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Guidance for Sponsors
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Muscular Dystrophy: Medical Imaging in Clinical Trials

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MRI has become one of the most valuable tools for measuring disease in muscular dystrophy. It shows which muscles are involved, how severely and how actively, and it can guide biopsy and monitor therapy. Since the first edition of this issue, quantitative MRI has moved from grading scales to precise fat-fraction measurement, and muscle fat fraction has been shown to predict loss of ambulation in Duchenne muscular dystrophy. With new therapies now approved, MRI is a key secondary endpoint and a candidate surrogate for future trials.

Muscle Diseases

Imaging of muscle disease has expanded and evolved considerably. MRI in particular provides clinically useful information on the extent, severity and activity of muscle involvement in muscular dystrophies, congenital and metabolic myopathies, motor neuron diseases, and inflammatory and infectious conditions. It is well suited to evaluating large regions of muscle, can help target biopsy and electromyography, and can track disease progression and response to therapy.

Muscular Dystrophy

The muscular dystrophies are a group of disorders characterized by weakness and hypotonia. Duchenne muscular dystrophy (DMD) is a fatal X-linked recessive disorder affecting approximately one in 3,500 to 5,000 boys, with onset at 4 to 6 years of age. Absence or mutation of dystrophin leaves muscle vulnerable to injury during eccentric contraction. Weakness is progressive and relatively symmetric, beginning in the pelvic girdle and spreading over time to the calves and shoulder girdle. In the thigh, fatty replacement is most prominent in the gluteal and adductor magnus muscles, with active inflammatory change in the adductor, quadriceps and biceps femoris. The gracilis is generally the most resistant muscle, followed by the sartorius, semitendinosus and semimembranosus.

Becker muscular dystrophy is also X-linked and caused by altered dystrophin, but is generally milder, with onset at about 11 years. Lower-extremity symptoms precede upper-extremity involvement by 5 to 10 years. Calf pseudohypertrophy, with enlargement of the soleus and gastrocnemius, is common, while the gracilis, sartorius, adductor longus, rectus femoris, semitendinosus and semimembranosus are relatively spared.

Clinical evaluation relies on functional scores, which are subject to variability and effort, particularly in young children. Muscle biopsy is painful and limited by sampling error, and serum creatine kinase is not a highly reliable marker of disease activity. Noninvasive MRI is therefore highly valuable for measuring progression and response to therapy.

Medical Imaging

A basic MRI protocol includes a fluid-sensitive sequence, such as fat-saturated fast spin-echo T2 or STIR, in at least one plane; the axial plane is generally most useful for identifying the muscles affected and distinguishing inflammation from fatty re-

placement. Axial and coronal T1-weighted images without fat suppression show fatty replacement.

Early quantitative approaches used MR grading. In 1993, Liu and colleagues published a DMD grading system based on the number of preserved muscle groups in the pelvic girdle and thigh, fatty infiltration of the pseudohypertrophied calf and increased subcutaneous fat, and correlated it with function, creatine kinase, age and disease duration.[1] Later, Kim and colleagues used T2 maps of 18 pelvic and thigh muscles and found that T2 values, highest in the gluteus maximus, correlated with fatty infiltration and clinical tests.[2]

Quantitative MRI Today

The field has since moved to chemical-shift (Dixon) imaging and proton MR spectroscopy, which measure muscle fat fraction directly and reproducibly. Water T2 mapping, measured separately from fat, reflects inflammation and edema. These measures change over months rather than years, allowing smaller and shorter trials. In two natural history cohorts, each one-percentage-point increase in vastus lateralis fat fraction was associated with a 15% higher hazard of losing ambulation in the Leiden cohort, independent of age.[3] Large natural history studies such as ImagingDMD have confirmed MR biomarkers as predictors of loss of ambulation.[4]

New therapies have raised the stakes. In March 2024, FDA approved givinostat (Duvyzat) for DMD in patients aged 6 and older, based on the EPIDYS trial of 179 ambulant boys, in which MRI assessment of muscle fat infiltration was a key secondary endpoint.[5] Phosphorus-31 spectroscopy of cardiac muscle, which can show reduced phosphocreatine-to-ATP ratios, and cardiac MRI extend imaging to the heart, a leading cause of death in DMD.

Guidance for Sponsors

Using MRI in a muscular dystrophy trial

- **Measure fat fraction quantitatively.** Use Dixon imaging or spectroscopy rather than visual grading alone.[3]
- **Pick sensitive muscles.** Target muscles such as the vastus lateralis and soleus that change measurably within the trial's time frame.[3,4]
- **Separate inflammation from fat.** Include water T2 mapping to capture disease activity and early treatment effect.
- **Standardize across sites.** Harmonize sequences, positioning and analysis on every scanner, with phantom checks.
- **Plan for children.** Keep protocols short, minimize motion and avoid sedation where possible.
- **Correlate with function.** Analyze MRI change with timed function tests and ambulation.[5]

Summary

Noninvasive monitoring of disease state, progression and response to therapy in muscular dystrophy is not only feasible but now quantitative. MRI fat fraction, water T2 and spectroscopy provide reproducible measures that correlate with function and predict clinical milestones. Combined with functional tests, creatine kinase, histopathology and genetic testing, they give sponsors a powerful set of endpoints for the new era of DMD therapies.

About the Author

Dr. Jennifer Swart, a board-certified radiologist with specialized training in orthopedic radiology, wrote the original edition of this issue at Intrinsic Imaging. She graduated summa cum laude in cognitive neuroscience from Harvard University and earned her M.D. from Columbia University College of Physicians and Surgeons, where she received the Janeway Prize, awarded to the graduate at the top of the class. As an American Academy of Neurology research scholar, she conducted research in neurology published in the journal *Stroke*. She completed her diagnostic radiology residency at Johns Hopkins Hospital in Baltimore, where she was chief resident, and subspecialized in musculoskeletal radiology at National Orthopedic Imaging Associates in San Francisco with Dr. David Stoller.

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