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Original Articles

The relationship between quantitative magnetic resonance imaging of the ankle plantar flexors, muscle function during walking and maximal strength in people with neuromuscular diseases

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ABSTRACT

Background: Progression of plantar flexor weakness in neuromuscular diseases is usually monitored by muscle strength measurements, although they poorly relate to muscle function during walking. Pathophysiological changes such as intramuscular adipose tissue affect dynamic muscle function independent from isometric strength. Diffusion tensor imaging and T2 imaging are quantitative MRI measures reflecting muscular pathophysiological changes, and are therefore potential biomarkers to monitor plantar flexor functioning during walking in people with neuromuscular diseases.

Methods: In fourteen individuals with plantar flexor weakness diffusion tensor imaging and T2 scans of the plantar flexors were obtained, and the diffusion indices fractional anisotropy and mean diffusivity calculated. With a dynamometer, maximal isometric plantar flexor strength was measured. 3D gait analysis was used to assess maximal ankle moment and power during walking.

Findings: Fractional anisotropy, mean diffusivity and T2 relaxation time all moderately correlated with maximal plantar flexor strength ($r > 0.512$). Fractional anisotropy and mean diffusivity were not related with ankle moment or power ($r < 0.288$). T2 relaxation time was strongly related to ankle moment ($r = -0.789$) and ankle power ($r = -0.798$), and moderately related to maximal plantar flexor strength ($r < 0.600$).

Interpretation: In conclusion, T2 relaxation time, indicative of multiple pathophysiological changes, was strongly related to plantar flexor function during walking, while fractional anisotropy and mean diffusivity, indicative of fiber size, only related to maximal plantar flexor strength. This indicates that these measures may be suitable to monitor muscle function and gain insights into the pathophysiological changes underlying a poor plantar flexor functioning during gait in people with neuromuscular diseases.

1. Introduction

The plantar flexors are essential for an efficient gait pattern (Waterval et al., 2018). During stance the plantar flexors control the forward movement of the center-of-pressure anterior of the ankle, thereby resisting a large external dorsiflexion moment, while later in the gait cycle the plantar flexors provide ankle push-off power (Neptune et al., 2001). In many neuromuscular diseases (NMD) the plantar flexors become progressively weaker, reducing walking ability as the maximal ankle moment and power diminish (Bouza et al., 2005; Reilly et al.,

Abbreviations: NMD, Neuromuscular disease; DTI, Diffusion tensor imaging; MVT, maximum voluntary torque; FA, fractional anisotropy; MD, mean diffusivity; T2, T2 transverse relaxation time; PCA, principle-component-analysis; EPG, extended phase graph; FOV, field of view; SENSE, sensitivity encoding; SPAIR, spectrally selective attenuated inversion recovery; SPIR, spectral pre-saturation with inversion recovery; SSGR, slice selection gradient reversal.

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2011; Sunnerhagen and Grimby, 2001; Waterval et al., 2021) and inefficient hip compensations are needed to maintain a steady state walking speed (Silverman et al., 2008; Waterval et al., 2018). Usually the decline in muscle function is monitored by isometric strength measurements. However, these strength measures lack sensitivity to change (Bickerstaffe et al., 2014; Bohannon, 2005; Horemans et al., 2004; Nollet and Beelen, 1999) and only moderately relate to plantar flexor function during daily life activities such as walking (Dallmeijer et al., 2011; Kahn and Williams, 2015).

Additionally, strength measures do not provide information about intramuscular pathophysiological changes, such as higher intramuscular fat tissue, underlying the reduced muscle function. These pathophysiological muscle changes can affect contractile functions such as muscle shortening velocity (Mota et al., 2018; Straight et al., 2019), power at high rotational speeds (Gerstner et al., 2017; Gerstner et al., 2018) and maximal torque (Frank-Wilson et al., 2018) independent from isometric muscle strength. This may, at least partly, explain why maximal isometric strength and dynamic muscle function during walking are not strongly related in patient populations. Pathophysiological muscle changes can be non-invasively assessed using conventional Magnetic Resonance Imaging (MRI) in combination with Diffusion tensor imaging (DTI) and quantitative T2 mapping (Budzik et al., 2014; Morrow et al., 2016; Simon et al., 2016). DTI measures the diffusivity of water within tissue. In skeletal muscle, diffusion is highest along the primary direction of the muscle fiber (Kuo and Carrino, 2007) while diffusion is lower in the perpendicular directions (Oudeman et al., 2016). As cellular membranes are barriers for diffusion, a higher Mean Diffusivity (MD) can reflect increases in the extracellular fluid due to cell damage (Froeling et al., 2015; Hooijmans et al., 2020), while reduced MD is indicative for muscle atrophy (Berry et al., 2018). Fractional Anisotropy (FA) is a measure of how well diffusion is aligned and might be indicative of muscle fiber size (Oudeman et al., 2016). Quantitative T2 mapping allows for the quantification of muscle water content and can detect muscle denervation (Kikuchi et al., 2003), muscle atrophy (Hatakenaka et al., 2006), intramuscular fat infiltration and edema preceding muscle fat replacement (Maillard et al., 2004; Morrow et al., 2016), and as such can be considered a more general biomarker for muscle status.

Unlike conventional strength measurements, DTI and T2 measures are sensitive to change and can provide detailed information about physiological changes in healthy adults (Farrow et al., 2020; Scheel et al., 2013). Consequently, these measures may more strongly relate to plantar flexor function during gait compared to strength measures. Additionally, such pathophysiological muscle changes can be used to individualize muscle properties in simulation models and thereby help gain insights into how pathophysiological changes affect walking ability in progressive plantar flexor weakness (Carbone et al., 2016). Therefore, this study aimed to 1) determine whether MD, FA and T2 relaxation time differ between persons with a minimal and severly reduced ankle moment during walking due to plantar flexor weakness and 2) whether these parameters relate with isometric plantar flexor strength and maximal ankle moment and ankle power in adults with slowly progressive NMD.

