the differences between age, treatment, patient VAS, HAQ, MMT deltoid and vastus lateralis between males and females were not statistically significant. However, males reported a higher HAQ score (p=0.247), higher pVAS score (p=0.418) and clinically a lower MMT VL (p=0.064) compared to females, although there were no significant differences in age, duration since diagnosis, treatment status, patient VAS, HAQ, MMT, deltoid or serum CK.

There was no significant difference in disease duration, which was similar between the sexes (majority five years).

B mode US data at baseline

The baseline imaging data are presented in Table II and Supplementary Table S1. At baseline, participants had respective median scores: FT deltoid of 0.07 (IQR: 0.06-0.08), FT VL of 0.07 (0.06-0.11), muscle bulk deltoid of 1.64 (IQR:143-2.06), muscle bulk VL of 0.75 (IQR: 0.60-1.05), echogenicity deltoid 2.00 (1.00-2.00), echogenicity VL of 3.00 (3.00-3.00), FDP/FCU ratio of 1.50, PD deltoid of 0.00 (0.00-1.00), PD VL of 0.00 (0.00-0.00), SWS deltoid of 2.89 (IQR: 2.19-3.29) and SWS VL of 2.52 (IQR: 1.98-3.13). When comparing findings of VL with deltoid, VL had a smaller muscle bulk (0.75cm *vs*. 1.64cm), and higher echogenicity (3.00 *vs*. 2.00) (Fig. 1), while FT and PD did not differ between the two muscles.

Table III. Clinical parameters and ultrasound domains across visits in whole cohort.

	Baseline Median (IQR)	2nd visit median (IQR)	3rd visit median (IQR)	4th visit median (IQR)	*p* value (differences between visits)
HAQ	0.65 (0.34-1.38)	0.88 (0.25-1.64)	1.38 (0,25-1.75)	1.25 (0.25-2.00)	0.546
MMT D/10	10.00 (10.00-10.00)	10.00 (10.0-10.0)	10.00 (9.00-10.00)	10.00 (10.00-10.00)	0.472
MMT VL/10	8.00 (3.00-9.00)	8.00 (3.00-9.00)	7.00 (3.00-9.00)	8.00 (3.00-9.50)	0.999
Patient VAS/10cm	4.50 (2.10-6.00)	5.00 (2.78-7.48)	5.90 (5.00-6.80)	5.40 (2.25-6.45)	0.501
FT D mm	0.07 (0.600-0.08)	0.09 (0.08-0.10)	0.10 (0.08-0.12)	0.10 (0.08-0.11)	<0.001*
FT VL mm	0.07 (0.06-0.80)	0.10 (0.07-0.12)	0.11 (0.09-0.11)	0.11 (0.09-0.13)	0.056**
Muscle bulk D cm	1.68 (1.43-2.06)	1.64 (1.40-1.98)	1.78 (1.44-2.03)	1.84 (1.71-2.01)	0.563
Muscle bulk VL cm	0.76 (0.60-1.05)	0.75 (0.52-1.24)	0.71 (0.53-1.04)	0.82 (0.52-1.07)	0.563
Echogenicity D/ 1-4	2.00 (1.00-2.00)	2.00 (1.00-3.00)	2.00 (1.00-2.00)	1.50q (1.00-2.75)	0.259
Echogenicity VL/1-4	3.00 (3.00-3.00)	3.00 (3.00-3.00)	3.00 (0.53-1.04)	4.00 (3.00-4.00)	0.081**
FDP/FCU	1.50 (1.00-2.00)	1.25 (1.00-3.00)	1.25 (1.00-2.00)	1.00 (1.00-2.00)	0.879
PD D/0-4	0.00 (0.00-1.00)	0.00 (0.00-1.00)	0.50 (0.00-1.00)	0.00 (0.00-0.00)	0.216
PD VL/0-4	0.00 (0.00-0.00)	0.00 (0.00-1.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.154

HAQ: health assessment questionnaire; MMT: manual muscle testing; VAS: visual analogue scale; FT: fascial thickness; D: deltoid; VL: vastus lateralis; SWS: shear wave speed; FDP: flexor digitorium profundus; FCU: flexor carpi ulnaris.
*p<0.05: statistically significant result; **p<0.10: interesting result.

