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TECHNICAL REPORT

Optimizing methods to quantify intramuscular fat in rotator cuff tears with normalization

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Abstract

Objective To determine which normalization method may best account for confounding individual factors, such as age or BMI, when quantifying fat infiltration on MRI in patients with rotator cuff tears, the effects of normalization using three different muscles (teres major; triceps brachii; teres minor) were compared.

Methods Thirty-seven consecutive patients diagnosed with rotator cuff pathology were included. MRI fat–water sequences were used to quantify rotator cuff intramuscular fat (%fat). Three reference muscles (teres major, triceps, teres minor) were used to derive normalized %fat. Relationships between intramuscular %fat and tear size, age, and BMI in each rotator cuff muscle, before and after normalization, were compared with Fisher transformations ($\alpha = 0.05$).

Results Normalization with teres major ameliorated confounding relationships of age and BMI on rotator cuff %fat. In contrast, normalization with triceps maintained the confounding relationships between %fat and age in supraspinatus ($p = 0.03$) and infraspinatus/teres minor ($p = 0.028$). Normalization with teres minor maintained the confounding relationship between %fat and BMI in subscapularis ($p = 0.039$). Normalization with teres major best-maintained relationships between tear size and infraspinatus/teres minor %fat ($p = 0.021$). In contrast, normalization with triceps or teres minor eliminated all significant relationships with tear size.

Conclusions Results of this pilot study suggest normalization to teres major using MRI-based %fat quantification methods can effectively control for individual factors, such as BMI or age, and may have utility in evaluating and monitoring rotator cuff fat infiltration attributed specifically to a tendon tear.

Keywords Dixon fat–water separation · Intramuscular degeneration · Fatty infiltration · Supraspinatus

Introduction

Rotator cuff (RC) intramuscular fat infiltration is progressive following RC tendon tear [1–3] and compromises repair healing, function, and patient-reported outcomes even when repair is achieved [4–8]. Thus, surgical repair before significant and irreversible fat infiltration has been advocated to optimize patient outcomes [5, 9]. However, results of recent randomized trials comparing rehabilitation to surgical repair in patients with small to medium-sized degenerative RC tears show no clinically significant differences in patient-reported outcomes at 2 and 5 years [10, 11]. As such, repeat imaging may be warranted in patients who seek non-operative treatment [12] as surveillance of disease progression that can occur [3, 9, 13].

RC fat infiltration is assessed clinically with the qualitative Goutallier classification originally described using computed tomography (CT) and later using magnetic resonance (MR) imaging [14, 15]. However, these methods lack precision and reproducibility [16–18]. Advances in MR imaging techniques overcome these limitations by providing rapid quantification of intramuscular fat fraction (%fat) [19–22]. In addition to using quantitative methods to evaluate RC muscle in the classic "y-view", the two-point Dixon sequence has been shown to have excellent reliability to quantify 3D %fat [23].

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While previous studies using quantitative fat–water MR imaging techniques demonstrate relationships between intramuscular RC %fat and tear size [1, 16, 24], intramuscular %fat is confounded by individual factors (age, gender, BMI), whereby a statistical correction has been proposed [16]. However, other within-patient confounders such as smoking, activity level, health co-morbidities [25, 26] have not been considered with this statistical correction. Known (age, gender, BMI) and unknown factors that may to contribute to intramuscular RC fat infiltration would be attributed to the RC tear. Thus, a quantitative method that controls for all individual confounders is needed. Normalization of %fat using a reference muscle is one method used to control for confounding effects of fat that has been previously validated in the assessment in liver disease [27]. Normalization may similarly control for confounding factors in the RC muscles. Thus, to determine which normalization method can best ameliorate confounding effects of individual factors [16] on RC intramuscular %fat in patients with RC tears, we compare the effects of normalization RC %fat using three different muscles (teres major, triceps brachii, and teres minor).

