Current approach to muscle imaging in myositis

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Purpose of review
Muscle imaging is commonly utilized in idiopathic inflammatory myopathies (IIM) for diagnostic evaluation, selection of muscle biopsy site, and differentiating between disease activity versus damage. In this review, we discuss the current state and recent developments in the use of muscle imaging modalities including muscle magnetic resonance imaging (MRI), ultrasound (US), and positron emission tomography (PET) scan.

Recent findings
Muscle MRI is a clinically useful tool in evaluation of IIM with studies showing good correlations between pattern of morphological changes on MRI and histopathological findings on muscle biopsy. The use of computer aided diagnostics to enable quantification of muscle pathology will be a welcome development for future studies and trials. New studies highlight that muscle US could be a particularly useful point of care tool in longitudinal monitoring of patients with active myositis. Muscle FDG-PET scan shows inflammatory activity in IIM muscle and can also provide additional information on extra-muscular manifestations and cancer screening. Utilization of novel tracers is an exciting development for IIM evaluation.

Summary
Muscle MRI remains the gold standard for muscle imaging in IIM. Growing literature on muscle US and PET scan highlight their promising applications in IIM.

Keywords
imaging, MRI, muscle, myositis, PET, ultrasound

INTRODUCTION

Idiopathic inflammatory myopathies (IIM) are a group of systemic autoimmune diseases primarily characterized by muscle inflammation [1]. Other organs such as the skin, lung, joints, heart, and gastrointestinal tract can be variably affected. As our understanding of these diseases has grown, so has our ability to categorize patients into more homogenous subgroups. Currently, IIM subtypes are generally accepted to include dermatomyositis, immune-mediated necrotizing myopathy (IMNM), antisynthetase syndrome, inclusion body myositis (IBM), overlap myositis, and polymyositis [1,2]. The diagnosis of these diseases requires appreciating pertinent findings on clinical history and exam, supported by a combination of features such as elevated muscle enzymes, the presence of myositis-specific and associated autoantibodies, evidence of end organ involvement by imaging, and a compatible muscle biopsy.

Muscle imaging is widely used both in clinical practice and research in IIM. The recent 255th European Neuromuscular Centre (ENMC) workshop defined recommendations on use of various muscle imaging modalities in IIM [3▪▪]. Imaging is often employed as part of the diagnostic evaluation, to demonstrate muscle involvement, recognize patterns of IIM, exclude mimics, and differentiate between disease activity versus damage. Further, it is advantageous for targeting a site for muscle biopsy. Finally, it may be useful as a biomarker to monitor disease progression and/or response to therapy, particularly in clinical trials.

Herein, we review the current state and recent developments in the use of magnetic resonance imaging (MRI), ultrasound (US), and positron emission tomography (PET) scan, the most commonly used imaging modalities for muscle in IIM. Evaluation for extra-muscular manifestations of arthritis, interstitial lung disease, myocarditis, calcinosis and dysphagia will not be covered in this review.

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Curr Opin Rheumatol 2024, 36:445–452
DOI:10.1097/BOR.0000000000001043

KEY POINTS

- MRI is the established imaging modality for inflammatory myopathies (IIM) and is superior for the evaluation of both muscle inflammation and damage.
- Muscle ultrasound is an alternative imaging modality when with expertise and is particularly sensitive for chronic changes.
- FDG PET can be helpful in the diagnosis of IIM as well as evaluation for several extra-muscular manifestations of IIM and cancer screening.

