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Lean tissue mass measurements by dual-energy X-ray absorptiometry and associations with strength and functional outcome measures in facioscapulohumeral muscular dystrophy

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Authors' contributions

LHW, RT, JS, KRW designed the study. LHW, RT, JS, KRW, MRP, DL executed the protocol. LHW drafted the manuscript. LHW and SL analyzed the data. DL, SL, RT, JS, MM, KRW edited the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Human Subjects Committee at KUMC, with written informed consent obtained for all participants.

Consent for publication

This was part of the informed consent.

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Abstract

Facioscapulohumeral muscular dystrophy (FSHD) is a slowly progressive disease of skeletal muscle. Dual energy X-ray absorptiometry (DEXA) is a widely available, cost-effective and sensitive technique for measuring whole body and regional lean tissue mass and has been used in prior clinical trials in neuromuscular diseases. The Clinical Trial Readiness to Solve Barriers to Drug Development in FSHD (ReSolve) study is a prospective, longitudinal, observational multisite study. We obtained concurrent DEXA scans and functional outcome measurements in 185 patients with FSHD at the baseline visit. We determined the associations between lean tissue mass in the upper and lower extremities and corresponding clinical outcome measures. There were moderate correlations between upper and lower extremity lean tissue mass and their corresponding strengths and function. Lean tissue mass obtained by DEXA scan may be useful as a biomarker in future clinical trials in FSHD.

Keywords

Facioscapulohumeral muscular dystrophy; Imaging markers; Patient reported outcome; Leg strength

1. INTRODUCTION:

Facioscapulohumeral muscular dystrophy (FSHD), one of the most common muscular dystrophies in adulthood, is heterogeneous in its presentation and progression of muscle weakness. FSHD type 1 is due to a contraction of the D4Z4 repeats at the 4q35 chromosome. The disease manifestations are variable and mostly slow in progression, necessitating the identification and validation of measures that can inform treatment efficacy over a time period that is feasible for the conduct of a clinical trial. An imaging biomarker is important because it can provide an objective endpoint not subject to the learning effect that can affect ambulatory functional outcome measures.[1] One imaging modality that has been studied in FSHD is muscle magnetic resonance imaging (MRI). Several groups have demonstrated that MRI measures can detect FSHD disease progression over a relatively short time scale. The primary finding is an increase in fatty infiltration of approximately 2-5% per year in actively progressing muscles.[2–5] MRI-based outcome measures have also been deployed as secondary outcome measures in a phase II placebo-controlled clinical trial of losmapimod in 80 patients (NCT04003974). However, muscle MRI is expensive and time consuming, both in acquisition and analysis of images. An imaging biomarker that is rapidly acquired and inexpensive can be useful in early phase exploratory studies or as a secondary outcome measure in larger efficacy studies.

DEXA has been used successfully in the assessment of whole-body and regional composition (upper extremities, lower extremities, trunk) in patients with neuromuscular diseases.[6–10] One advantage of DEXA scans is that they use very small amounts of x-ray energy (0.5 to 1.0 mREM compared to 20–30 mREM for a chest x-ray) to measure body composition in terms of the bone, muscle, and fat fractions. Two clinical trials in FSHD have

used DEXA scans to estimate lean tissue mass. In a 12-week study of prednisone, the lean tissue mass as measured by DEXA scans exhibited a nonsignificant decrease of 1.17 kg in 8 treated patients.[11] In a randomized, double-blind, placebo-controlled 52-week clinical trial of albuterol, a small, dose dependent albuterol-associated increase in lean tissue mass was detected.[12]

Studies in neuromuscular diseases have demonstrated that lean tissue mass measured by DEXA correlates with functional outcome measures and strength.[9, 10, 13–18] Skalsky et al. studied 14 FSHD patients and found that the amount of lean tissue mass in the arm and thigh correlated with arm and thigh strength, respectively.[10] In Duchenne muscular dystrophy, Sherlock et al. found that lean body mass correlated with functional outcome measures such as the time to climb 4 stairs and the North Star Ambulatory Assessment total score.[19]

The Clinical Trial Readiness to Solve Barriers to Drug Development in FSHD (ReSolve) study, a large international, prospective, longitudinal, observational study in FSHD (NCT03458832), obtained DEXA scans and functional outcome measurements in 185 ambulatory adult patients with FSHD type 1. The available baseline data allowed us to assess whether DEXA-scan-derived outcomes are associated with strength and function in FSHD patients.

