Imaging evaluation of the upper limbs in inclusion body myositis: an unmet need

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ABSTRACT

Inclusion body myositis (IBM) is an acquired myopathy belonging to the spectrum of idiopathic inflammatory myopathies. It commonly presents in individuals aged above 50 years of age. Characteristic clinical features of IBM include weakness of the quadriceps and finger flexors. There are currently no effective drug treatments for IBM. However as more clinical drug trials are being conducted it is important that more precise outcome measures are developed to track disease progression and assess treatment effects. Imaging techniques such as magnetic resonance imaging (MRI) and ultrasound have been increasingly used to study intramuscular changes within the thigh and calf muscles. In particular quantitative MRI assessments of the lower limb have started to be employed as endpoints for clinical trials in IBM patients. However, in comparison to the lower limb, there is a relative lack in robust imaging biomarkers for the upper limb muscles. It is prudent that this paucity is addressed as the majority of IBM patients have forearm involvement and, in many individuals, upper limb weakness is their main source of disability. Imaging focussed studies thus far indicate preferential flexor digitorium profundus involvement. In this review, we discuss the imaging modalities that have been used to evaluate intramuscular changes and the possible techniques which could be developed further as upper limb biomarkers for IBM.

Introduction

Inclusion body myositis (IBM) belongs to the spectrum of idiopathic inflammatory myopathies (IIMs). It is predominately seen in individuals aged over 50 years (1). IBM has very characteristic clinical features and patterns of involvement which often help separate it from other forms of IIMs. In the lower limb there is often early quadriceps weakness. Another distinctive feature of IBM is the presence of finger flexor weakness. Unlike other IIMs, IBM does not respond to conventional immunosuppression and no validated drug treatments are available to change disease trajectory. The pathophysiology driving the disease is still unclear. Neurodegenerative features of aberrant autophagy and protein trafficking are histopathological hallmarks (2). Recently, increasing evidence has emerged on the role of immunosenescence in driving IBM (3, 4).

Given the lack of therapeutics available for IBM, a variety of large clinical trials are underway or have been completed (3, 5, 6). As the frequency of clinical trials increase, there is a growing need for better outcome measures or biomarkers in IBM (7). The national institutes of health defines seven core categories of biomarkers (8). Of these 'diagnostic' biomarkers are key for detection of disease and supporting a clinical diagnosis. 'Monitoring' biomarkers are measures that accurately assess the disease status or severity. 'Response' biomarkers are tools that help determine a biological response to a medicinal product and can serve as an endpoint for a clinical trial. Accurate diagnostic, monitoring and response biomarkers are imperative for well-designed clinical trials and ensure a homogenous trial population. A lack of such biomarkers has probably been a weakness of some previous trials in IBM patients.

Imaging techniques predominantly focussing on the lower limb muscle changes in IBM patients have been explored as investigative tools and potential biomarkers. In particular ultrasound (US) and magnetic resonance imaging (MRI) investigations of the lower limb muscles in IBM have been evaluated

over the past decade (9-12). Quantitative MRI measures have already been utilised as secondary endpoints in smaller clinical trial cohorts of IBM patients (13, 14). However there has been a relative lack in the vigorous exploration of imaging biomarkers for the upper limb musculature. In many IBM patients forearm involvement is more predominant than lower limb weakness, and Rasch analysis of the IBM Functional Rating Scale (IBMFRS) has shown that upper and lower limb severity are independent disease dimensions (15). Therefore, it would be important to develop appropriate imaging tools to monitor disease progression in the upper limb especially the forearm. We discuss pertinent imaging findings and potential avenues that could be pursued to develop more robust imaging biomarkers for the upper limb.

Ultrasonography (US)

US has been the most studied technique to investigate intramuscular changes within the forearm muscles of IBM patients. US has a variety of practical advantages including relatively low costs, lack of contraindications, short procedure time and the ability to be performed at bedside. Intramuscular fat infiltration and fibrotic changes in skeletal muscle is indicated by higher echogenicity or echo intensity (EI) measurements of muscle tissue (16). Muscle atrophy can be inferred using muscle thickness. In the majority of such studies, it has been suggested that enhanced echogenicity of flexor digitorum profundus (FDP) is a useful diagnostic biomarker to distinguish IBM from other neuromuscular disorders (17-19).