MUSCLE MRI

MRI remains the gold standard for muscle imaging in IIM given its superior resolution for soft tissue and ability to clearly differentiate muscle inflammation (edema) from muscle damage (fat replacement). A routine muscle MRI for myositis evaluation should include fat sensitive T1-weighted (T1w) and fluid sensitive T2-weighted (T2w) sequences. T1w images are used to assess the presence, extent, and degree of degenerative changes (fatty infiltration). T2w images on the other hand, are used to assess for inflammatory changes (edema, hypervascularization) which will appear as hyperintensity on T2w sequences (Fig. 1). Hyperintensities on fluid-sensitive sequences make muscle MRI useful in the diagnosis of IIM with a sensitivity of approximately 90% [4]. However, it is important to note that muscle 'edema' seen on MRI is not specific or synonymous with inflammation or myositis. These changes can also be seen with exercise prior to imaging [5], denervation [6] or rhabdomyolysis among others [7]. The addition of gadolinium contrast to MRI

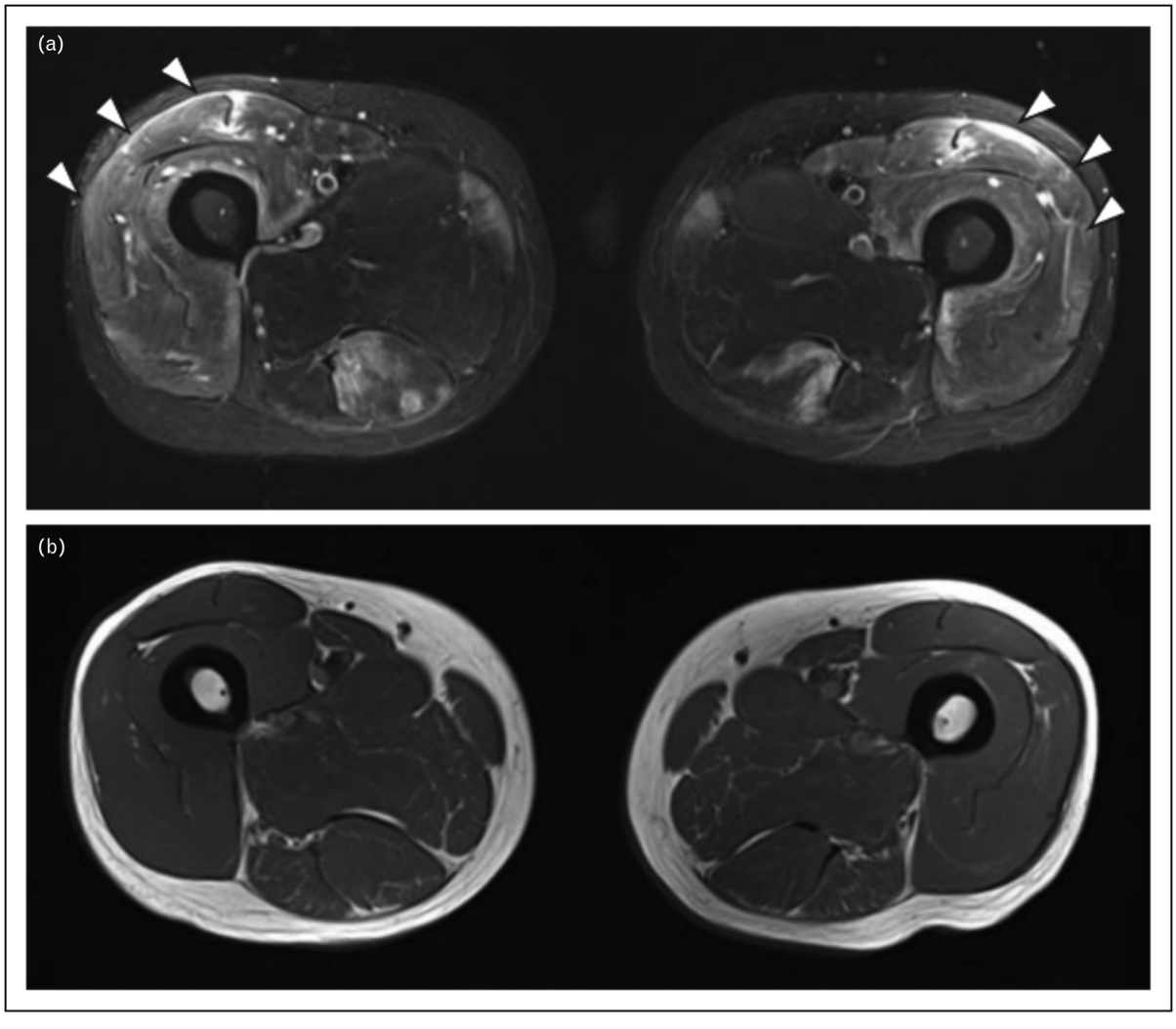

FIGURE 1. Thigh MRI in a patient with overlap myositis showing bilateral symmetric intramuscular edema in the anterior (arrowheads) and posterior compartments on STIR (a), and no evidence for muscle atrophy or fat replacement on T1 (b).

does not increase diagnostic yield [8▪]; therefore, contrast MRI is currently not recommended for routine evaluation of IIM.

Most MRI studies for myositis involve imaging the limbs. However, there is increasing use of whole-body MRI especially in children [9–11]. Although more information is obtained to appreciate the extent and pattern of muscle involvement, a comparison of whole body MRI with a restricted MRI (not involving trunk) showed similar diagnostic accuracies for IIM but 32.8% longer acquisition time for whole body MRI [12]. On the other hand, a larger retrospective study ($n = 129$) showed that whole body MRI was positive in 86.4% of cases, was similar to muscle biopsy, and picked up more cases than muscle enzyme levels or EMG [13]. Additionally, whole body MRI was also able to pick up interstitial lung disease, osteonecrosis and neoplastic lesions, which may be an additional advantage of an extended imaging survey. The most frequently affected muscle group in whole body MRI was the thigh muscles, which points to the adequacy of bilateral thigh MRI in most cases for picking up myositis. While only IBM has a specific pattern of muscle group involvement and other subtypes show variability [14], whole body MRI may play an important role for excluding mimics such as genetic myopathies [15].