When the cohort was stratified according to sex, males had lower FT VL (p=0.018) and higher muscle bulk deltoid (p=0.002) than females. There were no statistically significant differences in FT deltoid, muscle bulk VL, echogenicity deltoid and VL, FDP/FCU ratio (Fig. 2), nor in PD deltoid and PD VL between males and females (p>0.408).

Changes in clinical and US parameters over time in the whole cohort

Longitudinal data are presented in Table III and Supplementary Table S2; HAQ, MMT deltoid and VL, patient VAS and physician VAS all remained stable over time (p<0.999). However, individual MMT VL scores declined in 13/35 participants, the majority of whom were males (10 males vs 3 females) (Table I).

When analysing specific US domains, only FT-deltoid (p<0.001) showed statistically significant change over the follow-up period. However, increases were noted in FT (p=0.056) and echogenicity (p=0.081) in the VL over time, which did not reach statistical significance.

Differences between US domains in progressors and non-progressors in the vastus lateralis

Data are presented in Table IV and Supplementary Table S3. When participants were dichotomised into those who progressed and those who did not, based on changes in MMT-VL, only FT-baseline showed a significant difference between the two groups (0.06 *vs*. 0.09, p=0.017) and an increase from baseline in the progressor group, although not statistically significant (p=0.143). FT also increased from baseline in the deltoid (p=<0.001) over time. There was less of a change in the VL (p=0.056). Other US domains (muscle bulk, echogenicity, PD, SWS) at baseline and final visit, including FT at the final visit, did not show a difference between the groups (p>0.162).

Table IV. Difference in ultrasound domains between progressors and non-progressors at baseline and last documented clinic visit.

US domains in the vastus lateralis	Progressors Median (IQR) N=10	Non progressors Median (IQR) N=25	*p* value
Baseline			
FT mm(n=35)	0.06 (0.05-0.07))	0.09 (0.07-0.12)	0.017*
Muscle bulk cm (n=35)	0.75 (0.64-1.11))	0.75 (0.51-1.05)	0.568
Echogenicity (n=35)	3.00 (3.00-4.00)	3.00 (3.003.00)	0.162
PD (n=35)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.334
Last visit			
FT mm (n=29)	0.11 (0.07-0.13))	0.11 (0.09-0.11)	0.851
Muscle bulk cm (n=29)	0.76 (0.48-1.28))	0.79 (0.57-1.26)	0.380
Echogenicity (n=29)	3.00 (3.00-3.00)	3.00 (2.00-3.00)	0.984
PD (n=29)	0.00 (0.00-0.00)	0.00 (0.00-1.00)	0.924

FT: fascial thickness; PD: power Doppler; SWS: sheer wave speed.

Discussion

Although US has been shown to help differentiate IBM from other forms of IIM (9, 10, 14), it has yet to be applied to monitor disease progression in IBM. The primary focus of our study was to determine whether US could be useful as an imaging biomarker to detect changes in clinically affected muscles over time and if any US domains are more discriminating. Secondary aims were to determine whether US findings at baseline could predict subsequent disease progression and whether there are any sex-related differences in US changes.

The clinical and US findings in the present patient cohort were in keeping with the known selective pattern of limb muscle involvement in IBM. When we performed a subgroup analysis between the studied muscles, it was found that the VL was weaker, had a smaller muscle bulk and was more hy-

perechoeic compared to the deltoid, these findings being consistent with more severe disease activity in the VL compared to the deltoid. Similarly, the FDP is typically more severely affected in the forearm, while the FCU is relatively spared (2, 15). Our US study confirms this finding, with a median FDP/FCU ratio of at least 1.5, consistent with other studies. This highlights the potential diagnostic value of the US FDP/FCU ratio when investigating patients with a possible diagnosis of IBM, although we did not do a disease comparison in this study to confirm this finding (15).