Semi-quantitative echogenicity assessments have been investigated in IBM patients, using scales such as the Heckmatt grading scale (17, 19-21). In such studies, Heckmatt scores for the FDP have been shown to be significantly higher (worse) in IBM patients compared to other forms of myopathy (17, 19-21). The inter-rater reliability for Heckmatt grading in assessments of IBM, amyotrophic lateral sclerosis (ALS), IIMs and other neuromuscular disorders, was variable according to reader experience (19).

Noto *et al*. investigated the use of US in six IBM patients, six polymyositis (PM) or dermatomyositis (DM) patients and six ALS patients (17). Unlike the control groups, all IBM participants had increased Heckmatt scores for FDP, which were comparatively higher to flexor carpi ulnaris (FCU). The authors used cross-sectional area (CSA) as a marker for muscle thickness. CSA of the FDP did not significantly differ between the three disease groups. FCU CSA was significantly higher in IBM patients compared to ALS. The authors argued for this FDP/FCU 'echogenicity contrast' to be considered as a diagnostic feature for IBM. However, this contrast between FDP and FCU could not replicated in larger cohorts (19, 20).

Albayda *et al*. utilised quantitative US techniques to generate mean EI values, as a marker for fat infiltration in 18 IBM patients. Controls consisted of PM, DM and healthy participants.(22) EI values from FDP and medial gastrocnemius muscles were highest in IBM patients. Flexor carpi radialis (FCR) also had high EI values. Biceps and deltoid muscles had moderately elevated EI values. Muscle strength and duration of weakness had a significant association with mean EIs. Higher EIs within the FDP proved to have best discriminatory ability to distinguish IBM from PM or DM. When utilising EI values for other upper limb muscles (deltoid, biceps and FCR), IBM could not be distinguished from DM or PM patients.

Thus far the largest study to examine the use of US in IBM, performed quantitative US in 41 patients. This study recruited healthy individuals, PM, DM and neuromuscular disorder participants to act as controls (18). Two separate IBM cohorts were investigated, a group recruited at John Hopkins (n=25) and another at Radboudumc (n=16). In both cohorts, IBM patients had higher EIs in FDP compared to all control groups. Again, higher EIs within FDP helped differentiate IBM from other muscle disorders. In the 'John Hopkins' cohort FDP thickness was significantly lower in IBM patients but this was not replicated in the 'Radboudumc' cohort. The authors noted that patients within the John Hopkins cohort had a longer disease duration, which may account for the muscle thickness observations.

US elastography provides further details into muscle function and biomechanics by assessing muscle elasticity, referred to as muscle shear modulus (MSM) (9). US can be used to assess the elasticity of muscles in passive and active movements. The use of US elastography has been examined in IBM patients (21, 23). Shear wave elastography was studied in a cohort of 34 IBM patients (23). The authors focussed their assessments on the biceps brachii muscle. The technique itself demonstrated adequate satisfactory reliability, and significant associations were observed between MSM and predicted muscle strength. However no significant relationship was noted between bicep brachii thickness and elbow flexor strength.

A recent meta-analysis on the use of US in IBM was conducted by Abdelnaby *et al*. (16) The authors pooled together seven studies which met predefined quality criteria for analysis (17-22, 24). Although FDP echogenicity was significantly higher in IBM patients compared to controls across the studies evaluated, there was a significant degree of heterogeneity between the studies. When assessing the use of FDP muscle thickness, analysis revealed no significant differences between IBM patients and other controls. Again, there was a high degree of heterogeneity between studies assessing FDP thickness. In terms of diagnostic accuracy, the pooled sensitivity and specificity from US studies was found to be 82% and 98%, respectively.