There has been interest in determining whether subtypes of IIM display specific patterns on MRI based on a number of conventional morphological findings including degree of muscle edema, pattern of involvement and presence of subcutaneous and fascial high signal intensity [14,16–18,19▪]. A recent study classified the patterns of high signal intensity areas as subcutaneous, fascial, and honeycomb, foggy, peripheral, coarse or dense dot intramuscular patterns in axial STIR images and compared with histopathological findings [20▪▪]. They showed correlations between the honeycomb pattern on MRI and perimysial inflammatory cell infiltration, reticular pattern and interstitial edema, and foggy pattern and endomysial inflammatory cell infiltration. Patients with anti-Mi2 and anti-TIF-1γ had honeycomb and dense dot patterns on MRI, while the fascial pattern was commonly seen in those with antisynthetase antibodies [20▪▪]. The utility and specificity of such patterns remains to be seen. Notably, in a study using machine learning based models, the performance of muscle texture showed low accuracy in distinguishing IIM vs. its mimics. However, the results were promising in classification of patients as having antisynthetase antibodies with an acceptable sensitivity and specificity [21]. A summary of MRI patterns in myositis subtypes has been tabulated in the ENMC report [3▪▪]. While the subtypes share many similar findings, IBM has distinctive features appreciated on imaging which includes involvement of the distal portion of the quadriceps muscle (T1w and STIR) with a 'melted' appearance, anterior greater than posterior involvement in the thigh, involvement of the sartorius and medial gastrocnemius, and relative sparing of pelvic muscles (Fig. 2) [22]. For this reason, the recent 2024 ENMC diagnostic criteria for IBM now includes 'typical muscle MRI appearance' as supportive criteria for a diagnosis of IBM [23].

Qualitative or semi-quantitative assessments of the extent and severity of both muscle edema and fat infiltration are commonly employed in clinical practice. Although different scoring systems have been proposed considering distribution, intensity and patterns of MRI signals, none have been universally accepted [3▪▪]. For diagnostic purposes, these qualitative assessments are sufficient for determining the presence or absence of muscle involvement in IIM. However, for more sensitive monitoring and follow-up of disease in clinical studies, quantitative MRI with Dixon sequences has been gaining momentum [24]. Relying on the water-fat chemical shift difference, Dixon method generates water-only and fat-only images by summation and subtraction of the in-phase and out-of-phase images, respectively and allows for quantification [25]. Intramuscular fat fraction is increasingly being used as a biomarker and measure of disease progression, but other quantitative MRI measures are being studied, of particular use in IBM [26,27].

