



How useful is muscle ultrasound in the diagnostic workup of neuromuscular diseases?

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Purpose of review

This review focuses on developments in muscle ultrasound as a noninvasive and accurate tool for the diagnosis and follow-up of neuromuscular disease. It discusses current muscle ultrasound applications with already proven clinical value, and highlights recent technical developments that may further advance muscle ultrasounds' diagnostic qualities.

Recent findings

The sensitivity and specificity of muscle ultrasound for detecting a neuromuscular disorder are high (90–95%), and quantitative ultrasound is well suited to monitor disease progression in several disorders. Adding ultrasound to electromyography significantly improves diagnostic certainty in patients with suspected motor neuron disease, and ultrasound increases the detection of fasciculations with 30–50%. New developments include speckle tracking of tissue motion to quantify diaphragm excursions and diminished muscle contractility in dystrophy, and strain elastography to detect changes in muscle stiffness and anisotropy during contraction and in disease states. Deep learning algorithms are being developed to predict the presence of a muscle disease and differentiate between disorders.

Summary

Muscle ultrasound is excellent for screening, diagnosing, and follow-up of neuromuscular disease. New developments are underway to automate and objectify the diagnostic process, and to quantify tissue motion that can provide new insights in pathophysiology and serve as a biomarker.

Keywords

elastography, muscle ultrasound, neuromuscular disorders, quantitative ultrasound, speckle tracking

INTRODUCTION

Imaging techniques are becoming increasingly important in the diagnostic workup of a suspected neuromuscular disorder. Both MRI and ultrasound can show abnormalities in tissue composition, architecture and movement that point to neuromuscular pathology, and both allow for tracking such changes over time [1,2]. CT imaging is less desirable because of its low soft tissue resolution and use of ionizing radiation.

Ultrasound imaging of muscle tissue is a patient-friendly, noninvasive, and point of care technique to visualize muscle size, structure, movement, and function. Clinically it has been used since 1980s for diagnosing children and adults with neuromuscular disease [2,3]. Normal muscle has a relatively black appearance interspersed with thin white fascial lines, which has been dubbed as a 'starry night appearance' in transverse images (Fig. 1a). Longitudinal scans show the fascicular architecture of the muscle fiber bundles (Fig. 1c) that can be used to measure pennation angles and detect myofascial tears. Diseased or

denervated muscle will progressively become more echogenic, as normal tissue architecture is replaced by intramuscular fat and fibrosis (Figs. 1b and d).

Dynamic imaging can capture voluntary and spontaneous muscle movements, such as contractions and fasciculations, and assess parameters associated with tissue elasticity after pressure application [4,5], while the use of Doppler techniques can evaluate intramuscular blood flow and

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KEY POINTS

- Muscle ultrasound has excellent capabilities for diagnosis and follow-up in neuromuscular disease
- Quantitative muscle ultrasound analysis is most sensitive in neuromuscular disease, but needs further improvement to overcome system-dependent results and to facilitate widespread use
- New muscle ultrasound motion tracking techniques will increase pathophysiological insights in muscle disease and help develop new biomarkers for treatment trials.

inflammation. Muscle ultrasound can be evaluated visually, semiquantitatively by using the four-point Heckmatt grading scale [6] or quantitatively by calculating echogenicity or backscatter levels in a region of interest in images that are acquired with standardized settings [5]. Visual analysis has a reported sensitivity of around 70% for detecting neuromuscular disease, while quantitative muscle

ultrasound analysis has detection rates of more than 90% overall. Dynamic imaging is very useful for detecting fasciculations, with higher detecting rates than using clinical examination or needle electromyography (EMG) [7].

In this review, we will focus on new developments in muscle ultrasound as a tool for diagnosing neuromuscular disease. We will discuss the current muscle ultrasound applications that already have proven clinical value, and highlight recent technical developments that may further advance muscle ultrasounds' diagnostic qualities.