2. MATERIALS AND METHODS

2.1 Participants

The ReSolve study is an observational study conducted by the FSHD Clinical Trial Research Network in which participants were prospectively followed for up to 24 months between 2018 and 2023. Patients were genetically confirmed FSHD1 patients or clinically affected with a positive family history; clinically affected with limb weakness yet still independently ambulatory; and without other conditions affecting measurements. Participants who could potentially become pregnant had pregnancy tests performed prior to testing. One hundred eighty-five participants from eight sites in the United States and two sites in Europe (Netherlands and Italy) had DEXA scans performed at baseline.

2.2 Standard protocol approvals, registrations, and patient consents

For US centers, the study was approved by the Human Subjects Committee at a central Institutional Review Board at Kansas University Medical Center, with written informed consent obtained from all participants. For the European centers, the study was approved at each center.

2.3 DEXA body composition analysis

DEXA total body scans were performed at each site (using the Hologic or Lunar systems; see Supplemental Table 1) to obtain regional body composition measurements divided into three compartments: lean tissue mass, fat tissue mass, and bone mineral content. The entire body was scanned from the top of the head to the feet. Post-processing software divided the body into regional body compositions of upper extremity (UE), torso, and lower extremity

(LE). The upper extremity regions were measured from an upper border formed by drawing a vertical line passing through the shoulder joint to the tips of the fingers. The lower extremity regions were measured from an upper border formed by drawing an oblique line passing through the femoral neck to the tip of the feet. Percent lean tissue mass was calculated as the lean tissue mass divided by the sum of lean tissue mass, fat tissue mass and total bone mineral content. One site (n=15) did not separate arm and leg regions into right and left.

2.4 Strength testing

Strength testing was performed using manual muscle testing (MMT) and fixed quantitative muscle testing (QMT).[20] QMT was performed using a fixed myometry testing system, with a force transducer attached by an inelastic strap to a metal frame. QMT strength was measured bilaterally for the shoulder abductors, elbow flexors, and elbow extensors in the arms; knee flexors, knee extensors, and foot dorsiflexors in the legs; and converted to Newtons (N) and summated for each limb. For MMT, a modified Medical Research Council 10-point scale was used with standardized positions for each muscle.[11] The composite MMT score for the legs consisted of summed scores for the hip flexors, hip extensors, hip adductors, hip abductors, knee extensors, knee flexors, ankle plantar flexors, and ankle dorsiflexors.

2.5 Functional outcome assessments

Of the functional assessments obtained in the study, we focused our analysis on three established ambulatory functional assessments of lower extremity function: 6-minute walk test (6MWT), 10-meter walk/run (10MWR), and timed-up-and-go (TUG).[21] The 10MWR measures how fast one is able to traverse 10 meters walk or running and is expressed as meters per second. The 6MWT is a test of functional exercise capacity that measures the distance an individual can walk on a level surface in 6 minutes using a 20-meter length (40-meter lap) course. Timed-up-and-go is a measure of lower extremity function, mobility, and balance—measuring the amount time to stand up from a chair, walk three meters, turn around, and return to a sitting position in the same chair.

Upper extremity function was assessed with the Upper Extremity Function Index, a patient-reported outcome measure consisting of 20 questions on a 5-point rating scale querying activities of daily living involving the upper extremity.[22]

2.6 Clinical assessments

Clinical assessments used in this study included Clinical Severity Score (CSS), a validated, 10-grade overall clinical severity scale (0=unaffected, 10=wheelchair dependent).[23]

2.7 Statistical Analysis

Relationships between DEXA lean tissue mass and strength, and between percent lean tissue mass (normalized to the individual’s total mass) and functional measures, were explored by calculating Spearman rank correlation coefficients and corresponding 95% confidence intervals (CI). We also described relationships between lean tissue mass (X) and strength

and functional measures (Y) by creating scatter plots and overlaying locally weighted scatterplot smoothing (lowess) curves.