Despite the usefulness of muscle MRI in IIM as summarized here, some barriers exist such as difficulty of access to MRI in some regions, expense, and difficulty for those with claustrophobia or pacemakers. A wide heterogeneity exists among muscle MRI protocols used in clinical practice and harmonization is required to improve the comparability between different studies and improve the yield of muscle MRI in the study of IIM.

MUSCLE ULTRASOUND

Muscle ultrasound is an emerging point of care tool in the evaluation of IIM, which although more widely available, is heavily dependent on expertise. Muscle is well visualized by US, with the capacity for dynamic and real-time imaging [28]. Normal cross-sectional muscle appears as relatively anechoic or hypoechoic (gray) tissue with hyperechoic (white) speckles in the tissue representing perimysial septa (Fig. 3a) [29]. Longitudinally, muscle fibers are appreciated as hyperechoic parallel fibers. Parameters that can be assessed on B-mode or grey scale US include muscle echogenicity, architecture, size,

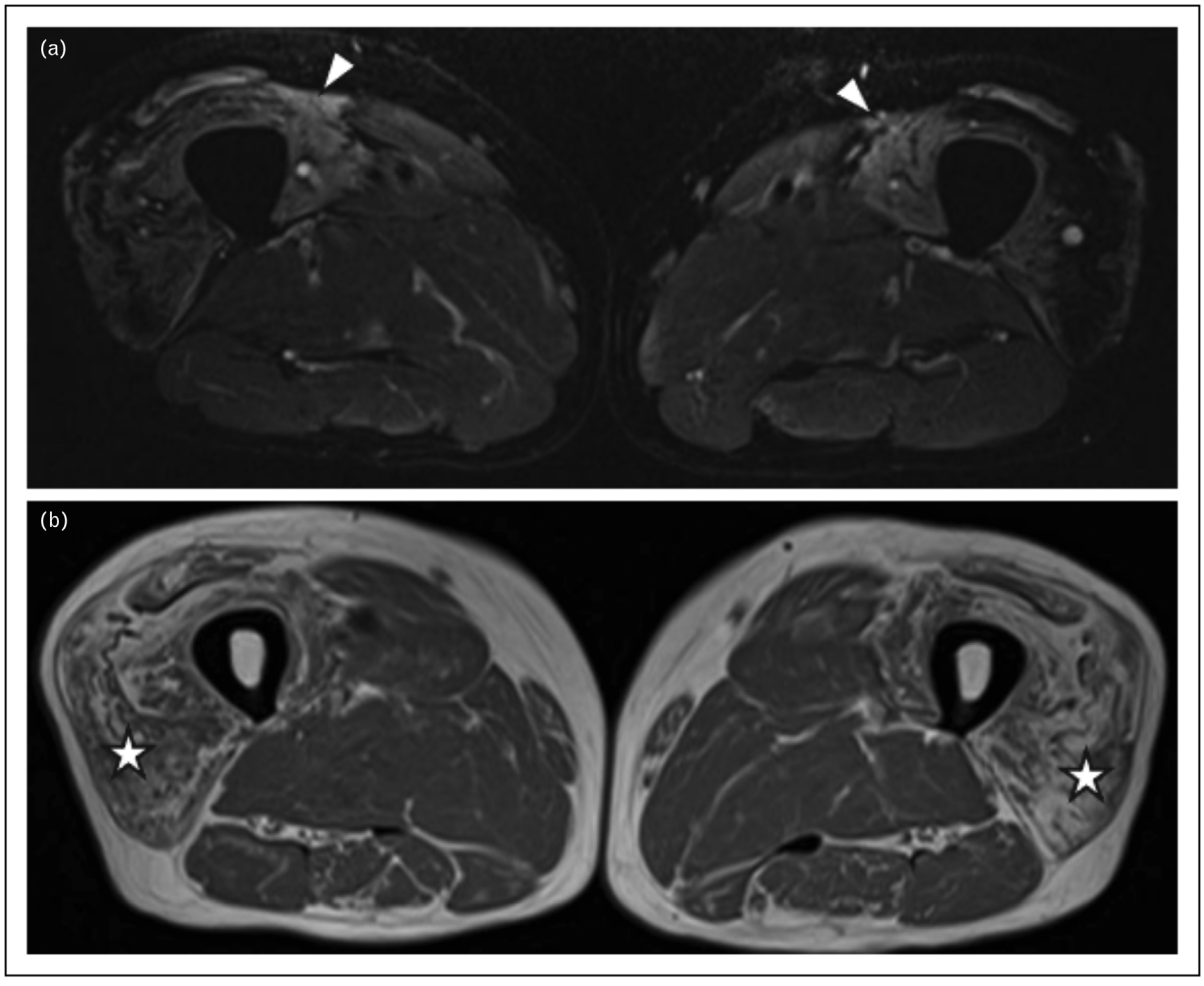

FIGURE 2. Thigh MRI in a patient with inclusion body myositis showing intramuscular edema most notable in the anterior compartment (arrowhead) on STIR (a) and atrophy with fat replacement (star) of quadriceps muscles on T1 (b).

fascial thickness, pennation angle and movement. Normal skeletal muscle has a low blood perfusion at rest, which can be assessed with Doppler sonography [30,31].

In myositis as with other myopathies, the cardinal parameter on muscle US indicating pathology is echogenicity. Increased sound reflections in the muscle are created by processes such as

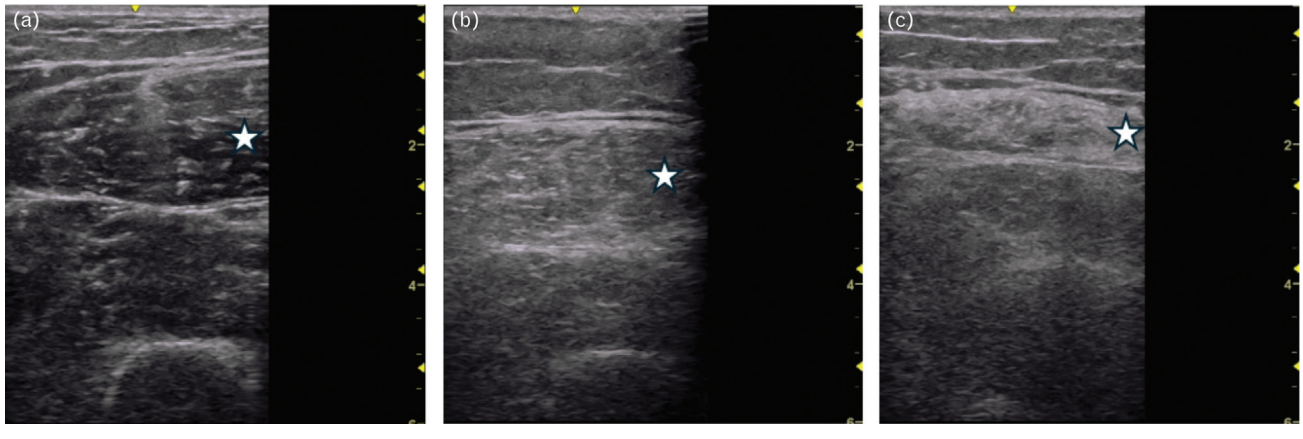

FIGURE 3. Muscle ultrasound of the rectus femoris (star) in a healthy control showing normal muscle architecture (a), a mild increase in muscle echogenicity representing muscle edema in a patient with dermatomyositis (b), and a marked increase in muscle echogenicity with atrophy in a patient with IBM (c).