RECENT CLINICAL MUSCLE ULTRASOUND APPLICATIONS AND DIAGNOSTIC VALUE

Muscle ultrasound is an excellent alternative to EMG for screening children with suspected neuromuscular disease. A systematic review that found 18 studies from 2000 to 2014 concluded that ultrasound is a reliable and useful method for the assessment of skeletal muscle disease, with a sensitivity

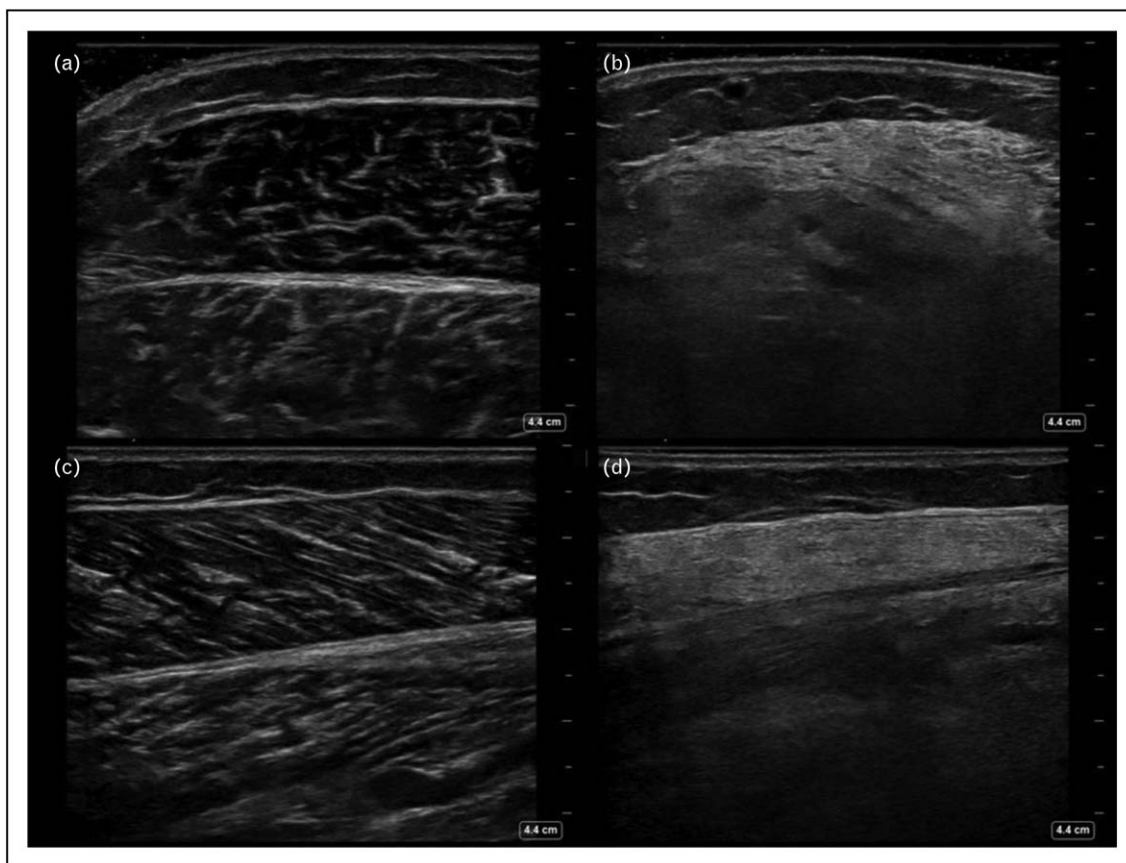


FIGURE 1. Transverse (a) and longitudinal (c) ultrasound image of a healthy calf, showing, from top to bottom, the skin, subcutaneous fat layer, medial gastrocnemius muscle and soleus muscle together with transverse (b) and longitudinal (d) ultrasound image of a severely denervated calf muscle, showing, from top to bottom, the skin, subcutaneous fat layer, a very hyperintense medial gastrocnemius with distorted muscle architecture, and a soleus muscle that is hardly visible because of attenuation of the ultrasound beam.

and specificity of around 90–95% [8]. No screening data are available for adults yet, but the proportion of abnormalities found in specific neuromuscular disorders such as motor neuron disease, myositis, facioscapulohumeral dystrophy (FSHD) and myotonic dystrophy is equally high [5]. Diagnostic sensitivity is lower (around 75%) in disorders and patients with less structural muscle abnormalities, such as pure metabolic myopathies, muscle edema in acute Intensive Care Unit (ICU)-acquired weakness and infants with myopathies [5]. An overview of specific types of pathology found in different neuromuscular disorders can be found in reviews by Pillen *et al.* and Zaidman *et al.* [2[•],5].