Materials and methods

Subjects

A retrospective case series of consecutive patients between January 2015 and November 2016 from one academic medical center was included in this pilot study. To be included in the series, patients were clinically diagnosed with rotator cuff pathology by one of two fellowship trained shoulder surgeons and evaluated with magnetic resonance (MR) imaging performed at the institution. This subset of patients was selected to maintain consistency in the scanner used for MR imaging and sequences available for analysis. Surgeon criteria for the diagnosis of rotator cuff pathology included shoulder pain or weakness with active range of motion and resistance testing in abduction or external rotation, positive lag signs, and positive Neer or Hawkins special tests. To maintain homogeneity of the sample, primary subscapularis tendon tears, and partial thickness RC tears were excluded due to the high prevalence of concomitant diagnoses (i.e., labral involvement/biceps pathology). Subject data were retrieved from electronic medical records. The study was conducted with IRB approval and in accordance with the Committee for Human Research.

MRI protocol

All images were obtained from a 3.0-T MR scanner (Siemens, Magnetom Skyra, USA) using a 16-channel shoulder coil. T1-weighted sequences included fast spin-echo sequences in oblique coronal and sagittal planes as well as a multiple echo data image continuation (MEDIC) sequence in the axial plane. T2-weighted fat-suppressed sequences were gathered in the axial plane, coronal oblique, and sagittal oblique planes. A 3D multi-echo, two-point Dixon fat–water imaging sequence was performed in the sagittal oblique plane, including all musculature from the medial boarder of the scapula to the glenoid. The sagittal oblique plane was selected for consistency with sequences used to clinically evaluate the rotator cuff muscles in the Y-view [28]. The imaging parameters were a slice thickness of 2.0 mm, TR/TE1/TE2 = 3.97 ms/1.29 ms/2.52 ms, flip angle of 9°, FOV of 380 mm, and acquisition matrix of 320 × 320 with 120 slices to produce a voxel resolution of 1.2 × 1.2 × 2.0 mm. Oversampling of 100 and 60% were used in order to reduce aliasing in both the phase and 3D direction, respectively. An acceleration factor of 2 was used in both the slice and phase directions to reduce the acquisition time.

Image analysis

A musculoskeletal radiologist, blinded to surgeon diagnosis, independently evaluated the MR images to determine the presence of tear and size (mm). Tear size was assessed in both longitudinal (anterior/posterior) and transverse (medial/lateral) dimensions with the largest dimension recorded (mm) and used in analyses [29]. Two medical students without prior experience reading MR images were trained by a musculoskeletal radiologist and two fellowship trained shoulder surgeons to identify the regions of interest for manual segmentation of the 3D multi-echo, two-point Dixon sequences. The regions of interest (Fig. 1) included the supraspinatus (SS), combined infraspinatus/teres minor (IS/TM),

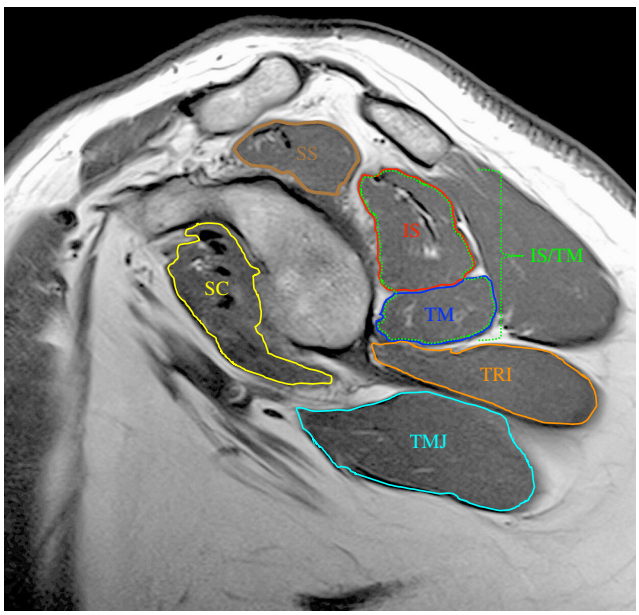

Fig. 1 Sagittal oblique MR image shown at the level of the glenohumeral joint with the outline of segmented regions: supraspinatus (SS); subscapularis (SC); infraspinatus (IS); teres minor (TM); infraspinatus/teres minor (IS/TM); triceps (TRI); teres major (TMJ)