inflammatory infiltrates, increased perfusion, and replacement of muscle by fat and fibrosis. Muscle echogenicity is most commonly assessed visually (should be of similar echogenicity with subcutaneous tissue) as normal or abnormal, or semi-quantitatively with the Heckmatt scale [29]. The Heckmatt scale is based on the intensity of muscle brightness and level of decrease in the underlying bone/fascial echo on a 4-point scale which was originally developed for use in muscular dystrophies [32]. Quantitative assessments of echointensity can also be utilized but require the use of standardized machine settings and reference values for normal muscles across age for that system. Muscle echointensity has shown significant correlations with creatine kinase (CK), muscle strength and the number of infiltrating $CD3^+$ inflammatory cells in non-IBM IIM [33]. A preliminary validation study in juvenile DM showed that echogenicity of the quadriceps correlated with physician global activity, manual muscle testing, childhood myositis assessment scale, and both STIR and T1 MRI [34].

In chronic myositis like IBM where the muscle becomes increasingly atrophic and replaced by fat, muscle echointensity is markedly abnormal and the underlying bone echo may be lost (Fig. 3c) [35]. In acute myositis where muscle edema predominates, the change in echointensity may be very slight and not detectable by quantitative measures (Fig. 3b) [36▪▪]. However, the abnormality may be appreciated as a change in texture, or as a loss of contrast between the hyperechoic perimysial septations and anechoic muscle tissue. In two recent small studies, incident cases demonstrated a reduction (or normalization) in echogenicity over time after starting treatment, while prevalent cases showed an increase in echogenicity and reduction in muscle bulk suggesting development of atrophy and damage over time [37,38].

While acute edema may be more difficult to detect by in inexperienced observer, a recent study of newly diagnosed patients started on intravenous immunoglobulin, showed visual assessments of muscle US were able to demonstrate changes over nine weeks of follow-up in these patients, while MRI did not reveal a significant change over this follow-up period [36▪▪]. These results point to the potential of muscle US as a practical and sensitive tool in monitoring patients with IIM when in the hands of experienced observers. The addition of power Doppler may be helpful to further characterize acute myositis and edema, and a recent study suggests that power Doppler is only seen in early, active myositis [39]. Power Doppler US may also be useful for detecting the increase in vascularity that accompanies fasciitis in DM [40].

In terms of sonographic patterns that can distinguish between IIM subtypes, US can differentiate IBM from other types of myositis and mimics [35,41,42]. Imaging the flexor digitorum profundus at the forearm is the most sensitive (73.3%) and specific (93.3%) [42], but detecting typical changes at the quads is also helpful [41]. In this manner, muscle US is particularly convenient to apply at the bedside in support of the diagnosis of IBM [23]. Active dermatomyositis also presents in a typical fashion with an increase in echogenicity of both the muscle and subcutaneous tissue [43]. Changes of fasciitis can also be noted, as can calcinosis which is easily detectable by US. Additionally, it is not only the increase in echointensity seen in muscle but also the pattern of its increase within the muscle that can distinguish between different processes and exclude mimics [29]. Machine learning and deep learning techniques have been applied to US images to automate the diagnosis of myositis utilizing a variety of these textural and sonographic features and is very promising [44–46].

While imaging is often used to help guide muscle biopsy, only US affords an easy and practical means for real-time image guidance. US guided needle muscle biopsies are well tolerated, improve the diagnostic yield while avoiding crucial structures, and expand the number of muscles that can be sampled safely [47–49].

Unlike MRI which utilizes different sequences to visualize and quantify inflammation and damage, grey scale US is unable to differentiate the contributions of each when they occur together. However, it performs extremely well in the setting of chronic changes such that it may in fact be the more optimal and practical tool for diagnosis of IBM. While MRI will remain as the imaging of choice for muscle imaging in myositis, US is a clear alternative with local expertise. More training opportunities need to be created in order to deploy muscle US beyond specialty centers.