More studies investigating the use of quantitative US measures in IBM patients are required to further determine their validity as an upper limb diagnostic and monitoring biomarker. There are no longitudinal studies in IBM patients, and little can be inferred about the utility of US in disease monitoring. Therefore, such studies are needed to determine the responsiveness of US derived measures.

Positron emission tomography (PET)

Beta-amyloid deposition associated with protein aggregation within muscle tissue is a histopathological feature that

has been observed in IBM patients (25). Recent studies have utilised these observations and explored the use of amyloid PET tracers in IBM patients (26-29). Maetzlter *et al*. were the first to document the use of amyloid PET tracers in IBM patients (26). The authors investigated the use of Pittsburgh Compound B ([^{11}C]PIB) in seven IBM patients. Three patients had evidence of increased [^{11}C] PIB uptake in the deltoid and finger flexors. Noto et al also explored the use of the [^{11}C]PIB tracer in nine IBM patients compared to four IIM patients (28). The authors found significantly higher standardised uptake values (SUVs) in forearm muscles of IBM patients, however no significant difference was seen with the upper arm. Furthermore, forearm muscle uptake demonstrated the highest degree of significance compared to all other muscle groups. Lilleker *et al*. investigated an alternative amyloid PET tracer; florbetapir (27). The authors scanned 10 IBM patients and six PM patients who acted as controls. SUV ratios for flobetapir was significantly increased in IBM patients for all muscle groups including forearm muscles and left upper arm muscle groups. These small studies did not demonstrate any significant association between amyloid tracer SUVs and clinical outcome measures such as the IBMFRS.

In 2023, Quinn *et al*. investigated the use of the unique PET tracer; ^{89}Zr-Df-crefmirlimab designed to determine the level of CD8+ T cells within all skeletal muscles (30). The authors scanned four IBM patients with this novel tracer. Age matched patients with cancer were used as a control for this particular study. Uptake within the skeletal muscles was fairly heterogeneous and diffuse. Interestingly, no signals were seen in muscles with complete fat replacement. However, bordering muscles showed higher levels of CD8+ T cell recruitment, and inflammation may be ongoing even in patients with more advanced disease. The forearm flexors demonstrated the highest degree of tracer uptake in all muscle groups investigated. Along with quadriceps muscles, biceps brachii had the greatest statistically significant difference from control participants. Other muscle groups in the upper extremities that demonstrated significantly increased uptake include thenar, triceps and deltoid muscles.

Tau is another protein that is present within protein aggregates observed in muscle tissue from IBM patients (31). A single case report has explored the use of the tau PET tracer; [^{18}F]THK5317 in a 46-year old IBM patient (32). This patient underwent whole body MRI-PET and demonstrated focal areas of increased uptake within the quadriceps. Although the authors did not note the degree of tau uptake in the upper limb muscles, the potential of the [^{18}F] THK5317 tracer in IBM patients should be investigated further.

Studies exploring the use of PET imaging in IBM patients have been conducted in small cohorts. Moving forward it is important that larger groups are investigated to get a better insight into the diagnostic performance, validity and responsiveness of these techniques. Unlike other techniques such as US, CT-PET does come with the disadvantage of radiation exposure. The use of MRI-PET is a potential avenue that should be explored, as it may provide further granularity into intramuscular changes and avoid repeated radiation exposure.

Dual energy x-ray absorptiometry (DEXA)

Traditionally, DEXA techniques have been used to estimate bone mass in the context of identifying individuals at risk of possible osteopenia or osteoporosis. However, DEXA imaging potentially allows the estimation of lean muscle mass and has the potential to be used as a monitoring biomarker in IBM (9, 10). Although this technique utilises (low level) radiation, DEXA is relatively cheap, fast and is in general more ubiquitously available for use. IBM studies investigating the use of bimagrumab, a human monoclonal antibody targeting activin type 2 receptors, employed lean muscle mass measured by DEXA as a secondary outcome measure (5, 33, 34). A small single-dose pilot study exploring the treatment effect in 13 IBM patients found that bimagrumab significantly halted the decline in lean body mass after 8 weeks, compared to placebo. Despite being a negative study, in the large RESILENT trial, a dose-dependent increase in lean body mass was noted with bimagrumab *versus* placebo at week 52, with significant differences recorded with bimagrumab 3 mg/kg and 10 mg/kg (but not 1 mg/kg) *versus* placebo (5). The studies thus far have not specified the focal changes in the mass of the upper limb muscles in isolation. Further investigations are required to assess the measurement properties of DEXA in the context of IBM.