Ultrasound for fasciculation detection in the diagnostic workup of Amyotrophic lateral sclerosis

Muscle ultrasound is a helpful adjunct in diagnosing peripheral nervous system involvement in amyotrophic lateral sclerosis (ALS), by detecting echotexture changes that imply denervation combined with detecting fasciculations. Adding muscle ultrasound to EMG can provide 25% of the patients with a more certain diagnosis at the time of presentation [7]. A recent study set out to see whether fasciculation screening alone would also be of diagnostic value to differentiate between ALS and mimics [9]. Overall, fasciculations were found in 49% of the ALS patients versus in 4% of the mimics. In this subgroup, a ‘fasciculation ultrasound score’ using a cut-off value of at least 2/9 muscles had a 92% sensitivity and 100% specificity for differentiating ALS from a mimic. Initial attempts toward the automatic detection of fasciculations have been reported, which may increase interobserver agreement and reduce time needed for manual annotation [10].

On a more basic neurophysiologic level it was shown that, using ultrasound as a reference, 33% of all fasciculations in ALS are EMG-negative, and the probability of detecting fasciculations decreased from 98% when the needle was centered within the fasciculating motor unit to 50% at a 5.4-mm distance from the fasciculation boundary [11].

Ultrasound as a biomarker for neuromuscular disease severity and progression

Muscle ultrasound quantification is currently performed by either mean grayscale measurement [3] or backscatter analysis measured using a calibrated phantom [12]. Both techniques were compared head-to-head and were found to be equivalent for detecting muscle pathology in dystrophinopathies [13^{••}]. Both techniques were found to be well suited

to monitor increasing echogenicity over time in Duchenne muscular dystrophy (DMD) from infant to adult patients, and both techniques correlated well with functional measurements [14^{••},15]. As a biomarker, quantitative muscle ultrasound would need only a quarter of the number of patients for a treatment trial, compared to the standard 6-min walking test to show a treatment effect [14^{••}]. While ultrasound can show nerve size enlargements in demyelinating hereditary polyneuropathy [16], quantitative muscle ultrasound showed increased echogenicity and atrophy in the lower leg and hand muscles of Charcot-Marie-Tooth patients that correlates with muscle strength and compound muscle action potential amplitude [17]. Neither nerve nor muscle ultrasound was correlated to functional status, making these techniques complementary biomarkers to clinical scoring systems.

Glycogen storage disease (GSD) patients can have a predominantly hepatic or myopathic phenotype. However, muscle ultrasound showed that both phenotypes have muscle involvement that stabilizes over time in the hepatic phenotype while abnormalities increase in the myopathic phenotype. The authors found muscle ultrasound to be an excellent tool for neuromuscular surveillance in GSD [18].

Imaging of oral and masticatory muscles in neuromuscular disorders

Dysphagia is common in neuromuscular disease. Weakness of the oral, submental, and pharyngeal muscles causes problems with chewing and transporting food in the mouth, and hampers well-coordinated swallowing, posing a risk of aspiration. A study of 72 DMD patients showed early changes in the masseter muscle, and progressive abnormalities of jaw and submental muscles correlated with chewing and mouth closure abnormalities [19]. A recent review advocates muscle ultrasound as a standard tool for the workup of neuromuscular dysphagia [20[•]]. Dynamic ultrasound imaging can show reduced lateral tongue movements in patients with dysphagia due to cerebral palsy [21], and identify fasciculations in cranial nerve innervated muscles in patients with ALS with similar sensitivity as needle EMG [22]. Facial muscle ultrasound can show muscle atrophy and increased echogenicity in patients with chronic facial palsy and myotonic dystrophy type I [23,24].

TECHNICAL DEVELOPMENTS IN MUSCLE ULTRASOUND AND POTENTIAL CLINICAL VALUE

The structure and function of muscles changes as a consequence of muscle denervation and myopathy,

with increased connective tissue and fat content interspersed with and replacing healthy muscle tissue. This will alter the elasticity and the contraction pattern of the muscle. There are several ultrasound techniques available that can assess these elastic and functional properties of tissue. The main techniques used in clinical practice include speckle tracking, deformation (strain) elastography, acoustic radiation force impulse (ARFI) imaging, and shear wave elastography.