We hypothesized that in persons with a severely reduced ankle moment due to plantar flexor weakness, pathophysiological muscle changes would be more profound and that they would have a lower MD, higher FA and higher T2 compared to those with a minimally reduced ankle moment. Additionally, we expected that T2 relaxation time best relates to ankle moment and power (Whittington et al., 2008) as it increases with more intramuscular fat infiltration and extracellular space (Hatakenaka et al., 2006; Kikuchi et al., 2003; Maillard et al., 2004), which affect dynamic muscle functioning.

2. Methods

Cross-sectional data used in this study originate from the PROOF-AFO trial (Waterval et al., 2017). The protocol of the PROOF-AFO trial was approved by the Medical Ethics Committee of the Amsterdam University Medical Center, location Academic Medical Center, The Netherlands and has been registered in the Dutch trial register (NTR 5170). All participants provided written informed consent.

2.1. Study participants

The main inclusion criteria for the PROOF-AFO trial were: diagnosed with a slowly progressive non-inflammatory neuromuscular disease, presence of non-spastic calf muscle weakness (i.e. Medical Research Council scale (MRC) score < 5) and the ability to walk barefoot (Waterval et al., 2017). Contraindications for an MRI scan such as the presence of metal corpora aliena were an exclusion criteria. In 14 out of 37 participants of the PROOF-AFO trial who met the inclusion criteria an MRI was obtained within 3-months of inclusion. The remaining 14 participants (6 males, mean age ± SD age: 60.7 ± 11.2 years, weight: 85.3 ± 18.5 kg) were diagnosed with: peripheral nerve damage ($n = 4$, a herniated disc or radiculopathy causing unilateral calf muscle weakness); post-polio syndrome (n = 4); Charcot-Marie-Tooth type 1 (n = 4); myotonic dystrophy ($n = 1$); and Myoshi myopathy (n = 1).

2.2. Magnetic resonance imaging protocol

MRI datasets of both lower legs were acquired on a 3.0 T Ingenia scanner (Philips Healthcare, Best, The Netherlands) with a 16-channel surface body coil and 12-channel table top coils. The MR examination comprised 1) a multi-echo gradient echo scan for muscle segmentation, 2) a multi-echo gradient echo scan for fat quantification, 3) Diffusion Tensor Imaging (DTI) to assess muscle microstructure and 4) multi slice multi echo spin echo (MESE) sequence for T2 relaxometry. For the DTI scan, we applied a combination of three fat suppression techniques (SPectral Attenuated Inversion Recovery (SPAIR) + Spectral Presaturation with Inversion Recovery (SPIR) + Slice-Selective Gradient Reversal (SSGR)) (Kahn and Williams, 2015). The total scan duration was approximately 45 min. Participants were placed in supine position with their legs parallel to each other and with their feet positioned in approximately 15 degrees plantar flexion to match the position of the isometric strength measurement (see below). The images were made from the knee joint to the ankle joint in two stacks with 30 mm overlap (for the MR imaging acquisition specifics see Table 1) (Schlaffke et al., 2019).

2.3. Isometric strength of the plantar flexors

Maximal isometric strength, measured as the maximal voluntary torque (MVT) of the plantar flexors of both legs was assessed with a fixed dynamometer during the first visit of the PROOF-AFO trial (System 3 PRO, BIODEX, Shirley, USA). Participants were placed in a slight supine position at 75°, with the hip and knee in approximately 90° and 60° flexion, respectively. The lower leg was placed horizontal and the ankle in 15° plantar flexion, as in this position the passive structures are unlikely to produce meaningful torque (Moseley et al., 2001). MVT was recorded three times during a 5-s maximal effort interval with 30 s rest between each assessment.

2.4. Ankle moment and power

A 3D-gait analysis for walking with shoes at comfortable speed (mean ± SD = 0.95 ± 0.22 m/s) was performed to determine the maximal ankle moment and power, which are surrogates for plantar flexor functional ability during gait. We placed markers according to the full-body PlugInGait model, which trajectories were recorded during walking with an 8-camera 100 Hz Vicon MX 1.3 system (VICON, Oxford, UK). Ground reaction forces were measured using four force plates (1000 Hz, OR6–7, AMTI, Watertown, USA). Three walking trials where each foot was placed completely on a force plate and all markers were

Table 1
MR imaging acquisition parameters.

Parameter	Multi echo gradient echo scan	DTI	T2
	3 echoes (multi-acquisition)	Spin-echo Echo-planar	Multi echo spin echo
FOV *(mm)*	384x156x200	384x156x200	384x157x199
Voxel size *(mm^3)*	1x1x10	3x3x5	1.4 × 1.8 × 7
Data matrix	384 × 156	128 × 52	276 × 87
No. of slices	14	40	9
Slice gap *(mm)*	4.65	none	17
Echo time *(msec)*	4.41	41	8
Delta Echo time *(msec)*	0.76	–	8
Repetition time *(msec)*	210	9143	3000
Flip angle *(degrees)*	8	90/180	90/180
Bandwidth (Hz/pixel)		46	
Number of b = 0 / b = 400 images		3 / 12	
b-value (s/mm^2)	–	400	–
No. of directions	–	15	–
half scan	–	0.69	–
Big delta (msec)		20.6	
Small delta (msec)		8.8	
Slope gradient (msec)		0.9	
No. of echoes	–	–	17
Refocusing angle (°)	–	–	180
Fat suppression	–	SPAIR+SPIR+SSGR	–
SENSE factor	2	–	1.5
Partial Fourier transform technique	–	0.625	–

Abbreviations. DTI = diffusion tensor imaging, T2 = quantitave T2, FOV = field of view, SENSE = sensitivity encoding, SPAIR = spectrally selective attenuated inversion recovery, SPIR = spectral pre-saturation with inversion recovery, SSGR: slice-selection gradient reversal.

visible were captured.

