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Quantitative T_2-Mapping Magnetic Resonance Imaging for Assessment of Muscle Motor Unit Recruitment Patterns

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Abstract

Introduction: In this study, we aimed to determine whether muscle transverse relaxation time (T_2) magnetic resonance (MR) mapping results correlate with motor unit loss, as defined by motor unit recruitment patterns on electromyography (EMG).

Methods: EMG and 3-Tesla MRI exams were acquired no more than 31 days apart in subjects referred for peripheral nerve MRI. Two musculoskeletal radiologists qualitatively graded T_2-weighted, fat-suppressed sequences for severity of muscle edema- like patterns and manually placed regions of interest within muscles to obtain T_2 values from T_2-mapping sequences. Concordance was calculated between qualitative and quantitative MR grades and EMG recruitment categories (none, discrete, decreased) as well as interobserver agreement for both MR grades.

Results: Thirty-four muscles (21 abnormal, 13 control) were assessed in 13 subjects (5 females and 8 males; mean age, 46 years) with 14 EMG-MRI pairs. T_2-relaxation times were significantly ($P < .001$) increased in all EMG recruitment categories com- pared with control muscles. T_2 differences were not significant between EMG grades of motor unit recruitment ($P = .151$-$.702$). T_2 and EMG score concordance was acceptable (Harrell's concordance index [c index]: rater A, 0.71; 95% confidence interval [CI], 0.51-0.87; rater B, 0.77; 95% CI, 0.57-0.91). Qualitative MRI and EMG score concordance was poor to acceptable (c index: rater A, 0.60; 95% CI, 0.50-0.79; rater B, 0.72; 95% CI, 0.55-0.89). T_2 values had moderate-to-substantial ability to distinguish between absent vs incomplete (ie, decreased or discrete) motor unit recruitment (c index: rater A, 0.78; 95% CI, 0.50-1.00; rater B, 0.86; 95% CI, 0.57-1.00).

Discussion: Quantitative T_2 MR muscle mapping is a promising tool for noninvasive evaluation of the degree of motor unit recruitment loss.

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Keywords

electromyography; MRI; muscle; musculoskeletal; T_2 mapping

1. Introduction

Muscle denervation and changes in motor unit recruitment secondary to peripheral neuropathies are conventionally evaluated via needle electromyography (EMG), the results of which not only inform diagnosis but help to prognosticate recovery. Although EMG is considered the clinical "gold standard," drawbacks include its invasive nature, the need to individually test each muscle, and inherent operator dependence associated with intra- and interobserver variability.[1,2]

Magnetic resonance imaging (MRI) can serve as a noninvasive complement to EMG for the diagnosis of peripheral neuropathies[3] and evaluation of regional changes associated with muscle denervation and motor unit recruitment. MR signal intensity changes within denervated muscle can be attributed to increased muscle perfusion and capillary permeability, leading to extracellular fluid accumulation[4] and, subsequently, increased transverse relaxation time (T_2 prolongation). On conventional, fat-suppressed, T_2-weighted qualitative MR images, actively denervated muscle and motor unit dropout manifest as diffusely homogeneous signal hyperintensity (hereafter referred to as an "edema pattern").[5] In chronic phases (>6 months) of denervation and loss of motor unit function, irreversible fatty infiltration of muscle (in addition to reduced bulk) may occur, which further increases T_2 and reduces longitudinal relaxation time (T_1). These long-term changes are most apparent on either T_1-weighted or fat images derived from Dixon in/out-of-phase sequences.[6-8]

Correlation of EMG with MRI results may provide improved characterization of muscle denervation and quantification of motor unit function. To that end, qualitative MR signal intensity (SI) changes have been found to correlate with the level of motor unit recruitment on EMG.[3,9] However, SI changes remain subjective, as MR SI is inherently dependent on hardware and software settings that are not quantitative in nature. To improve the quantitative aspect, one previous study attempted to calibrate SI levels across different scans on the same MRI magnet to evaluate denervated muscles in the hand.[10] However, this method is semi-quantitative and neither repeatable nor reproducible across different scanners or other anatomical regions.

T_2 mapping is a quantitative MR technique, unbiased by arbitrary SI levels, whereby the transverse relaxation time parameter, T_2, is derived. T_2 parameters provide information about the biochemical and structural characteristics of tissue.[11,12] T_2 mapping studies have been performed in different myopathies,[7,13,14] but correlation with EMG findings in humans has yet to be reported. Correlation between T_2 muscle values and EMG parameters has been reported in rodent models of nerve transection,[15-17] but the evolution and pattern of denervation both in traumatic and nontraumatic peripheral neuropathies in humans are likely different.[18] Given that T_2 parameters are promising preclinical biomarkers of denervation and that published MRI studies of denervation in humans are sparse, there is strong

motivation to evaluate the relationship between T_2 values and the level of motor unit recruitment, secondary to denervation, measured on EMG.