MUSCLE PET SCAN

PET combined with computed tomography (CT) scan or MRI is frequently used in oncology but has utility for evaluating a range of inflammatory conditions [50]. PET/CT typically utilizes glucose analogues to quantify the glycolytic metabolic shift that occurs in diseased organs and provide information on morphological and functional changes in tissues. The most commonly used radiotracer in PET scans is [^{18}F] fluorodeoxyglucose ([^{18}F] FDG). FDG enters the cells through glucose transporters; however, unlike glucose, it does not get metabolized and gets trapped inside the cells [51]. The degree of FDG uptake of a cell depends on its metabolic state. At

rest, skeletal muscles utilize fatty acid as their major source of energy; therefore, maximum standardized uptake value (SUV) ranges between 0.5 and 2.2 for healthy muscles [52]. Activities such as strenuous exercise, muscle spasm, or food intake can lead to an increase in FDG uptake of skeletal muscles. Therefore, it is important to recognize the physiologic causes of increased FDG uptake in skeletal muscles and encourage the patients to follow the preparation protocol which involves fasting for 4–6 h and avoiding exercise before the scan.

Patients with IIM generally have a significantly higher FDG uptake compared to controls with a predominantly symmetric uptake in proximal muscle groups (Fig. 4) [53,54]. FDG uptake shows correlations with muscle strength; however, correlations with CK levels have conflicting results in the literature [53]. In a study by Matuszak *et al.* mean SUV max threshold of 0.66 was able to differentiate high muscle disease activity from no-low disease activity with 92% sensitivity and 90% specificity in patients with IIM [53]. FDG uptake also demonstrated a change that correlated with the change in muscle disease activity over time [53]. PET/MRI had a sensitivity of 100% and specificity of 93% for diagnosis of IIM with significant correlations observed between FDG uptake and muscle strength and CK levels [55]. In addition to assessment muscle disease activity, PET/CT scan may also offer additional information including screening for cancer and other potential manifestations of IIM such as interstitial lung disease, myocarditis, and inflammatory arthritis [56]. These benefits make PET scans highly useful in clinical practice; however, its variable availability and high cost limit its use and further studies are required to justify the yield of information over other imaging tools.

Although FDG is the most commonly used radiotracer in PET scans, other tracers including [^{18}F]florbetapir and Pittsburgh Compound B ([^{11}C]PIB) have also been studied in IIM [57–59]. Both [^{18}F]florbetapir and Pittsburgh Compound B are used to image amyloid deposits; both were primarily studied in IBM where accumulation of intra-muscular beta amyloid is frequently observed. A significantly higher uptake of both amyloid tracers was observed in comparison to patients with polymyositis and other IIM; however, no significant correlations were observed between the tracer uptake and clinical measures including muscle strength, disability index, and functional rating scale [57,59]. Excitingly, a recent study evaluated a novel investigational PET tracer ^{89}Zr-Df-crefmirlimab for in vivo imaging of whole-body skeletal muscle CD8^{+} T cells in IBM [60▪▪]. In the four patients that completed imaging, quantitation revealed increased uptake in the quadriceps, biceps brachii, triceps and forearms finger flexors in IBM patients compared to age-matched patients with cancer. This holds promise as a noninvasive biomarker that could be particularly useful for clinical trials for IBM targeting inflammation. On the other hand, selective fibroblast activation protein inhibitors (FAPI) can be used to quantify profibrotic and proinflammatory fibroblasts when coupled to radioactive tracers. Although [^{68}GA]Ga-FAPI was initially developed as a tumor-targeting agent, it has been gaining use in rheumatologic diseases. Fibroblasts in chronically inflamed tissue such as in patients with myositis, express fibroblast activation protein and can be quantified by FAPI-PET/CT. There are already a handful of cases showing utility in dermatomyositis with cancer [61,62], MDA5 dermatomyositis [63] and juvenile polymyositis [64]. When coupled with