2.5. Data processing

All MRI data processing was performed using QMRItools for Mathematica (github.com/mfroeling/QMRITools) (Froeling et al., 2012; Schlaffke et al., 2019) and included the following steps:

- Multi echo gradient echo scan data was processed with an iterative decomposition of water and fat with echo asymmetry and least squares estimation (IDEAL) (Reeder et al., 2005) using eight reference fat peaks (Triplett et al., 2014). The algorithm was initialized with a B0 and T2* map calculated from the first and last echo.
- The DTI data were first filtered with a principle-component-analysis (PCA)-noise suppression algorithm (Veraart et al., 2013). After which the noise suppressed data were corrected for motion and eddy currents using affine registration (Leemans and Jones, 2009). Finally, the tensor was calculated with an iterative weighted linear least-squares algorithm (iWLLS) with REKINDLE outlier rejection (Tax et al., 2015; Veraart et al., 2016).
- The T2 data was processed using an extended phase graph (EPG) fitting approach (Keene et al., 2020; Marty et al., 2016). First, the T2 fat relaxation time of each subject was obtained from the subcutaneous fat. Second, with a fixed value for the T2 fat relaxation, both T2 water relaxation times and B1+ were fitted for each voxel using a dictionary method.

Using the multi-echo gradient echo, the soleus muscle and the medial and lateral head of the gastrocnemius muscle were manually segmented using ITK-SNAP (version 3.6.0, itksnap.org) (Yushkevich et al., 2006). For all three muscles, we calculated the fat fraction (using the multi-echo gradient echo scan), fractional anisotropy (FA) and mean diffusivity (MD) (using the DTI scan) and T2 relaxation time (using the T2 relaxometry scan) over the whole muscle volume (Le Bihan et al., 2001).

Total volume of the plantar flexors was calculated by summing the volume of the soleus muscle, and medial and lateral head of the gastrocnemius muscle. Additionally, we averaged the FA, MD and T2 relaxation time of these muscles to obtain the average value for all plantar flexors combined.

2.5.1. Isometric muscle strength

The highest recorded torque of the three maximal voluntary contractions was used for analysis. To account for the effect of weight on maximal muscle force, the maximal torque was divided by the participants weight to calculate MVT per kilogram (MVT/kg). If the MVT/kg was within one standard deviation of our laboratories reference database the leg was classified as minimally affected, otherwise as severely affected.

2.5.2. Ankle moment and power

Within VICON Nexus (VICON, Oxford, UK), the gait cycles were identified based on ground reaction forces, e.g. first frame with a recorded force, which was checked using the video recordings. For each gait cycle, we checked whether all markers were visible and correctly labelled during the steps on the force plate before processing the marker trajectories. After validation of correct marker trajectories, the maximal ankle moment and power during the stance phase were calculated. Before averaging the maximal ankle moment and power across the three recorded trials, we checked whether no unexplained large variation in gait parameters existed between the trials.

2.6. Statistical analysis

To avoid dependency between the legs we only analyzed data of the strongest leg, as determined by the MVT/kg. First, we classified the plantar flexors as having a minimally reduced or severely reduced plantar flexor function during gait based on the maximal ankle moment, with a cut-off of 1.2 Nm/kg, and analyzed whether these plantar flexors differed in remaining muscle strength, total muscle volume, fat fraction, FA, MD and T2 relaxation time using independent *t*-test. Secondly, we tested the relation of maximal plantar flexor strength (MVT/kg), ankle moment and ankle power with total muscle volume, fat fraction, FA, MD and T2 relaxation time using Pearson's correlation coefficients (or Spearman in case of non-normally distributed data). As a comparison the correlation between MVT/kg and ankle moment and ankle power was tested. A correlation coefficient < 0.3 was considered weak, between 0.3 and 0.5 fair, between 0.5 and 0.7 moderate and above 0.7 strong (Chan, 2003).

The level of significance was set at $p < 0.05$ for comparing the legs with a minimally and severely reduced plantar flexion function during gait. For the correlation analysis, we set the significance level to $p < 0.01$ to correct for multiple testing. All statistical analyses were performed using SPSS statistical software (version 24.0, SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Difference between muscle with normal and reduced plantar flexor strength

Of the 14 participants, seven had a minimally reduced ankle moment and seven a severely reduced ankle moment. Severely affected plantar flexors had a significant higher T2 relaxation time ($p = 0.001$) compared to plantar flexors with a minimally reduced ankle moment, while no

significant difference for MD ($p = 0.665$), FA ($p = 0.494$), MVT/kg ($p = 0.173$), muscle volume ($p = 0.917$) or fat fraction ($p = 0.727$) was found (Table 2).

3.2. Relation of QMRI measures with maximal ankle moment and ankle power during walking

FA and MD were not correlated with maximal ankle moment or power ($r < 0.28$, $p > 0.318$), while T2 relaxation time was strongly and significantly correlated with maximal ankle moment ($r = -0.79$, $p = 0.001$) and ankle power ($r = -0.80$, $p = 0.001$). Muscle volume and fat fraction were not correlated with maximal ankle moment or power ($r < 0.20$, $p > 0.493$). MVT/kg was moderately correlated, although not significantly, with ankle moment ($r = 0.60$, $p = 0.023$) and with ankle power ($r = 0.54$, $p = 0.047$) (Fig. 1, Table 3).

3.3. Relationship of QMRI measures with maximal plantar flexor strength

MD showed a strong significant correlation ($r = 0.67$ $p = 0.009$) with MVT/kg, while FA ($r = -0.51$) and T2 relaxation time ($r = -0.63$) were non-significant moderately related with MVT/kg ($p < 0.061$) (Fig. 2, Table 3). Additionally, muscle volume ($r = 0.593$, $p = 0.026$) and fat fraction ($r = -0.66$, $p = 0.011$) were moderately correlated with MVT/kg ($r = 0.521$, $p = 0.056$).