In this study, we evaluated correlations between muscle T_2-relaxation metrics and EMG in the setting of peripheral neuropathies and motor unit recruitment loss in humans. Our objective was to determine whether muscle T_2 values could serve as reliable biomarkers of muscle motor unit function. We hypothesized that muscle T_2 values would correlate with EMG scores of motor unit recruitment and be more sensitive than conventional MRI sequences (qualitative SI) to changes in motor unit recruitment.

2. Methods

This institutional review board–approved prospective study involved the analysis of data obtained between December 2015 and September 2017 in subjects with the clinical suspicion of peripheral neuropathy who were referred for both EMG and MRI evaluation and who provided informed consent. Patients with symptom onset beginning at least 2 years earlier, or in whom EMG and MRI studies were obtained more than 1 month apart, were excluded from analysis. Cases in which a control muscle (ie, normal motor unit recruitment on EMG) was not included within the imaged field of view (FOV) on the T_2-mapping MR sequence were also excluded.

2.1 MRI Acquisition

In addition to standard-of-care MRI sequences (ie, axial proton density and T_2-weighted fat-suppressed sequences), a quantitative T_2- mapping sequence was prospectively obtained in all subjects. All MRI studies were acquired on a clinical 3-Tesla MRI system (Discovery MR750; GE Healthcare, Waukesha, Wisconsin). Axial, T_2-weighted fat-suppressed sequences, which were qualitatively evaluated for the presence of an edema pattern, were obtained with the following imaging parameters: TE: 85 ms; repetition time (TR): 3500 to 5000 ms; readout bandwidth (RBW): ±62.5 kHz; number of excitations (NEX): two; acquisition matrix: 320 × 192; FOV: 12 to 20 cm; slice thickness 2.5 to 3.0 mm (no gap). In addition, axial T_2-mapping sequences for quantitative muscle evaluation were acquired: TR: 1000 ms; TE: eight echoes between 0 and 90 ms; inter-echo spacing: 10 ms; RBW: ±62.5 kHz; NEX: one; acquisition matrix: 320 × 256; FOV: 10 to 20 cm; slice thickness: 2 mm (no gap).

2.2 MRI Analysis

Two musculoskeletal radiologists (rater A [D.B.S.]: 5 years of subspecialty musculoskeletal imaging experience; rater B [J.S.W.]: 1 year of subspecialty experience) independently graded the presence and severity of MRI muscle denervation edema pattern (T_2-weighted signal hyperintensity relative to expected signal intensity of skeletal muscle) on a qualitative scale from 0 to 3 (0 = none; 1 = mild; 2 = moderate; 3 = severe). Postprocessing of acquired T_2-mapping sequences and calculation of T_2-relaxation times in affected muscles were performed on the vendor-provided software (AW Server version 3.2, ext 1.2; GE Healthcare). Each rater manually placed standardized regions of interest (25 mm2) within

normal and affected muscles, being careful to exclude any central tendon slip or fascia that could bias measurements.

2.3 EMG Acquisition and Analysis

Needle EMGs were performed for each of the 13 patients, with all studies performed by one of five experienced practitioners. A single provider (J.H.F.) with 30 years of electrodiagnostic experience was responsible for the evaluation of 14 of the 21 involved muscles tested on EMG. The degree of motor unit recruitment, from highest to lowest (ie, full [normal], decreased [mild], discrete [moderate], and none [severe]), was obtained from EMG reports and recorded for each muscle interrogated on the T_2-mapping MR sequence.

2.4 Statistical Analysis

Concordance between subjective MRI edema pattern scores, quantitative T_2 values, and EMG motor unit recruitment scores were evaluated using Harrell's concordance index (c index), obtained by fitting ordinal logistic regression models.[19,20] EMG scores were also dichotomized to compare cases of absent with incomplete (decreased or discrete) motor unit recruitment. The rationale for this dichotomization was that management of patients in these two subgroups often differs, particularly in the setting of traumatic injury. The c indices were also obtained for dichotomized analyses. Analogous to an area under the receiver-operating characteristic curve, c indices were interpreted as follows: <0.5 indicative of no predictive ability; 0.5 to 0.7 considered poor discrimination; 0.7 to 0.8 considered acceptable discrimination; and 1.0 indicative of perfect discrimination.