Magnetic resonance imaging (MRI)

MRI investigations of the skeletal muscle provide a detailed assessment of intramuscular structure using a variety of parameters. Fat infiltration is a key end stage sequalae in a variety of neuromuscular diseases including IBM (11). In particular fat infiltration and loss in muscle bulk can be elucidated using T1 weighted sequences (7). Muscle oedema can be inferred using fat suppressed T2 sequences (for example short tau inversion recovery; STIR) which can give insight into the degree of active inflammation (7, 10, 35).

Few studies have investigated the appearance of muscles in the forearm and upper limb on MRI. Again, MRI studies have so far demonstrated a predilection for the involvement of the FDP muscle (Fig. 1) (24, 36-40).

In one of the earliest of such investigations, Sekul *et al*. explored the MRI appearances of forearm muscles in cohort of 21 IBM patients (36). The authors qualitatively assessed the degree of fat infiltration, atrophy and inflammation in the forearm. The FDP was the muscle most frequently observed to demonstrate fat infiltration (n=20/21) and atrophy (n=16/21). Four patients had increased signal within the FDP on STIR images, inferring inflammation in this muscle. A variety of other muscles also demonstrated varying degrees of involvement including FCU and flexor digitorum superficialis (FDS). The authors described an association between fat infiltration of FDP and clinical severity.

Phillips *et al*. used a qualitative approach to determine the degree of fat

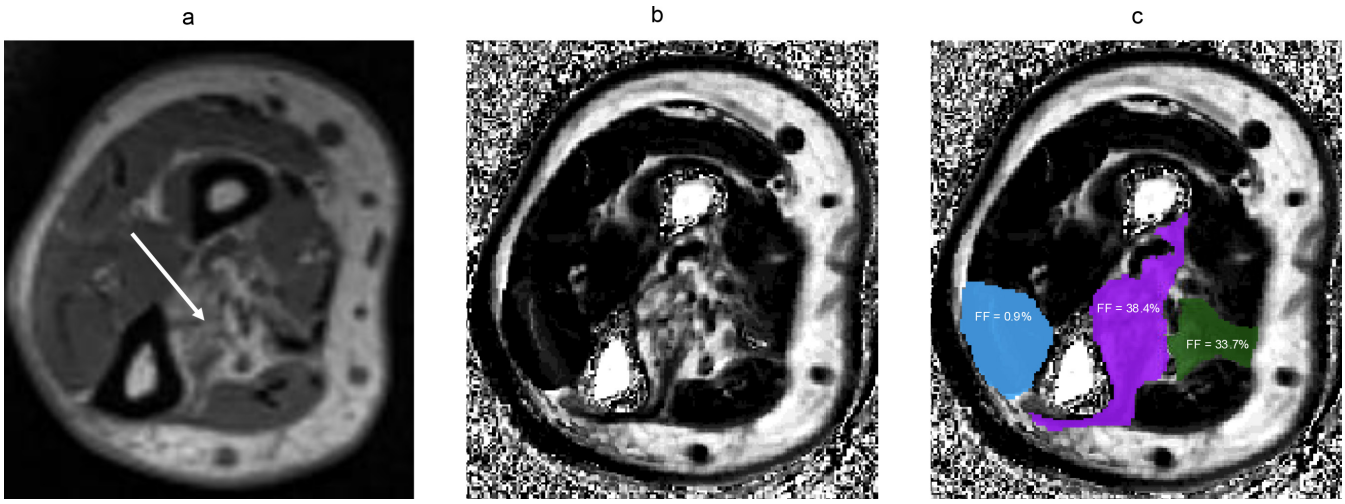

Fig. 1. MRI features and Fat fraction (FF) map seen in the forearm of an IBM patient. Axial MRI images through the mid-forearm illustrating characteristic forearm changes observed in a 63-year-old male IBM patient. Images demonstrating generalised atrophy of forearm muscles and fat infiltration.
a: T1-weighted image (Volumetric interpolated breath-hold examination [VIBE] Dixon in-phase). In particular there is a predilection for FDP atrophy and fat infiltration (arrow).
b: Three-point Dixon FF map (c) Three-point Dixon FF map with superimposed regions of interest for FDP (purple), FDS (green) and extensor carpi ulnaris (blue), overlaid FF shown in %.