3. RESULTS

3.1 Demographics

We studied 185 patients with DEXA scans at baseline. There was a slight male predominance (101 male: 84 female). The median age of the cohort was 52 (Table 1). Most patients self-identified as non-Hispanic white.

3.2 Whole body composition analysis

There was a wide distribution of whole-body lean tissue mass (Table 2). There were no notable correlations between lean body mass and age of symptom onset, disease duration since symptom onset, D4Z4 repeat size contraction at the FSHD1 locus/chromosome 4q35, and CSS (Supplemental Table 2). Females had lower average lean tissue mass than males at all ages (data not shown).

3.3 Upper extremity lean tissue mass is moderately correlated with arm strength

Regional upper extremity lean tissue mass was evaluated separately on each side. Only 140 patients had QMT scores for the upper extremities and a DEXA scan. One site did not measure QMT (n=26), one site did not separate regional lean tissue mass into right and left upper and lower extremities (n=15), and four other patients did not perform the QMT. There were moderate correlations between upper extremity strength and lean tissue mass in both the right and left upper extremities (Spearman's rho 0.48-0.50, Table 3). The correlation between upper extremity percent lean tissue mass and the Upper Extremity Function Index was weaker (Spearman's rho = 0.33, Figure 1C).

3.4 Lower extremity lean tissue mass is moderately correlated with leg strength and function

Regional leg lean tissue mass was evaluated based on the side of the legs. There were moderate correlations between lower extremity strength and lean tissue mass in both the right and left lower extremities (Spearman's rho 0.66-0.69, Table 4, Figure 2A–B). We explored the associations between percent lean tissue mass and the clinical outcome measures. There were moderate correlations between the lower extremity percent lean tissue mass and timed functional outcome measures (Spearman's rho 0.56 for 6MWT, 0.58 for 10MWR, and −0.40 for TUG) (Figure 3).

4. DISCUSSION

FSHD is a slowly progressive disease of muscle loss. The slow and uneven loss of strength and function necessitates identifying objective measurements that are associated with function and strength, widely available, easily acquired, and economically/conveniently analyzed. Muscle MRI has been recently and quickly adopted by the field and assessed in a phase II clinical trial of losmapimod. However, as of now, the acquisition of MR images necessitates standardization, time, and sufficient financial investment. The analysis

of images is the most expensive component, making this endpoint only available only in well-funded studies. An alternative radiological modality, such as DEXA scan, provides a measurement that is quickly obtained and more economical—perhaps for safety and dose-finding studies. However, there have been few data thus far evaluating whether the measurements found on DEXA are associated with strength and function. Skalsky et al. assessed 14 patients with FSHD and found strong correlations between arm and thigh lean tissue mass and strength (r=0.79 and 0.88, respectively).[10] The availability of baseline data from the ReSolve FSHD study allows for further confirmation of those findings in a larger patient cohort in an international multi-center setting, while also evaluating associations between lean tissue mass and functional outcome measures.

We found moderate correlation between arm strength and lean tissue mass in both the right and left upper extremities and between leg strength and lean tissue mass in both the right and left legs. These correlations are weaker than those reported by Skalsky et al., and perhaps reflect the heterogeneity of a larger multi-center study.

We found that percent lean tissue mass normalized to total volume of tissue was more strongly associated with functional tasks where the relative proportion of lean mass to the total volume including other body compartments better reflects disease state, whereas the lean tissue mass (in raw kg) better corresponded to quantitative strength for a given muscle/region.

Our findings suggest that DEXA scans could serve as an easy and economical outcome measure in early-phase studies (e.g., safety and dose-ranging studies) and as a secondary endpoint in efficacy trials. However, DEXA does not provide the level of detail seen on muscle MRIs. For instance, it cannot provide the amount of muscle or fat fraction for each compartment, allowing for direct comparison between muscle compartments/groups and specific muscle function such as the biceps and elbow flexion. Furthermore, DEXA only estimates lean tissue mass and not lean muscle mass, as it has contributions from skin, connective tissue, and interstitial fat. DEXA images only provide 2-dimensional images of lean tissue mass, in contrast to MRI images, which can provide 3-dimensional volumes of the whole muscle.