4. Discussion

We demonstrated that in people diagnosed with NMD and slowly progressive plantar flexor weakness, T2 relaxation time was the only quantitative MRI measure that differed between plantar flexors with a minimally reduced and severely reduced ankle moment. Additionally, T2 relaxation time strongly related with ankle moment and power, while MD and FA were not. Contrary, MD and FA were in addition to T2 moderately correlated with muscle strength. These findings imply that DTI and T2 relaxation time reflect different muscle properties affecting muscle function and can, in combination, help gain insight into pathophysiological changes underlying a poor muscle function.

Contrary to our hypothesis, only T2 relaxation time differed significantly between plantar flexors with a minimally and severely reduced function during walking, while these muscle groups did not differ for FA or MD. We expected the muscles with a severely reduced function during walking to be more affected by the disease, and hence have a lower strength and smaller muscle fibers demonstrated by differences in FA and MD (Scheel et al., 2013). However, apparently muscle function during walking deteriorates already before changes are reflected by FA and MD, likely due to alterations in muscle architecture reflected by T2 imaging (Thom et al., 2007). Given these outcomes it is not surprising that T2 relaxation time was the only variable demonstrating a strong relation with ankle moment and ankle power. That T2 relaxation time correlated better with muscle moment and power compared to FA and MD has been demonstrated previously in the quadriceps and hamstring muscles of elderly subjects (Farrow et al., 2020). Where FA and MD are mainly indicative for muscle atrophy, changes in T2 relaxation time can be indicative for multiple pathophysiological changes occurring with slowly progressive NMD such as increase in extracellular water content (Maillard et al., 2004), muscle atrophy (Hatakenaka et al., 2006), increase in type 1 fibers (Azzabou et al., 2015) and ongoing intramuscular fat accumulation (Morrow et al., 2016). These pathophysiological changes, not all reflected by FA and MD, can affect the passive elements and contractile properties of the muscle which substantially contribute to plantar flexor function during walking (Whittington et al., 2008). Moreover, these pathophysiological changes may cause a lower shortening velocity (Mota et al., 2018), reduce force production at higher rotational speeds (Gerstner et al., 2017; Gerstner et al., 2018) and, consequently, are likely to require the activation of more muscle mass to produce the same power output (Umberger et al., 2003). These effects are not reflected by MD, FA, or even maximal muscle strength, explaining why T2 relaxation time is the only MRI parameter related to plantar flexor function during walking.

As hypothesized, a lower MD, higher FA and higher T2 were all related with a lower plantar flexor strength, which is in agreement with findings from previous studies in spinal muscular atrophy patients (Otto et al., 2020), elderly (Farrow et al., 2020) and patients with diabetes (Stouge et al., 2020). A lower MD and higher FA are caused by increases in the extracellular fluid and more aligned diffusion, indicative of muscle atrophy (Malis et al., 2019; Otto et al., 2020). Atrophy is hypothesized to first affect type 2 fibers, explaining its relation with maximal strength (Sinha et al., 2015). However, our correlations between MRI variables and strength were somewhat lower compared to previous studies in healthy subject where very strong correlations have been reported (Scheel et al., 2013). Likely, the fact that some neuromuscular diseases also affect maximal neural drive (Allen et al., 1994), which can lower maximal voluntary strength irrespective of pathophysiological changes, contributed to the lower relation.

The more generic measures muscle volume and fat fraction were not related with muscle function during walking, although moderately related with maximal strength. In previous studies in polio survivors and children with Duchenne, also only fair to moderate relationships between muscle strength and volume or fat fraction were reported (Bickerstaffe et al., 2015; Grimby et al., 1996; Janssen et al., 2016; Trappe et al., 2001; Wokke et al., 2014). Although fat fraction and volume are, contrary to muscle strength, reliable and sensitive to change in NMD (Janssen et al., 2016), low muscle volume and high fat fraction are end-stage effects of pathophysiological muscle changes in case of NMD. Apparently, as our results indicate, volume and fat fraction are not related with muscle function during walking as muscle function deteriorates before these end-stage effects occur (Thom et al., 2007). MD, FA and T2 relaxation time can change before the accumulation of fat (Froeling et al., 2015; Morrow et al., 2016; Oudeman et al., 2016), making them more suitable to monitor disease progression in the early stages and to be able to quickly evaluate treatments.

Although, this cross-sectional study provided valuable insights into the relationship between quantitative MRI and muscle function during walking in slowly progressive NMD, in order to use them as biomarker for disease progression and walking performance, prospective studies with sufficient sample sizes are needed to establish its reliability and sensitivity to change. Furthermore, with larger cohorts, multivariate regression analyses can be conducted to determine which parameters are best associated with muscular function. Lastly, we related quantitative MRI variables with ankle moment and power during gait at self-selected comfortable speed, while measuring gait outcomes and plantar flexor activations at various slow and fast walking speeds would

Table 2
Comparison between plantar flexors with minimally and severely reduced ankle moment.

	Minimally reduced ankle moment ($n = 7$)	Severely reduced ankle moment ($n = 8$)
T2 relaxation time (ms)	31.33 ± 3.43	38.87 ± 3.01
FA	0.33 ± 0.06	0.31 ± 0.06
MD	1.51 ± 0.18	1.45 ± 0.24
MVT/kg (Nm/kg)	0.48 ± 0.28	0.19 ± 0.10
Muscle volume (cm2)	374 ± 176	385 ± 193
Fat fraction (%)	37.3 ± 32.9	42.6 ± 22.5
Ankle moment (Nm/kg)*	1.37 ± 0.18	0.62 ± 0.37
Ankle power (W/kg)*	3.61 ± 1.15	1.12 ± 0.76

Abbreviations. FA = Fractional Anisotropy, MD = Mean Diffusivity, MVT/kg = Maximal Voluntary Torque normalized to body mass.
* Significantly different between the groups ($p < 0.05$).