Ultrasound speckle tracking

Speckle tracking techniques were developed to quantify tissue motion. Although conventional B-mode ultrasound of the diaphragm has already been proven to be an excellent alternative for other diagnostic tests to diagnose diaphragm dysfunction in both phrenic neuropathy and myopathy [25,26], it is challenging to quantify diaphragm excursion during breathing. M-mode ultrasonography can measure tissue moving toward or away from the ultrasound probe [27], but as this technique is one-dimensional it is unable to track the same region of tissue passing through the M-mode line. To overcome this, speckle tracking combined with standard B-mode imaging has two distinct advantages: it can track diaphragm movement in two dimensions throughout the respiratory cycle, and it can quantify left hemidiaphragm motion, which is nearly impossible with M-mode due to its difficult anatomical localization behind the stomach and spleen [28].

Ultrasound strain elastography

Ultrasound strain (i.e., deformation) elastography is a technique to quantify tissue deformation, also by

tracking the speckle pattern in the ultrasound images over time and subsequently calculating the difference in displacement between points. This deformation can be induced by an external force such as the transducer, or an internal force like a pulsating artery or breathing motion. Strain elastography depicts information that is associated with the mechanical properties of tissue. A large deformation will occur in soft(er) tissues, whereas little deformation will occur in hard(er) tissues [29]. Using this technique, intramuscular epidermoid tumors, plantar fasciitis, and congenital muscular torticollis have been diagnosed [30]. The disadvantage of strain elastography is that it is subjective, as the magnitude of the force applied by the operator is variable, and is unknown for internal tissues.

Strain elastography can be used to quantify muscle contractility, using active muscle contractions as the deformation source [31]. *In vivo*, this can provide new insights in how pathological tissue contracts and transmits force, which leads to a better understanding of weakness in muscle disease, and might provide a functional outcome measure for disease evolution. A study that applied speckle tracking to quantify the deformation of the tibialis anterior muscle in patients with fascioscapulohumeral dystrophy and compared it to healthy muscle motion, showed that the deformation pattern of muscles with abnormal echogenicity is different from that of healthy or only mildly affected muscles without ultrasound abnormalities [32]. Severely affected muscles showed decreased motion of the central tendon aponeurosis (Fig. 2), which suggests a decrease in force transferred to this tendon and thus a diminished force output when dorsiflexing the ankle. The resulting deformation patterns showed good agreement with clinical outcome measures,

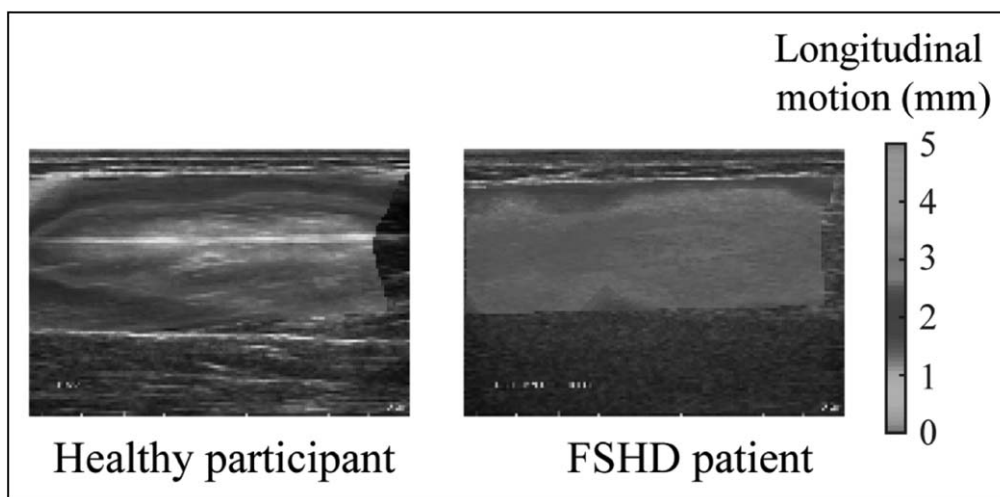


FIGURE 2. Longitudinal motion estimation using strain elastography reveals that the muscle deformation pattern of patients suffering from FSHD is altered compared to healthy participants.

muscle echogenicity values, and maximum exerted force.

ARFI, viscoelastic response, and anisotropy imaging of muscle

To overcome the problem that strain elastography does not provide direct information on the elastic modulus, ARFI imaging was developed. In ARFI imaging, the tissue displacement as result of an ultrasound push pulse is standardized. It is measured by speckle tracking of the raw ultrasound signal between echo signals that are acquired before and after the push [33]. The magnitude of the displacement is related to the local stiffness of the tissue at that location, but can still not be directly transferred into the elastic modulus, resulting in a qualitative output.