In addition to the inexactness of the measurement of muscle mass, the other limitation of our study is that we only measured the QMT strength of selective limb muscles because those measurements are more reproducible. This makes for imprecise comparison of the QMT strength of our selected limb muscles to the lean muscle mass of the whole limb.

Another limitation is that our study acquired images from different machines, which had different analytic systems for delineating arms and legs, and one site did not report the lean tissue mass of the separate (right/left) arms or legs. More standardization in acquisition and analysis could perhaps decrease variance. The next step in validation of DEXA as an outcome measure would be determining whether progressive loss of muscle strength and function is reflected in the loss of lean tissue mass longitudinally, and whether it could be detected within a relatively short period of time. The analysis of the longitudinal data in the ReSolve study will be illuminating and is anticipated soon.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Competing interests:

LHW reports consultancy/advisory board for Fulcrum Therapeutics, Argenx, Avidity, Ultragenyx, PepGen, data safety monitoring board for Scholar Rock. KE has served on advisory boards or has received consulting fees from Biogen, Acceleron, PTC, Ionis Pharmaceuticals, Fulcrum Therapeutics, Dyne Therapeutics, Avidity Biosciences and Roche. RNT reports consultancy with Fulcrum Therapeutics, Arrowhead, Dyne Therapeutics, Acceleron, MT Pharma, miRecule, and Roche Pharma. JS has served as consultant for Arrowhead, ML Bio, MT Pharma, Epic Bio, Armatus; served on a Scientific Advisory or Data Safety Monitoring board for Dyne Therapeutics, Avidity, Fulcrum Therapeutics, Roche. PS has served as consultant for Sarepta, Genentech, Biogen, Alexion, Argenx, UCB; served on speakers' bureaus for CSL Behring, Grifols, Alexion, Biogen, Genentech, Argenx, Catalyst. KRW is an employee of F. Hoffmann-La Roche Ltd. BE received research funding from Biogen, Genentech, Alexion, Pharnext, and Viela Bio and served as a consultant for Biogen, Genentech, and Argenx. NJ has received grant funding from NINDS (R01NS104010), NCATS (21TR003184), CDC (U01DD001242-02) and the FDA (7R01FD006071-02). He receives royalties from the CCMDHI and the CMTHI; receives research funds from Dyne, AveXis, Takeda, Sanofi Genzyme, Pepgen, Vertex Pharmaceuticals, Fulcrum Therapeutics, Sarepta, and AskBio; has provided consultation for Takeda, Pepgen, Arthex, AveXis, AMO Pharma, Fulcrum Therapeutics, Dyne, Avidity, and Vertex Pharmaceuticals. KM reports consultancy for Avidity Biosciences. RJB reports consultancy/advisory board for Aavanti Bio, Scholar Rock, Avexis, Pfizer, Reata, and Sarepta Therapeutics. SLO, MRP, MD have no disclosures.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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HIGHLIGHTS

1. There is moderate correlation between upper extremity lean tissue mass as measured by DEXA scans and their corresponding strengths measured by quantitative muscle testing
2. There is moderate correlation between lower extremity lean tissue mass and corresponding strength measured by quantitative muscle testing and manual muscle testing
3. There is moderate correlation between bilateral lower extremity lean tissue mass and 6-minute walk test, 10-meter walk/run, and timed-up-and-go