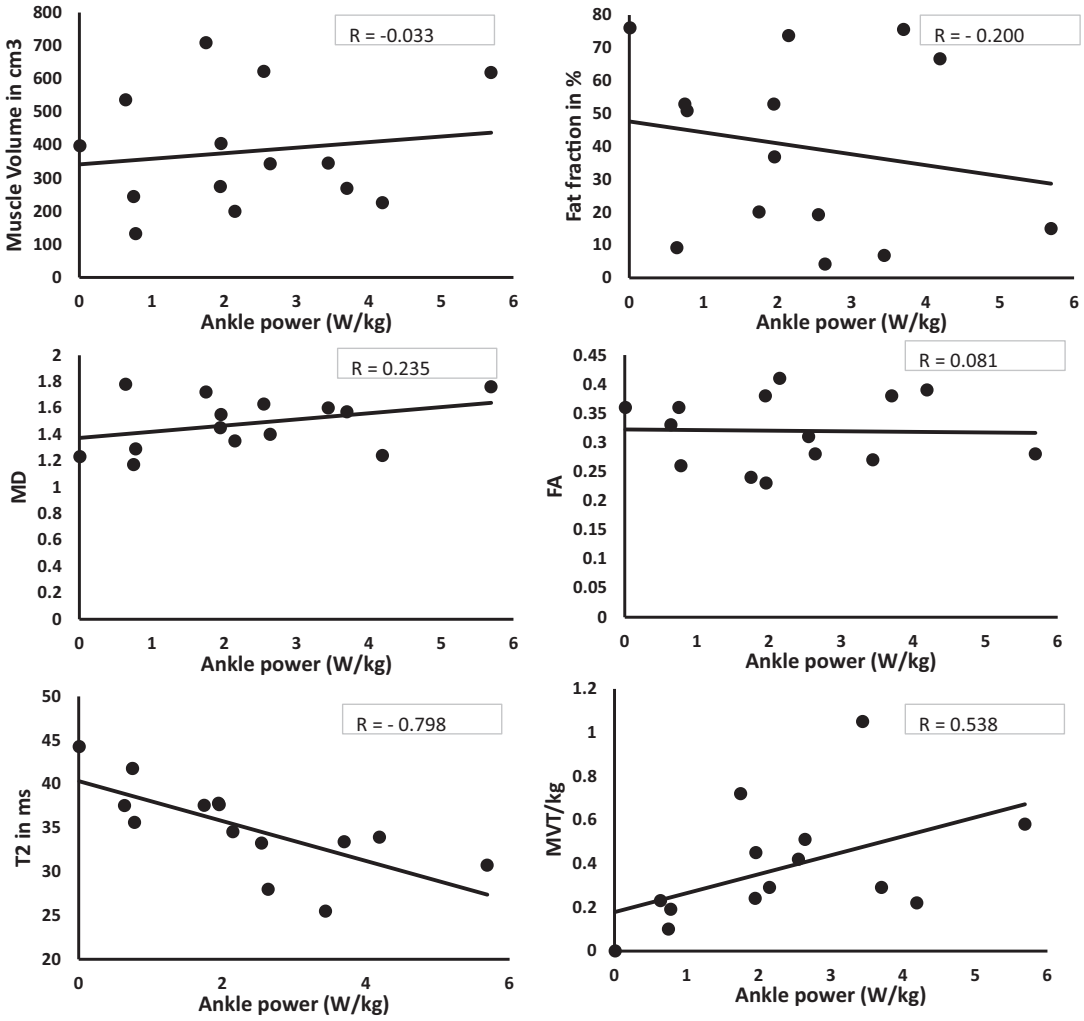

Fig. 1. Correlation between quantitative MRI parameters averaged across the plantar flexors and maximal muscle strength. Abbreviations. FA = fractional anisotropy, MD = mean diffusivity, T2 = T2 transverse relaxation time, MVT/kg = maximal voluntary torque normalized for body mass. The Spearman correlation coefficient was used.

Table 3
Correlation coefficients.

	MVT	*p*	Ankle moment	*p*	Ankle power	*p*
FA	−0.512	0.061	0.073	0.805	0.081	0.782
MD	0.670*	0.009	0.288	0.318	0.235	0.418
T2	−0.631	0.016	−0.789*	0.001	−0.798*	0.001
Volume	0.521	0.056	−0.007	0.982	−0.033	0.911
Fat Fraction	−0.657	0.011	−0.165	0.573	−0.200	0.493
MVT/kg	–	–	0.600	0.023	0.538	0.047

Abbreviations. FA = Fractional Anisotropy, MD = Mean Diffusivity, T2 = T2 transverse relaxation time, MVT/kg = Maximal Voluntary Torque normalized to body mass.

* Significant at $p < 0.01$.

provide more insight into how muscular pathophysiological changes affect gait.

5. Conclusion

In conclusion, T2 relaxation time, a general marker for muscle status, strongly related to plantar flexor function during walking, while MD and FA correlated with muscle strength. These findings highlight the potential of these biomarkers to help better understand how pathophysiological changes affect plantar flexor function during walking in neuromuscular diseases, which warrants further large prospective studies.