Table I. Imaging techniques and relevant upper limb findings in IBM.

Imaging technique	Qualitative or semi-quantitative assessments	Quantitative measures	Key upper limb findings observed in IBM
US	Visual evaluation Heckmatt scale	Quantitative echo intensities Muscle thickness CSA Shear wave elastography: muscle shear modulus, shear wave speed	Increased echogenicity in FDP, FDS, FCR, FCU, biceps, deltoid Reduced thickness of FDP Reduced muscle shear modulus in biceps brachii
PET Beta amyloid tracers: *[^{11}C]PIB, Flopbetapir* CD8 T cell tracer: *^{89}Zr-Df-crefmirlimab* Tau tracer: *[18F]THK5317*	Visual evaluation	Standardised uptake values (SUV)	Increased [^{11}C]PIB SUV in the forearm flexors and deltoid. Increased flobetapir SUV ratios in forearm flexors and upper arm muscles. Increased ^{89}Zr-Df-crefmirlimab SUVs in thenar muscles, forearm flexors, triceps, biceps and deltoid.
DEXA		Muscle mass	Reduced body muscle mass (no specific reports on upper limb muscle mass)
MRI	Visual evaluation Mercuri scale Goutallier scale Morrow scale	Fat fraction CSA Functioning remaining muscle area or contractile CSA T2 relaxation time Muscle water T2 Magnetisation transfer ratio	Fatty infiltration in variety of muscles including FDP, FDS, FCU, brachioradialis, brachialis, biceps, subscapularis Hyperintense STIR signals in FDP, FCU, extensor carpi ulnaris, deltoid Increased T2 relaxation time within the FDP, FDS, extensor digitorum, extensor carpi radialis

infiltration and oedema was estimated using T2 relaxation times (37). Out of eight patients who had their forearm muscles examined, FDP demonstrated the highest frequency of fatty infiltration (n=7/8). The authors scanned both forearms in five patients and one forearm in three patients, therefore a total of 13 forearms were imaged. Of the 13 forearms imaged, prolonged T2 relaxation times were observed in FDP (n=12/13), FDS (n=6/13), extensor digitorum (n=5/13) and extensor carpi radialis (n=5/13). Only three patients had imaging of the upper arm which revealed variable patterns of involvement involving the biceps, brachialis and triceps muscles.

The most detailed MRI examination of upper limb muscles to date was conducted by Cox *et al*. in 30 patients (38). Fat infiltration was semi-quantitatively examined using the Mercuri grading scale. Atrophy and muscle oedema was merely scored as either present or absent, using T1 and STIR weighted images, respectively. FDP was found to be the most severely affected muscle in the upper limb, with fatty involvement seen in 22 patients and 18 patients demonstrat-

ing atrophy. Interestingly, individuals without FDP involvement demonstrated complete sparing of all the forearm muscles. Patients who were observed to have fat infiltration within FDP were found have lower manual muscle testing (MMT) scores. In the upper arm, both the triceps and biceps muscles had the highest frequency of intramuscular fat. Of the shoulder girdle muscles, the subscapularis had the highest frequency of fatty involvement (n=18/30). In upper limb extremities, inflammation was most prevalent in the extensor carpi ulnaris and deltoid muscles.