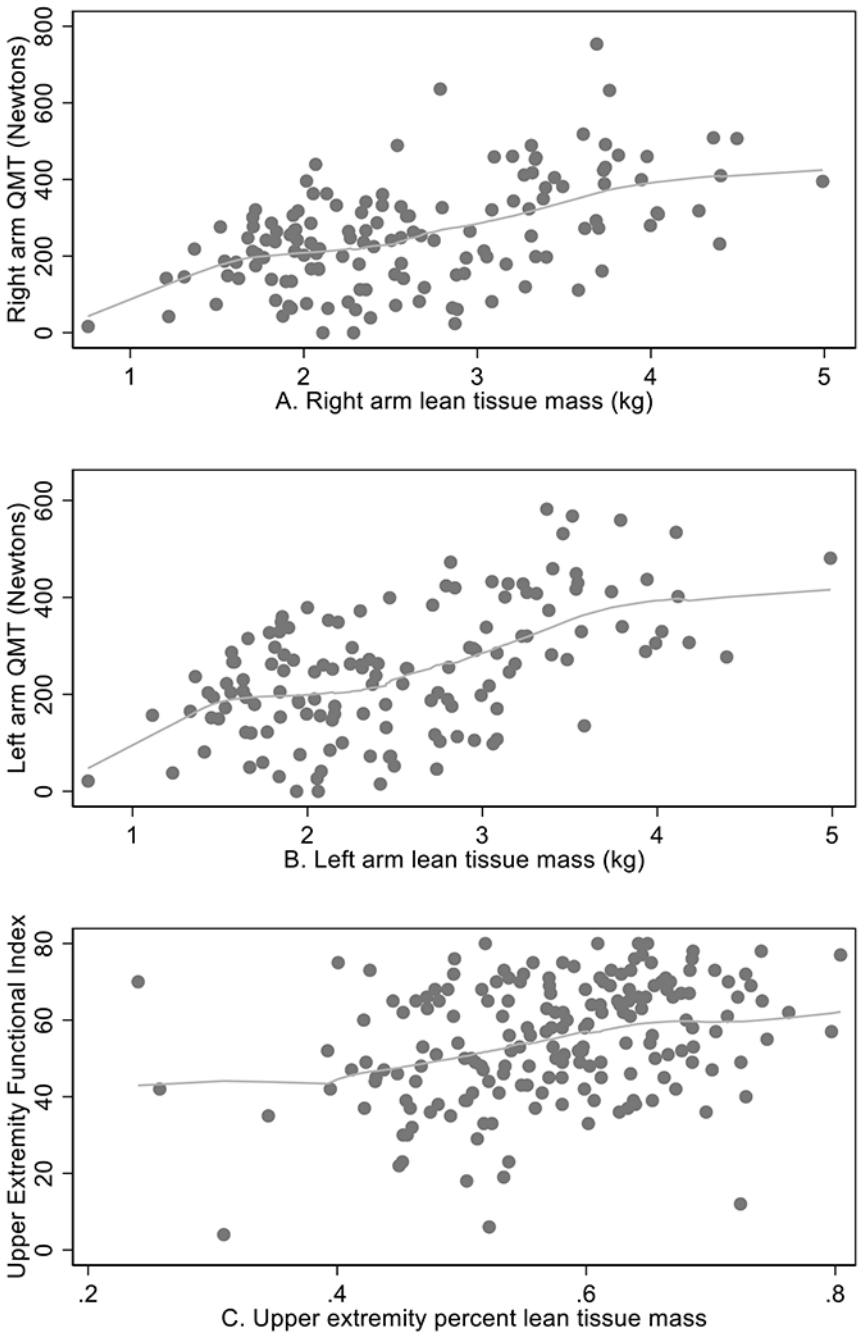

Figure 1.

Associations between upper extremity lean tissue mass (kg) and strength and functional outcome measures.

A. QMT strength of right shoulder abduction, elbow flexion, and elbow extension (Newtons) vs right upper extremity lean tissue mass (Spearman's rho = 0.48, 95% CI 0.34-0.60) with an overlaid lowess curve

B. QMT strength of left shoulder abduction, elbow flexion, and elbow extension (Newtons) compared to left upper extremity lean tissue mass (Spearman's rho = 0.50, 95% CI 0.36-0.61) with an overlaid lowess curve

C. Upper extremity function index vs bilateral upper extremity percent lean tissue mass (Spearman's rho = 0.33, 95% CI 0.19-0.45) with an overlaid lowess curve