Conflict of interest statement

None of the authors has any conflict of interest to disclose.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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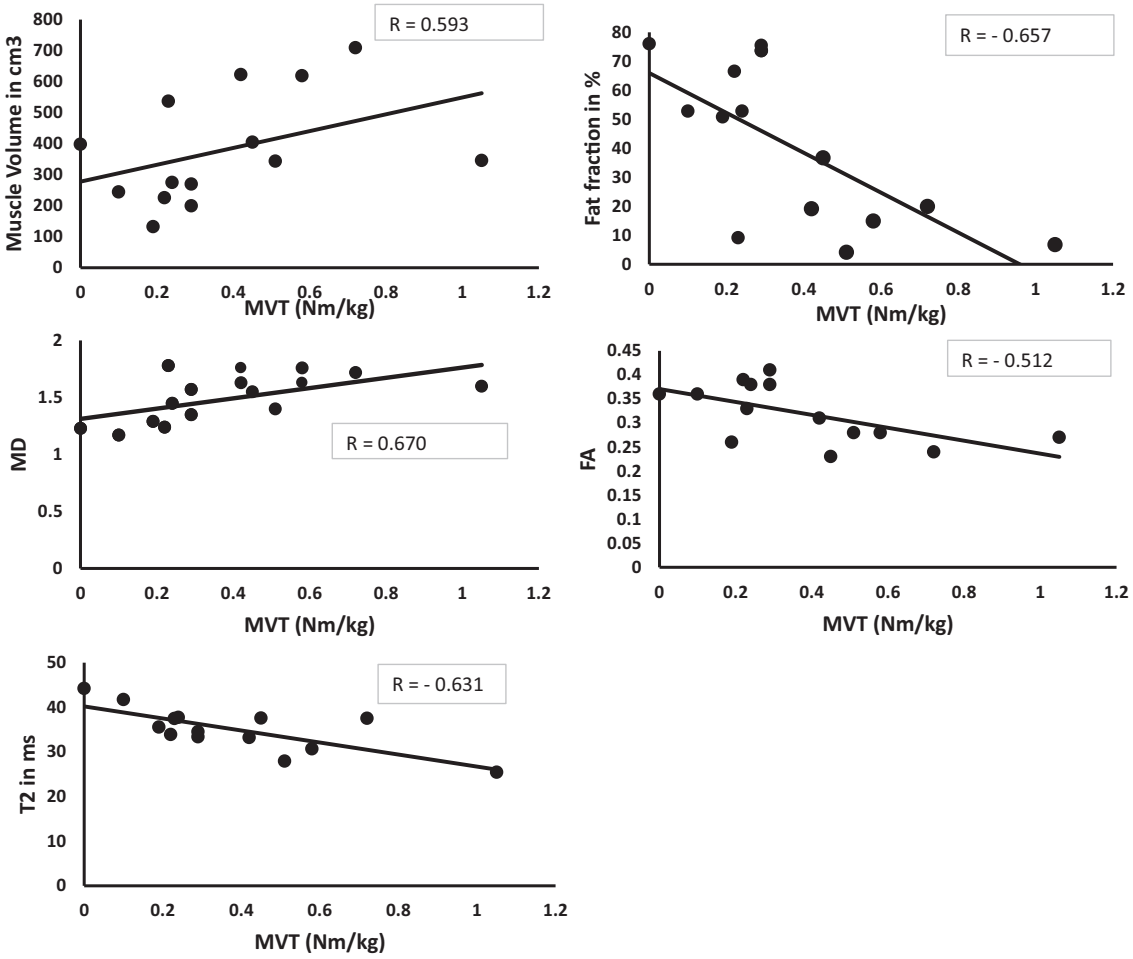

Fig. 2. Correlation between quantitative MRI parameters averaged across the plantar flexors and maximal ankle power. Abbreviations. FA = fractional anisotropy, MD = mean diffusivity, T2 = T2 transverse relaxation time, MVT/kg = maximal voluntary torque normalized for body mass. The Spearman correlation coefficient was used.

number W.OR 14–21] and Amsterdam Movement Sciences, which were not involved in any way during the study and in writing this manuscript.

References

Allen, G., Gandevia, S., Neering, I., Hickie, I., Jones, R., Middleton, J., 1994. Muscle performance, voluntary activation and perceived effort in normal subjects and patients with prior poliomyelitis. Brain. 117 (4), 661–670.

Azzabou, N., Hogrel, J.-Y., Carlier, P.G., 2015. NMR based biomarkers to study age-related changes in the human quadriceps. Exp. Gerontol. 70, 54–60.

Berry, D.B., Regner, B., Galinsky, V., Ward, S.R., Frank, L.R., 2018. Relationships between tissue microstructure and the diffusion tensor in simulated skeletal muscle. Magn. Reson. Med. 80 (1), 317–329.

Bickerstaffe, A., van Dijk, J.P., Beelen, A., Zwarts, M.J., Nollet, F., 2014. Loss of motor unit size and quadriceps strength over 10 years in post-polio syndrome. Clin. Neurophysiol. 125 (6), 1255–1260.

Bickerstaffe, A., Beelen, A., Zwarts, M.J., Nollet, F., van Dijk, J.P., 2015. Quantitative muscle ultrasound and quadriceps strength in patients with post-polio syndrome. Muscle Nerve 51 (1), 24–29.

Bohannon, R.W., 2005. Manual muscle testing: does it meet the standards of an adequate screening test? Clin. Rehabil. 19 (6), 662–667.

Bouza, C., Muñoz, A., Amate JMa., 2005. Postpolio syndrome: a challenge to the health-care system. Health Pol. 71 (1), 97–106.

Budzik, J.-F., Balbi, V., Verclytte, S., Pansini, V., Thuc, V.L., Cotten, A., 2014. Diffusion tensor imaging in musculoskeletal disorders. Radiographics. 34 (3), E56–E72.

Carbone, V., van der Krogt, M., Koopman, H.F., Verdonschot, N., 2016. Sensitivity of subject-specific models to hill muscle–tendon model parameters in simulations of gait. J. Biomech. 49 (9), 1953–1960.

Chan, Y., 2003. Biostatistics 104: correlational analysis. Singap. Med. J. 44 (12), 614–619.

Dallmeijer, A., Baker, R., Dodd, K., Taylor, N., 2011. Association between isometric muscle strength and gait joint kinetics in adolescents and young adults with cerebral palsy. Gait Posture 33 (3), 326–332.

Farrow, M., Biglands, J., Tanner, S., Clegg, A., Brown, L., Hensor, E., et al., 2020. The effect of ageing on skeletal muscle as assessed by quantitative MR imaging: an association with frailty and muscle strength. Aging Clin. Exp. Res. 1-11.

Frank-Wilson, A.W., Chalhoub, D., Figueiredo, P., Jónsson, P.V., Siggeirsdóttir, K., Sigurdsson, S., et al., 2018. Associations of quadriceps torque properties with muscle size, attenuation, and intramuscular adipose tissue in older adults. J. Gerontol. 73 (7), 931–938.