Evaluation of the comparative ability of quantitative T_2 values vs subjective MRI edema pattern scores to predict EMG scores was accomplished by calculating the differences in their respective c indices. Interobserver agreement for MRI edema pattern and quantitative T_2 values was assessed with the ordinal-weighted Cohen's kappa coefficient and intraclass correlation coefficient (ICC [2,1], two-way random effects, absolute agreement, single rater), respectively.[21] Strength of agreement was interpreted as follows: <0.00 = poor; 0.00 to 0.20 = slight; 0.21 to 0.40 = fair; 0.41 to 0.60 = moderate; 0.61 to 0.80 = substantial; 0.81 to 1.00 = almost perfect.[22]

The c indices, differences in c indices, weighted kappa, and ICC (2,1) were reported as point estimates with cluster-robust, 95% percentile bootstrapped confidence intervals (CIs) calculated from 1000 resamples to account for the dependency from multiple muscles per subject.[23] Statistical significance of the differences in c indices is implied by bootstrapped 95% CIs that exclude the null value of 0. All statistical analyses were performed with R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

A total of 13 subjects (5 females, 8 males; mean age, 46.0 years; age range, 29.0-67.0 years) met the inclusion criteria. Patients were evaluated based on the clinical suspicion of neuralgic amyotrophy (5), peroneal neuropathy (5), postganglionic L4 radiculopathy (1), axillary neuropathy (1), and posterior interosseous neuropathy (1). One patient had two separate sets of EMG and MRI studies of the brachial plexus that met the criteria, whereas

all other patients had one set of EMG and MRI studies each, yielding a total of 14 EMG-MRI pairs. Within these data sets, 34 muscles (21 muscles with motor unit loss and 13 control muscles) were evaluated.

Average time between symptom onset and MRI acquisition was 8.8 months (median, 8.3 months; range, 8 days to 20 months). There was a median of 6 days between MRI and EMG. Of the 14 EMG-MRI pairs, 7 were of the upper extremity, including the brachial plexus (4), arm (2), humerus (1), and elbow (1), and 6 were of the lower extremity, including the knee (5) and lower leg (1). Table S1 provides a detailed breakdown of the subject demographics and abnormal muscles and their corresponding recruitment patterns. Of the 21 abnormal muscles evaluated with EMG, 5 had decreased recruitment, 9 had discrete recruitment, and 7 had no recruitment. Positive sharp waves and fibrillation potentials were detected in 17 of 21 abnormal muscles and all abnormal muscles had motor unit recruitment loss. All 13 control muscles had full EMG motor unit recruitment and no edema pattern on MRI. Figure 1 shows examples of three cases of varying severity of edema pattern, as graded by the radiologists, with corresponding T_2 maps.

Concordance between quantitative T_2 values and EMG scores was considered acceptable for both readers; c indices were 0.71 (95% CI, 0.51-0.87) for rater A and 0.77 (95% CI, 0.57-0.91) for rater B. The concordance between subjective MRI edema pattern scores and EMG scores was poor for rater A at 0.60 (95% CI, 0.50-0.79), but acceptable for rater B at 0.72 (95% CI, 0.55-0.89). No statistically significant differences were found between c indices of quantitative T_2 mapping and qualitative edema pattern scores for predicting EMG scores for either observer, with a difference of +0.11 (95% CI, −0.31 to 0.22) for rater A and +0.045 (95% CI, −0.29 to 0.25) for rater B.

Differences in T_2-relaxation times between abnormal and control (normal) muscles were also evaluated as a means of normalizing data for intersubject comparisons (Supplemental Table 1). T_2-relaxation times increased significantly ($P < .001$) in abnormal muscle for all EMG categories of motor unit recruitment (none, discrete, decreased) compared with normal control muscle. However, mean T_2 differences (10.11-18.48 ms) (ie, abnormal muscle T_2 – normal control muscle T2) between groups were not statistically significant.

Data were also dichotomized to compare two subgroups: cases of absent motor unit recruitment to decreased or discrete recruitment. Using these dichotomized data, the agreement between T_2 mapping and EMG was stronger in both raters, with c indices of 0.78 (95% CI, 0.50-1.00) for rater A and 0.86 (95% CI, 0.57-1.00) for rater B, indicating an acceptable predictive ability of T_2 mapping to distinguish between cases of absent vs some level of motor unit recruitment. In contrast, dichotomization resulted in the agreement between subjective edema pattern assessment and EMG becoming weaker for rater A and stronger for rater B, with c indices of 0.56 (95% CI, 0.50-0.85) and 0.79 (95% CI, 0.58-0.96) for the two respective raters.