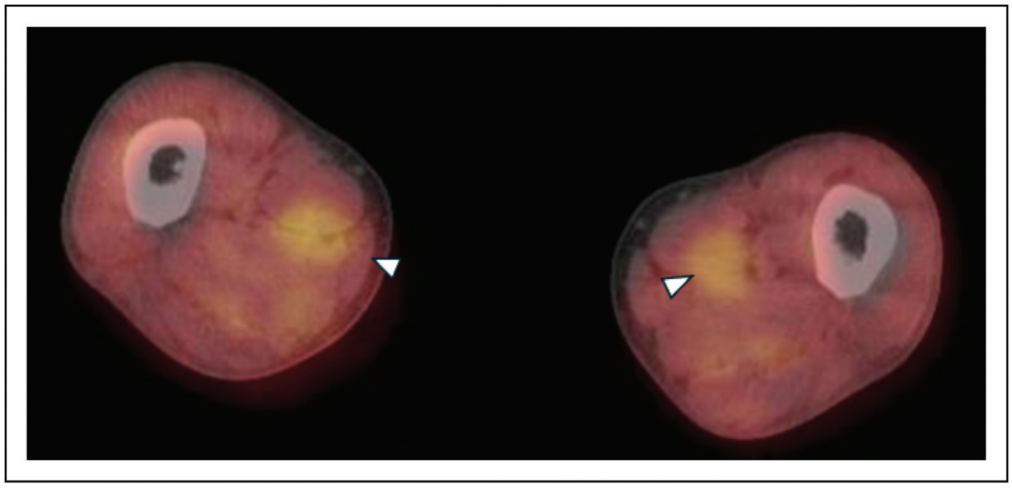

FIGURE 4. PET CT of a patient with dermatomyositis showing symmetric bilateral increased FDG uptake in pelvic adductors (arrowheads).

[^{18}F] FDG, muscles with increased FDG uptake have also been shown to be FAPI-avid and often have higher uptake values in multiple muscles compared to [^{18}F] FDG PET/CT [63]. This may enable quantification of the tissue response with chronic inflammation and fibrosis and will likely gain momentum in the coming years.

PET scans are attractive for use in IIM, particularly with tracers that may provide additional information about disease state or severity. However, obtaining PET studies may be more difficult clinically given cost and restrictions. Its role in IIM evaluation over and above existing modalities needs to be evaluated further.

FUTURE DIRECTIONS

One of the major roadblocks in conducting multicenter muscle imaging research studies is the wide variability in the muscle imaging protocols used across different sites. Therefore, future work should focus on development and implementation of muscle imaging protocols (for MRI, US and PET). This approach will ensure consistent image quality, enhance the comparability between images performed across diverse clinical settings, and accelerate the research conducted in this field.

Current methods used to quantify image findings (such as muscle edema or fat) primarily rely on semi-quantitative assessments that are not standardized and require specific expertise. Quantification of muscle imaging findings could be useful in monitoring disease activity and damage in patients with IIM and improve the objectivity and reliability of disease assessment. Therefore, novel computerized methods that can accurately distinguish between disease activity and damage on each modality and quantify these changes could be paradigm changing in both clinical practice and trials in the near future. Indeed, future work with muscle imaging will involve more frequent utilization of machine learning and artificial intelligence to automate muscle segmentation and detect and quantify muscle pathology. Such advances in muscle imaging will hopefully improve the efficiency in diagnostic evaluation of IIM, decrease the need for invasive testing, and lead to improved outcomes for patients.

CONCLUSION

Muscle imaging modalities are used in the diagnostic work-up of IIM, selection of muscle biopsy site, disease activity assessment, and monitoring response to treatment. Currently, muscle MRI is the gold standard imaging modality in IIM; however, muscle US is an alternative modality that may be increasingly utilized as expertise increases. The use of PET scans, particularly with novel tracers, are exciting developments for the field.

Acknowledgements

None.

Financial support and sponsorship

Dr Albayda is supported by the Jerome L. Greene Foundation, Dr Saygin is supported by the Rheumatology Research Foundation Scientist Development Award.

Conflicts of interest

There are no conflicts of interest.

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