Guimares *et al*. utilised the Goutallier grading technique to assess fat infiltration in 12 IBM patients (39, 41). FDP was the third most fat infiltrated muscle (n=9/12) after vastus lateralis and medial gastrocnemius (39). The authors used a scale developed by Morrow *et al*. to grade hyperintensities on STIR sequences, which demonstrated four patients to have inflammation within the FDP (35, 39). Recently, the same group investigated fat infiltration within the FDP muscles of 24 IBM patients using the Mercuri scale (24). All patients demonstrated some degree of fatty replacement in the FDP; grade II (mild infiltration) being the most frequent observation (n=12/24). The majority of patients had an atrophic FDP (n=20/24).

It should be noted that all the MRI focussed studies of upper limb muscles in IBM cohorts to date, have conducted investigations using lower resolution scanners such as 0.5T or 1.5T scanners (24, 36-39). Following the advent of higher resolution 3T MRI scanners, the use of quantitative MRI (qMRI) has recently been increasingly adopted in the context of research in neuromuscular disorders and qMRI is being developed as a biomarker (11, 42). Our group have demonstrated validity and responsiveness for a variety of qMRI derived measurements for the thigh and calf in IBM patients (11, 12). FF and CSA values can be used to calculate the functioning remaining muscle area (RMA). In particular, FF was shown to correlate with a variety of clinical measures including IBMFRS and myometry. Longitudinal change in the quadriceps RMA was shown to have a strong correlation with the change in myometric strength of knee extension. Muscle oedema in the lower leg can be more specifically estimated by using T2 relaxometry to obtain the muscle water T2 (14, 43). Magnetisation transfer ratio (MTR) gives insight in the macromolecular integrity of muscle, which is reduced in the lower limb muscles of IBM patients (11, 12). These observations have led to the use of lower limb muscle qMRI assessments as secondary outcome end points in early phase trials for IBM patients (14, 34).

The vast majority of studies investigating the use of MRI to assess upper limb muscles in IBM patients have mainly employed qualitative or semi-quantitative approaches. There has been a lack in investigations exploring the application of qMRI to examine these specific muscle groups. The utility of forearm qMRI has started to be explored in other neuromuscular disorders. In a cohort of Becker's disease patients, qMRI demonstrated significantly higher Dixon derived FF in the forearm flexors compared to healthy controls (44). Our group have previously used qMRI to investigate intramuscular changes within the forearms of non-ambulant Duchenne muscular dystrophy (DMD) patients over the course of 12 months (45). Whole forearm FF was significantly higher in DMD patients compared to age matched healthy controls. In addition, a longitudinal increase in FF over the course of 12 months was observed.

There are limitations to the widespread use of muscle MRI. Firstly, MRI investigations are expensive to perform. Given the age of most IBM patients, they are more likely to have acquired co-morbidities or undergone procedures that may act as contraindications to undergo MRI (46). As mobility declines with disease progression, it can be difficulty to position patients for optimum scanning. Furthermore, larger bore MRI scanners maybe required to image the upper limbs.

Conclusions

There have only been a few imaging techniques which have been used to study upper limb muscle changes in IBM patients. Further work is required to both characterise patterns of involvement in more detail and develop such techniques into biomarkers. Over the last 10-15 years there has been increasing efforts to evaluate US as a diagnostic biomarker, especially investigating its ability to detect FDP involvement and differentiate IBM from other muscle disorders with this finding. More detailed studies are required to investigate the psychometric properties of US assessments in IBM patients and explore its role in disease monitoring. A small number of studies have started to evaluate the role of different PET tracers in IBM. Although potentially promising, much of the work utilising PET in IBM is at its infancy and requires further study in larger populations. Cumulative radiation exposure is a drawback to CT-PET that may limit recurrent follow-up visits. MRI is a modality that has been increasingly used in clinical practice and research. In particular, qMRI allows the examination of a variety structural parameters and has been used as a secondary outcome endpoint in recent clinical trials. The majority of studies utilising qMRI measurements in IBM have focussed on the lower limbs as monitoring or response biomarkers. Studies employing MRI to characterise changes within the upper limb musculature have mainly used qualitative or semi-quantitative approaches. We advocate for future studies to investigate the use of qMRI in the upper limb, in particular the forearm.

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