The strength of interobserver agreement was moderate for both MRI techniques, with an ICC of 0.59 (95% CI, 0.30-0.75) for quantitative T_2 mapping and an ordinal weighted Cohen’s kappa coefficient of 0.51 (95% CI, 0.19-0.77) for subjective edema pattern scoring.

4. Discussion

The results of this study suggest that quantitative T_2 mapping may useful to evaluate the degree of motor unit recruitment loss in the setting of denervation. Loss of motor unit recruitment, an indicator of muscle function loss, can be secondary to denervation and/or neuropraxia. Similar to trends in animal studies,[15-17] abnormal muscles exhibited prolonged T_2 values when compared with control muscles. Although T_2 values positively trended with the degree of muscle abnormality, as assessed both by qualitative MRI and EMG, no significant differences were found between quantitative and qualitative MR to distinguish individual EMG grades. However, when EMG grades were subsequently dichotomized, quantitative T_2 mapping was better than qualitative MRI in discriminating complete from incomplete loss of motor unit recruitment on EMG. This suggests that our sample size was only adequate to coarsely resolve EMG grades (complete vs incomplete).

EMG results are severity- and time-dependent; it can take weeks for denervation to become apparent on EMG. In animal experiments, T_2-weighted MRI has been shown to be sensitive to muscle changes as early as 24 hours after nerve injury,[24,25] and these changes pre- ceded detection of abnormal spontaneous activity on EMG. Anecdotally, however, we have not witnessed these changes on T_2-weighted pulse sequences in human, clinical exams. As T_2-mapping results agreed more strongly than subjective MRI with EMG in this study, it is possible that T_2 mapping could be more sensitive to muscle injury changes than T_2-weighted morphological imaging, especially at earlier timepoints. Therefore, an objective T_2-mapping biomarker may provide both reduced subjectivity and increased sensitivity to EMG and qualitative T_2-weighted MRI, and afford longitudinal assessment of muscle in a more reliable, noninvasive manner. Previous research has shown that muscle MRI can be used as a tool for monitoring nerve regeneration over time, where changes in signal intensity serve to predict functional recovery.[10] In addition, MRI can provide a single snapshot of multiple muscles as compared with EMG, which interrogates one muscle at a time. Moreover, qualitative MRI edema patterns can be occasionally confused with traumatic muscle injury, myopathy, compartment syndrome, and rhabdomyolysis. This is particularly so when these patterns are diffuse, as is seen in denervation.[26,27] Herein a quantitative metric (T_2 value rather than subjective T_2-weighted pixel intensity) may provide a means to evaluate these pathologies.

We acknowledge several study limitations. Sample size was relatively small, and we therefore analyzed more than one abnormal muscle from the same exam when information about that muscle was available on both EMG and MRI. Muscle regions of interest were manually selected, which could have led to increased interrater variability. We did not analyze correlations of MRI against other electrodiagnostic measurements; one rationale is that the degree of motor unit recruitment is the most uniform measurement across the muscle and best reflects motor function. In comparison, spontaneous activities may vary more widely, which may be less reliable and may not correlate as well with MRI.

One reason for not performing T_2 mapping more routinely is the relatively long scan time of the commercially available sequence used (approximately 10 times as long as nonquantitative T_2-weighted MRI for the same spatial resolution). The T_2-mapping

sequence could benefit from accelerated techniques, including a more recently developed simultaneous multislice acquisition[28] that interleaves k-space acquisition with echo times to reduce the number of echoes acquired for T_2 mapping.[29] Another limitation of T_2 mapping is that its accuracy is likely biased by spatial nonuniformity in the transmit radiofrequency (B1+) field,[30] which occurs inherently in MRI due to spatial variation in electrical conductivity and body habitus.[31] This results in over-estimation of T_2 values, but this could be corrected in subsequent studies by acquiring fast B1+ maps[32] and using these to correct T_2- value fitting.[33] In this study, we also utilized a simple, linear regression method for fitting to obtain the T_2 values. More robust fitting methods, as described elsewhere,[11] could be implemented to improve accuracy and sensitivity to T_2 changes.

In this study we also did not account for regions of fatty infiltration that may have been present in some chronically denervated muscles, although the patient cohort comprised mostly acute injuries (median time from injury to imaging = 4.2 months). Fat, similar to fluid, would increase T_2 values of skeletal muscle.[7,13] This effect could be obviated in the future by incorporating fat-suppression schemes[34,35] during T_2 mapping or by obtaining separate fat fraction maps, typically acquired using Dixon fat/water separation techniques,[36,37] to determine the relative contribution of fat to the measured T_2 value. Another promising biomarker is diffusivity, which could elucidate microstructural changes related to the caliber and permeability of muscle fibers, as well as the presence of fibrosis and edema.[38] Diffusion MRI has also been previously investigated in other muscle denervation studies.[16,39] We are currently developing a multiparametric neuromuscular MRI exam that would not only incorporate morphological and T_2 mapping assessments but also generate fat fraction and diffusion measurements to more comprehensively characterize the states of muscle abnormality.