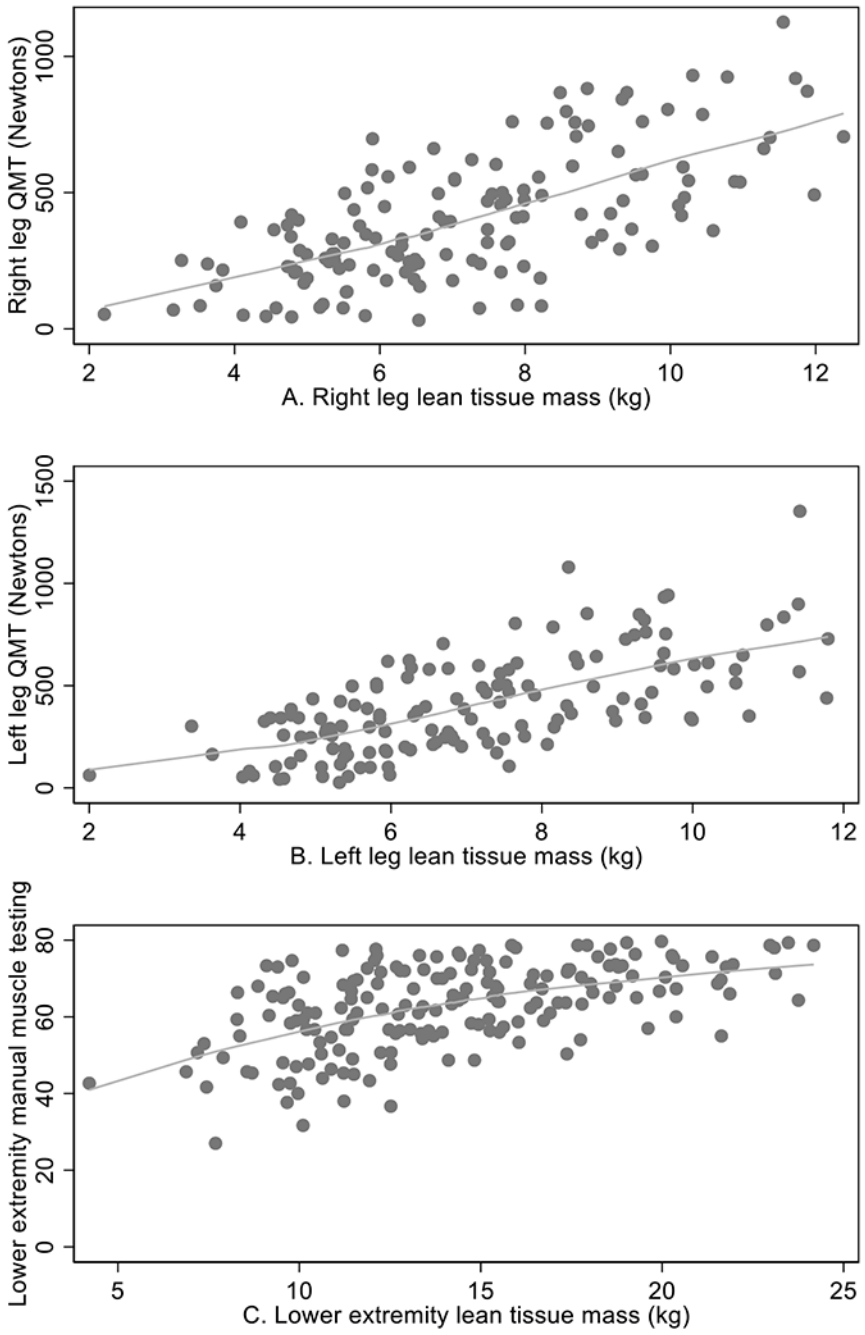

Figure 2.

Associations between lower extremity lean tissue mass (kg) and strength and functional outcome measures.

A. QMT strength of right knee extension, knee flexion, and ankle dorsiflexion vs right leg lean tissue mass (Spearman's rho = 0.66, 95% CI 0.55-0.74) with an overlaid lowess curve

B. QMT strength of left knee extension, knee flexion, and ankle dorsiflexion vs left leg lean tissue mass (Spearman's rho = 0.67, 95% CI 0.57-0.75) with an overlaid lowess curve

C. Lower extremity manual muscle testing (MMT) strength vs lower extremities lean tissue mass (Spearman’s rho = 0.52, 95% CI 0.41-0.62) with an overlaid lowess curve