We investigated changes in clinical and ultrasound parameters over time. Our longitudinal analysis indicated that although patient-reported outcomes remained relatively stable over time, there were detectable changes in several US domains in the final follow-up study. These included increasing FT in the deltoid and VL over time. There was less of an effect in the VL, although it is a more severely affected muscle than the deltoid in IBM. There was also an interesting increase in echogenicity in the VL, although not statistically significant, which was not seen in the deltoid. There could be other influences on the deltoid findings, being a less affected muscle in IBM. Most of our participants had physiotherapy support throughout the study, and it is unclear whether the changes in US domains could be due in part to a treatment related improvement in function or more likely due to the progressive nature of the disease and a reduction in inflammation and accumulation of fibrous and adipose tissue in the affected muscles with time. In a previous cross-sectional study of a mixed IIM group of subjects, we found that increased echogenicity correlated with fatty infiltration and atrophy on MRI. In contrast, changes in FT had poor discrimination between muscle pathologies on MRI and muscle biopsy (8).

Recent studies have discussed IBM trajectories (3). We divided our participants into those that progressed and those who remained stable based on whether there was a change in the MMT-VL during the follow-up period. In our study, FT at baseline appears to be associated with progression. Our earlier preliminary study suggested a thinner FT in IBM compared to healthy controls(10). In our current study, a thinner FT at baseline was seen in progressors compared to non-progressors, likely indicative of a disease effect. IBM is not known to affect the fascia, but muscle atrophy and the effects of immunosuppressives such as prednisolone on muscle fascia are unknown. The FT increase in the deltoid over time, a less affected muscle in IBM, indicates the potential for other influences, such as age or sex, on the muscle fascia over time.

Interestingly, in animal models, studies have shown thickening of the epimysium with aging (16). Studies have shown that a thicker fascia, such as seen in the elderly, limits flexibility(17). It is unclear whether a thinner FT at baseline in IBM primes the fascia to other influences, such as age over time, causing progression. This requires further exploration.

In contrast to FT, PD did not show detectable changes over time, either in the deltoid or VL and does not, therefore, appear to be a useful tool for monitoring disease progress.

Our study cohort was predominantly male. Female patients exhibited a less severe clinical phenotype, with less weakness than males. Sex-related differences were also observed in several US domains in different muscles, with females having a higher FT in the VL and lower muscle bulk in the deltoid. These differences suggest that other factors, beyond muscle inflammation and fibrosis, may influence the US changes in females with IBM. Our previous work had alluded to the possible influence of other factors, such as body mass index (BMI) being an influencer in the deltoid, although we did not investigate this specifically in the current study (10). It is plausible that other factors such as sex may influence changes, particularly in clinically less affected muscles such as the deltoid in IBM.

Limitations

The authors acknowledge the limitations of this study, including the relatively small sample size and largely observational study design, reflecting the nature of the US measures recorded, which limit the opportunities for statistical comparisons and make probability values and regression analyses problematic. As IBM is a chronic disease, a longer follow-up may have shown clearer trends. Larger and longer duration studies would be needed. Although we did not perform intra-observer reliability testing in this study, we have done so in our previous studies, which have followed a similar methodology and found substantial to perfect agreements in the US domains with repeat testing (10, 11). We also did not account for the possible effects of medications or exercise in this study, which could have impacted the findings. In addition, as US remains operator-dependent, measured parameters may vary between studies. Such effects were minimised by adherence to a carefully standardised experimental protocol and the experience of the operator who performed all the studies (SP).

Conclusion

This study explores the utility of US longitudinally in IBM. It contributes to the growing body of evidence on the utility of US as a monitoring imaging tool in IBM. US domains such as FT, echogenicity and muscle mass did show detectable changes over time. However, as the magnitude of the changes were not sufficiently conclusive, and in view of the chronicity of the disease, further studies in larger IBM cohorts and with longer follow-up periods are required to determine whether these domains may be suitable to be developed as US biomarkers and outcome measures for use in therapeutic trials. FT appears to be associated with disease progression; however more studies would need to analyse this further. Our study also highlights other potential influences on US domains, particularly in the deltoid, such as age or sex, which warrants further investigation.

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