Froeling, M., Nederveen, A.J., Heijtel, D.F., Lataster, A., Bos, C., Nicolay, K., et al., 2012. Diffusion-tensor MRI reveals the complex muscle architecture of the human forearm. J. Magn. Reson. Imaging 36 (1), 237–248.

Froeling, M., Oudeman, J., Strijkers, G.J., Maas, M., Drost, M.R., Nicolay, K., et al., 2015. Muscle changes detected with diffusion-tensor imaging after long-distance running. Radiology. 274 (2), 548–562.

Gerstner, G.R., Giuliani, H.K., Mota, J.A., Ryan, E.D., 2017. Age-related reductions in muscle quality influence the relative differences in strength and power. Exp. Gerontol. 99, 27–34.

Gerstner, G.R., Giuliani, H.K., Mota, J.A., Ryan, E.D., 2018. Influence of muscle quality on the differences in strength from slow to fast velocities in career firefighters. J. Strength Cond. Res. 32 (10), 2982–2986.

Grimby, G., Kvist, H., Grangård, U., 1996. Reduction in thigh muscle cross-sectional area and strength in a 4-year follow-up in late polio. Arch. Phys. Med. Rehabil. 77 (10), 1044–1048.

Hatakenaka, M., Soeda, H., Okafuji, T., Yabuuchi, H., Shiokawa, S., Nishimura, J., et al., 2006. Steroid myopathy: evaluation of fiber atrophy with T2 relaxation time—rabbit and human study. Radiology. 238 (2), 650–657.

Hooijmans, M.T., Monte, J.R., Froeling, M., van den Berg-Faay, S., Aengevaeren, V.L., Hemke, R., et al., 2020. Quantitative MRI reveals microstructural changes in the upper leg muscles after running a Marathon. J. Magn. Reson. Imaging 52 (2), 407–417.

Horemans, H.L., Beelen, A., Nollet, F., Jones, D.A., Lankhorst, G.J., 2004. Reproducibility of maximal quadriceps strength and its relationship to maximal voluntary activation in postpoliomyelitis syndrome. Arch. Phys. Med. Rehabil. 85 (8), 1273–1278.