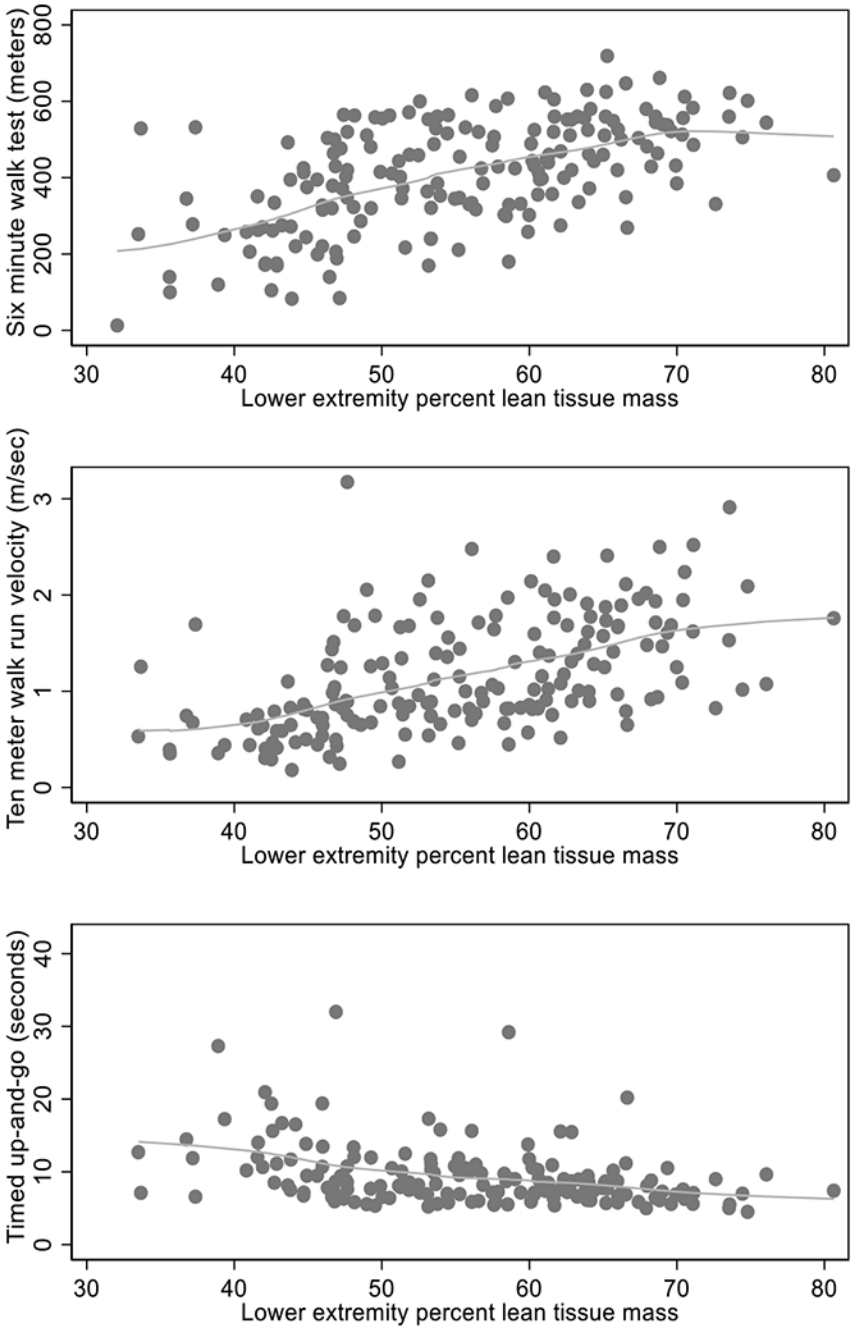

Figure 3.

Associations between lower extremity percent lean tissue mass and functional outcome measures (6MWT, 10MWR, TUG)

A. Six-minute walk test (6MWT) (seconds) vs lower extremity percent lean tissue mass (Spearman's rho = 0.56, 95% CI 0.45 to 0.65; n=183) with an overlaid lowess curve

B Ten meter walk run gait speed (10MWR) (meters per second) vs lower extremity percent lean tissue mass (Spearman's rho = 0.58, 95% CI 0.48-0.67; n=181) with an overlaid lowess curve

C. Timed up-and-go (TUG) (seconds) vs lower extremity percent lean tissue mass (Spearman's rho = −0.40, 95% CI −0.52 to −0.26; n=169) with an overlaid lowess curve

Table 1:

Demographic and clinical characteristics at baseline.