One logistic limitation we faced in our study was the time interval between EMG and MRI exams, which could confound results, as muscle denervation can improve or deteriorate depending on the nerve injury type.[10,26] This problem was partially mitigated by excluding patients with EMG and MRI exams performed more than 1 month apart.

In conclusion, our study of T_2 mapping and EMG in peripheral neuropathies suggests that quantitative T_2 MR mapping may provide objective, reliable information about loss of motor function secondary to muscle denervation. Although we only evaluated muscles at a single timepoint, T_2-mapping techniques could be used to longitudinally monitor muscle denervation and nerve recovery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement

The anonymized data that support the findings of this study are avail- able from the corresponding author upon reasonable request.

Abbreviations

CI	confidence interval
C-index	Harrell's concordance index
EMG	electromyography
FOV	field-of-view
ICC	intraclass correlation coefficient
MRI	magnetic resonance imaging
NEX	number of excitations
RBW	readout bandwidth
SI	signal intensity
T_1	longitudinal relaxation time
T_2	transverse relaxation time
TE	echo-time
TR	repetition-time

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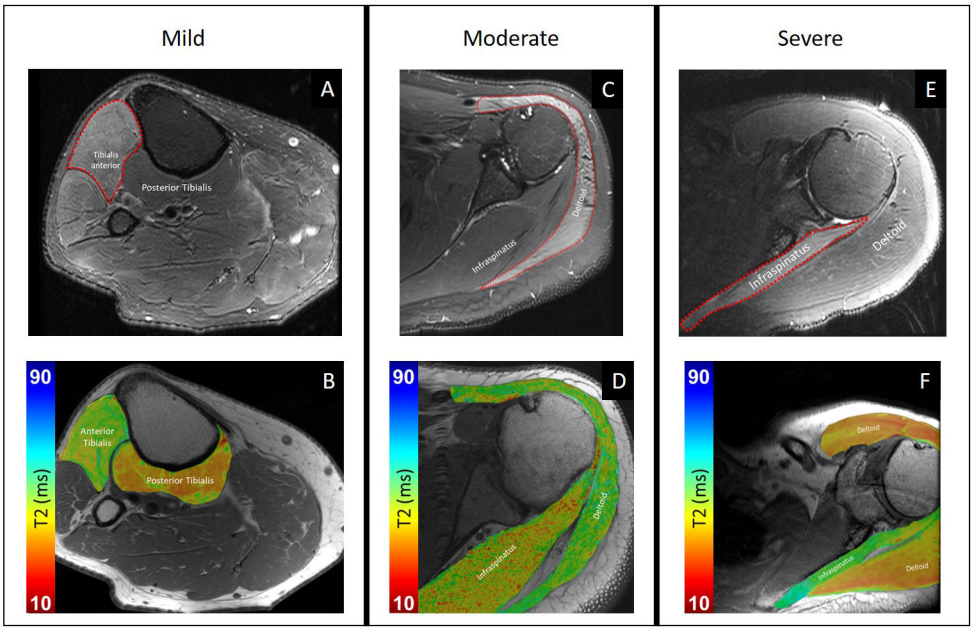

Figure 1:

Morphological, Dixon fat-suppressed T_2-weighted images (top row) and T_2 maps (bottom row), superimposed on proton-density weighted images, for patients with varying edema pattern severity by morphological grading. (A) 72-year-old man with recent onset right foot drop status post lumbar laminectomy two weeks prior, with mild edema pattern of the tibialis anterior muscle and normal signal intensity arising from the posterior tibialis. (B) Corresponding representative axial T_2 mapping image demonstrates elevated T_2 of the anterior tibialis. (C) 42-year-old man with weakness of shoulder abduction status post glenohumeral capsular repair surgery 1.5 years prior, with moderate edema pattern of all three deltoid muscle heads and normal signal intensity of the infraspinatus. (D) Corresponding representative axial T_2 mapping image demonstrates elevated T_2 of the deltoid. (E) 54-year-old man with spontaneous onset of severe pain followed by left shoulder abduction weakness, 8 months prior and attributed to neuralgic amyotrophy, with severe edema pattern of the infraspinatus muscle and normal signal intensity of the deltoid. (F) Corresponding representative axial T_2 mapping image demonstrates elevated T_2 of the infraspinatus.