Janssen, B., Voet, N., Geurts, A., van Engelen, B., Heerschap, A., 2016. Quantitative MRI reveals decelerated fatty infiltration in muscles of active FSHD patients. Neurology. 86 (18), 1700–1707.
Kahn, M., Williams, G., 2015. Clinical tests of ankle plantarflexor strength do not predict ankle power generation during walking. Am. J. Phys. Med. Rehabil. 94 (2), 114–122.
Keene, K.R., Beenakker, J.W.M., Hooijmans, M.T., Naarding, K.J., Niks, E.H., Otto, L.A., et al., 2020. T2 relaxation-time mapping in healthy and diseased skeletal muscle using extended phase graph algorithms. Magn. Reson. Med. 84 (5), 2656–2670.
Kikuchi, Y., Nakamura, T., Takayama, S., Horiuchi, Y., Toyama, Y., 2003. MR imaging in the diagnosis of denervated and reinnervated skeletal muscles: experimental study in rats. Radiology. 229 (3), 861–867.
Kuo, G.P., Carrino, J.A., 2007. Skeletal muscle imaging and inflammatory myopathies. Curr. Opin. Rheumatol. 19 (6), 530–535.
Le Bihan, D., Mangin, J.F., Poupon, C., Clark, C.A., Pappata, S., Molko, N., et al., 2001. Diffusion tensor imaging: concepts and applications. J. Magn. Reson. Imaging 13 (4), 534–546.
Leemans, A., Jones, D.K., 2009. The B-matrix must be rotated when correcting for subject motion in DTI data. Magn. Reson. Med. 61 (6), 1336–1349.
Maillard, S., Jones, R., Owens, C., Pilkington, C., Woo, P., Wedderburn, L., et al., 2004. Quantitative assessment of MRI T 2 relaxation time of thigh muscles in juvenile dermatomyositis. Rheumatology. 43 (5), 603–608.
Malis, V., Sinha, U., Csapo, R., Narici, M., Smitaman, E., Sinha, S., 2019. Diffusion tensor imaging and diffusion modeling: application to monitoring changes in the medial gastrocnemius in disuse atrophy induced by unilateral limb suspension. J. Magn. Reson. Imaging 49 (6), 1655–1664.
Marty, B., Baudin, P.Y., Reyngoudt, H., Azzabou, N., Araujo, E.C., Carlier, P.G., et al., 2016. Simultaneous muscle water T2 and fat fraction mapping using transverse relaxometry with stimulated echo compensation. NMR Biomed. 29 (4), 431–443.
Morrow, J.M., Sinclair, C.D., Fischmann, A., Machado, P.M., Reilly, M.M., Yousry, T.A., et al., 2016. MRI biomarker assessment of neuromuscular disease progression: a prospective observational cohort study. Lancet Neurol. 15 (1), 65–77.
Moseley, A.M., Crosbie, J., Adams, R., 2001. Normative data for passive ankle plantarflexion–dorsiflexion flexibility. Clin. Biomech. 16 (6), 514–521.
Mota, J.A., Giuliani, H.K., Gerstner, G.R., Ryan, E.D., 2018. The rate of velocity development associates with muscle echo intensity, but not muscle cross-sectional area in older men. Aging Clin. Exp. Res. 30 (7), 861–865.
Neptune, R.R., Kautz, S., Zajac, F., 2001. Contributions of the individual ankle plantar flexors to support, forward progression and swing initiation during walking. J. Biomech. 34 (11), 1387–1398.
Nollet, F., Beelen, A., 1999. Strength assessment in postpolio syndrome: validity of a hand-held dynamometer in detecting change. Arch. Phys. Med. Rehabil. 80 (10), 1316–1323.
Otto, L.A., van der Pol, W.L., Schlaffke, L., Wijngaarde, C.A., Stam, M., Wadman, R.I., et al., 2020. Quantitative MRI of skeletal muscle in a cross-sectional cohort of patients with spinal muscular atrophy types 2 and 3. NMR Biomed. 33 (10), e4357.
Oudeman, J., Nederveen, A.J., Strijkers, G.J., Maas, M., Luijten, P.R., Froeling, M., 2016. Techniques and applications of skeletal muscle diffusion tensor imaging: a review. J. Magn. Reson. Imaging 43 (4), 773–788.
Reeder, S.B., Pineda, A.R., Wen, Z., Shimakawa, A., Yu, H., Brittain, J.H., et al., 2005. Iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL): application with fast spin-echo imaging. Magn. Reson. Med. 54 (3), 636–644.
Reilly, M.M., Murphy, S.M., Laura, M., 2011. Charcot-Marie-tooth disease. J. Peripher. Nerv. Syst. 16 (1), 1–14.
Scheel, M., Prokscha, T., von Roth, P., Winkler, T., Dietrich, R., Bierbaum, S., et al., 2013. Diffusion tensor imaging of skeletal muscle–correlation of fractional anisotropy to muscle power. In: RöFo-Fortschritte auf dem Gebiet der Röntgenstrahlen und der bildgebenden Verfahren. © Georg Thieme Verlag KG.
Schlaffke, L., Rehmann, R., Rohm, M., Otto, L.A., de Luca, A., Burakiewicz, J., et al., 2019. Multi-center evaluation of stability and reproducibility of quantitative MRI measures in healthy calf muscles. NMR Biomed. 32 (9), e4119.
Silverman, A.K., Fey, N.P., Portillo, A., Walden, J.G., Bosker, G., Neptune, R.R., 2008. Compensatory mechanisms in below-knee amputee gait in response to increasing steady-state walking speeds. Gait Posture 28 (4), 602–609.
Simon, N.G., Noto, Y.-i., Zaidman, C.M., 2016. Skeletal muscle imaging in neuromuscular disease. J. Clin. Neurosci. 33, 1–10.
Sinha, U., Csapo, R., Malis, V., Xue, Y., Sinha, S., 2015. Age-related differences in diffusion tensor indices and fiber architecture in the medial and lateral gastrocnemius. J. Magn. Reson. Imaging 41 (4), 941–953.
Stouge, A., Khan, K.S., Kristensen, A.G., Tankisi, H., Schlaffke, L., Froeling, M., et al., 2020. MRI of skeletal muscles in participants with type 2 diabetes with or without diabetic polyneuropathy. Radiology. 297 (3), 608–619.
Straight, C.R., Voigt, T.B., Jala, A.V., Chase, J.D., Ringham, O.R., Ades, P.A., et al., 2019. Quadriceps lipid content has sex-specific associations with whole-muscle, cellular, and molecular contractile function in older adults. J. Gerontol. 74 (12), 1879–1886.
Sunnerhagen, K.S., Grimby, G., 2001. Muscular effects in late polio. Acta Physiol. Scand. 171 (3), 335–340.
Tax, C.M., Otte, W.M., Viergever, M.A., Dijkhuizen, R.M., Leemans, A., 2015. REKINDLE: robust extraction of kurtosis INDices with linear estimation. Magn. Reson. Med. 73 (2), 794–808.
Thom, J.M., Morse, C.I., Birch, K.M., Narici, M.V., 2007. Influence of muscle architecture on the torque and power–velocity characteristics of young and elderly men. Eur. J. Appl. Physiol. 100 (5), 613–619.
Trappe, S., Trappe, T., Lee, G., Costill, D., 2001. Calf muscle strength in humans. Int. J. Sports Med. 22 (03), 186–191.
Triplett, W.T., Baligand, C., Forbes, S.C., Willcocks, R.J., Lott, D.J., DeVos, S., et al., 2014. Chemical shift-based MRI to measure fat fractions in dystrophic skeletal muscle. Magn. Reson. Med. 72 (1), 8–19.
Umberger, B.R., Gerritsen, K.G., Martin, P.E., 2003. A model of human muscle energy expenditure. Comput. Meth. Biomech. Biomed. Eng. 6 (2), 99–111.
Veraart, J., Sijbers, J., Sunaert, S., Leemans, A., Jeurissen, B., 2013. Weighted linear least squares estimation of diffusion MRI parameters: strengths, limitations, and pitfalls. Neuroimage. 81, 335–346.
Veraart, J., Novikov, D.S., Christiaens, D., Ades-Aron, B., Sijbers, J., Fieremans, E., 2016. Denoising of diffusion MRI using random matrix theory. Neuroimage. 142, 394–406.
Waterval, N.F., Nollet, F., Harlaar, J., Brehm, M.-A., 2017. Precision orthotics: optimising ankle foot orthoses to improve gait in patients with neuromuscular diseases; protocol of the PROOF-AFO study, a prospective intervention study. BMJ Open 7 (2), e013342.
Waterval, N.F., Brehm, M.-A., Ploeger, H.E., Nollet, F., Harlaar, J., 2018. Compensations in lower limb joint work during walking in response to unilateral calf muscle weakness. Gait Posture 66, 38–44.
Waterval, N., Veerkamp, K., Geijtenbeek, T., Harlaar, J., Nollet, F., Brehm, M., et al., 2021. Validation of forward simulations to predict the effects of bilateral plantarflexor weakness on gait. Gait Posture 87, 33–42.
Whittington, B., Silder, A., Heiderscheit, B., Thelen, D.G., 2008. The contribution of passive-elastic mechanisms to lower extremity joint kinetics during human walking. Gait Posture 27 (4), 628–634.
Wokke, B., Van Den Bergen, J., Versluis, M., Niks, E., Milles, J., Webb, A., et al., 2014. Quantitative MRI and strength measurements in the assessment of muscle quality in Duchenne muscular dystrophy. Neuromuscul. Disord. 24 (5), 409–416.
Yushkevich, P.A., Piven, J., Hazlett, H.C., Smith, R.G., Ho, S., Gee, J.C., et al., 2006. User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. Neuroimage. 31 (3), 1116–1128.