	median (IQR)
Age (years)	52.0 (38.0, 61.0)
Age at diagnosis (years)	34.0 (21.0, 48.0)
Age at symptom onset (years)	19.5 (14.0, 33.5)
Years since diagnosis	13.0 (6.0, 20.0)
Years since symptom onset	21.0 (14.0, 35.0)
Number of D4Z4 repeats	6.0 (5.0, 7.0)
Clinical severity score	6.0 (3.0, 7.0)
	N (%)
Sex	
Female	84 (45.4%)
Male	101 (54.6%)
Race	
American Indian	1 (0.5%)
Asian American	4 (2.2%)
Black American	1 (0.5%)
Mixed race	4 (2.2%)
Unknown	4 (2.2%)
White	171 (92.4%)
Hispanic	
No	175 (94.6%)
Yes	10 (5.4%)
Country	
Italy	24 (13.0%)
Netherlands	23 (12.4%)
US	138 (74.6%)

IQR: interquartile range. Data missingness for all variables shown was <2%

Table 2:

DEXA values at baseline.

	Median (IQR)	N
Whole body lean tissue mass (kg)	44.9 (37.1, 51.9)	185
UE lean tissue mass (kg)	4.8 (3.9, 6.4)	185
LE lean tissue mass (kg)	13.8 (11.2, 17.3)	185
Right UE lean tissue mass (kg)	2.4 (2.0, 3.3)	170
Left UE lean tissue mass (kg)	2.4 (1.9, 3.1)	170
Right LE lean tissue mass (kg)	6.9 (5.4, 8.5)	170
Left LE lean tissue mass (kg)	6.7 (5.4, 8.4)	170
Whole body percent lean tissue mass	57.7 (52.5, 63.1)	185
UE percent lean tissue mass	58.0 (50.8, 64.2)	185
LE percent lean tissue mass	55.3 (47.1, 63.3)	185
Right UE percent lean tissue mass	57.0 (50.4, 64.7)	170
Left UE percent lean tissue mass	57.6 (50.4, 65.1)	170
Right LE percent lean tissue mass	53.9 (46.8, 63.3)	170
Left LE percent lean tissue mass	55.2 (47.1, 62.7)	170

IQR: Interquartile range; UE: Upper extremity; LE: Lower extremity

Table 3:

Correlations between upper extremity (UE) DEXA lean tissue mass and QMT strength of shoulder abduction, elbow flexion, and elbow extension (Spearman's rho)

	Spearman's rho (95% CI)		
	Left UE lean tissue mass (kg)	**Right UE lean tissue mass (kg)**	**N**
Left UE lean tissue mass (kg)	1.00		
Right UE lean tissue mass (kg)	0.95 (0.94-0.97)	1.00	170
UE lean tissue mass (kg)	0.99 (0.98-0.99)	0.99 (0.98-0.99)	170
Left UE QMT strength (N)	0.50 (0.36-0.61)	0.56 (0.44-0.66)	140
Right UE QMT strength (N)	0.44 (0.30-0.56)	0.48 (0.34-0.60)	141
Bilateral UE QMT strength (N)	0.48 (0.34-0.59)	0.53 (0.40-0.64)	140

CI: Confidence interval; UE: Upper extremity; LE: Lower extremity

Table 4:

Correlations between lower extremity (LE) DEXA lean tissue mass and QMT strength of knee extension, knee flexion, and dorsiflexion (Spearman's rho)

	Spearman's rho (95% CI)		
	Left leg lean tissue mass (kg)	**Right leg lean tissue mass (kg)**	**N**
Left LE lean tissue mass (kg)	1.00	0.96 (0.94 to 0.97)	170
Right LE lean tissue mass (kg)	0.96 (0.94 to 0.97)	1.00	170
LE lean tissue mass (kg)	0.99 (0.98 to 0.99)	0.99 (0.99 to 0.99)	170
Left LE QMT strength (N)	0.67 (0.57 to 0.75)	0.68 (0.58 to 0.76)	141
Right LE QMT strength (N)	0.69 (0.59 to 0.77)	0.66 (0.55 to 0.74)	142
Bilateral LE QMT strength (N)	0.69 (0.59 to 0.77)	0.68 (0.58 to 0.76)	140

CI: Confidence interval; UE: Upper extremity; LE: Lower extremity