Viscoelastic response imaging

Viscoelastic Response (VisR) ultrasound is an ARFI-based technique that provides information about the viscoelasticity of muscle, and can be used to measure the anisotropy of the muscle. This technique can quantify muscle fiber direction [34]. In a stroke patient, the magnitude and direction of anisotropy as quantified with VisR appeared to have changes compared to the healthy controls [35]. The anisotropy in the rectus femoris muscles in boys with DMD was also significantly higher compared to healthy boys, suggesting increased transverse relative to longitudinal elastic and viscous moduli, which is consistent with expected muscle fiber fragmentation, fibrosis, and fatty deposition in DMD [36].

Ultrasound shear wave velocity measurement

Shear wave elastography is an extension of the ARFI technique. A shear wave traveling longitudinally through the muscle is generated by an ARFI push pulse, inducing tissue displacement that is detected by ultrafast image acquisitions. From the tracked tissue displacement the shear wave velocity can be derived, which can be directly related to the elastic modulus ($E = 3\rho c_{sw}^2$, with ρ is density of the tissue and c_{sw} is the shear wave speed). The resulting stiffness value is graphically represented in a region of interest by superimposing color over the B-mode images, with warm colors corresponding to hard tissues and cold colors to soft ones [37]. Under rigorous laboratory conditions, shear wave elastography of skeletal muscle acquired reliable, real-time, noninvasive, high resolution, and quantitative data [38[•]]. However, under clinical conditions the

reproducibility will most likely be limited. This is in part due to the anisotropic properties of muscle tissue, as this makes shear waves travel faster parallel to the direction of muscle fibers versus perpendicular to them, with better reproducibility of muscle elasticity values in longitudinal acquisitions [38[•]]. Muscles with a more complex anatomy, such as pennate muscles, make it difficult to assess the main fiber orientation and require careful consideration of the muscle anatomy before using shear wave elastography.

Shear wave elastography has been applied to assess resting muscle stiffness in boys with DMD [39]. An increased stiffness of the proximal limb muscles and calf was found, without changes in a distal hand muscle, as fits the clinical pattern of the disease [39]. A follow-up study showed an increased stiffness up to 145% for different muscles after 12 months [40[•]]. Muscle stiffness assessment may provide further information as a surrogate disease marker, and improve the accuracy of patient monitoring during therapeutic interventions in DMD.

Quantitative muscle ultrasound imaging

Based on the pioneering work of Pillen *et al.*, quantitative ultrasound imaging of muscles (QMUS) for detection and follow-up of neuromuscular disease is becoming more mature. Quantitative analysis is highly dependent on the settings and image post processing of the ultrasound machine [41]. Consequently, rigidly fixed settings need to be applied during scanning, and system- and software-specific references values need to be collected for every machine [5]. To see if a dedicated system without postprocessing of images can overcome these limitations, O'Brien *et al.* investigated the inter- and intra-observer variability of mean grayscale analysis by using four identical, dedicated systems, and three sonographers who on two different days measured six different muscles [42[•]]. They found excellent reproducibility, with inter- and intrarater correlations of approximately 0.90 and an inter-system correlation of 0.96. A further development is the analysis of muscle ultrasound images using machine learning. Burlina *et al.* performed a study in which ultrasound images acquired with fixed machine settings were analysed by such a network to differentiate inclusion body myositis (IBM), polymyositis, dermatomyositis, and normal subjects [43[•]]. The authors showed that a deep convolutional neural learning strategy performed better than conventional machine learning algorithms in all comparisons, including normal versus diseased and IBM versus other types of myositis, with diagnostic accuracies of 76–86%.

CONCLUSION

Muscle ultrasound is a valuable and clinically proven imaging technique for the diagnosis of neuromuscular disorders and needle guidance during invasive diagnostic procedures. QMUS is the most sensitive technique, but it is currently very software- and hardware dependent, which hampers widespread use. Visual evaluation augmented with dynamic imaging can already save patients from more invasive procedures. New techniques such as strain imaging, dedicated QMUS machines without postprocessing, and deep learning systems are promising developments to overcome current limitations and further optimize the diagnostic use of muscle ultrasound.

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Conflicts of interest

There are no conflicts of interest.

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