subscapularis (SC), infraspinatus (IF), and teres minor (TM) muscles. The %fat in each segmented region of interest was generated using a customized MATLAB program (MathWorks, Natick, MA, USA). All sagittal oblique images from the articular surface of the glenoid to the medial border of the scapula were manually segmented by examiners and averaged to calculate mean 3D %fat of each rotator cuff muscle. Infraspinatus and teres minor muscles were segmented in two ways: individually to isolate fat–muscle changes and collectively to accommodate comparisons to prior studies grouping the two adjacent muscles [20, 21]. Anatomic landmarks and fascial planes were used to guide segmentation between infraspinatus and teres minor muscles. All muscles were segmented just within the borders of muscle fascia, excluding perimuscular fat [16, 21]. Examiners performing the segmentation were blinded to tear size results provided by the musculoskeletal radiologist. The %fat from 3D water-fat imaging was created from the co-registered images using the mean pixel intensity of fat-only and water-only images with the following calculation: %fat = fat/(fat + water). Before conducting the study, examiners established good-to-excellent intra-rater ($ICC_{3,1}$ = 0.93–0.99) and inter-rater ($ICC_{3,1}$ = 0.82–0.99) reliability of the segmentation methods to quantify %fat in the RC muscles in 13 subjects. The %fat of three ipsilateral uninvolved muscles, including teres major, the long head of triceps brachii, and teres minor were also quantified. For teres major and the long head of triceps, three slices (one before and one after the level of the glenohumeral joint) were measured and averaged to calculate mean %fat in each normalization muscle. Teres major and the long head of the triceps muscles were chosen because they are anatomically adjacent to the rotator cuff, yet have no involvement in cuff tears with largely different function and innervation [20]. Teres minor was chosen because it is rarely involved, even in the setting of massive posterior-superior rotator cuff tears and has been previously shown to be resistant to fat infiltration following cuff tears [30, 31].

Statistical analyses

Mean non-normalized %fat in each RC muscle and uninvolved muscle were calculated based on the data from the respective region of interest in each slice. Normalized %fat ratios were then calculated by dividing the mean %fat in each RC muscle by mean %fat in triceps, teres major, or teres minor muscles. Pearson correlation coefficients were used to examine relationships between %fat and BMI or age, in each rotator cuff muscle (SS, IS/TM, SC, IS) before and after normalization. Additionally, relationships between %fat and tear size (mm) were evaluated with Pearson correlation coefficients under normalized and non-normalized conditions for SS, IS/TM, SC, and IS. Relationships between %fat in each of the three reference muscles and tear size (mm) were also evaluated with Pearson coefficients. Correlation coefficients before and after normalization were then tested for equality after converting each Pearson coefficient into a z-score using Fisher's r-to-z transformation, accounting for dependency using paired observations [32–34]. SAS statistical software (JMP 11.0, SAS Institute, Cary, NC, USA) was used for analyses and significance was set at $\alpha < 0.05$.

Results

Relationships to age and BMI

The subject characteristics are shown in Table 1. The relationships between %fat and BMI or age before and after normalization to each reference muscle are detailed in Table 2. Before normalization, there were significant linear relationships ($p < 0.05$) between %fat and either BMI or age in all rotator cuff muscles (r_{BMI} = 0.27–0.42; r_{AGE} = 0.45–0.61). After normalization with teres major, there were no statistically significant relationships ($p > 0.05$) between %fat and either BMI or age in any of the muscles. Figure 2 shows linear regression plots demonstrating these relationships between %fat (before and after normalization to teres major) and either age or BMI in the supraspinatus muscle. In contrast to normalization with teres major, normalization with triceps maintained significance between %fat and age in two muscles (SS: $r = 0.36$, $p = 0.030$; IS/TM: $r = 0.36$, $p = 0.028$) and normalization with

Table 1 Subject characteristics

Subject characteristics	*N* / mean ± SD
Age (years) (*N* = 37)	58.3 ± 13.4
Body mass index (kg/m^2) (*N* = 35)	29.0 ± 5.4
Sex	
Male	24
Female	13
Dominant hand	
Right	28
Left	2
Involved shoulder	
Right	21
Left	16
Rotator cuff tear size (mm) %fat (*N* = 37)	17.7 ± 16.5
Intramuscular %fat in the supraspinatus by tear size	
No tear (*N* = 6)	11.0
Small tear (*N* = 9)	19.4
Medium tear (*N* = 14)	16.4
Large tear (*N* = 3)	27.5
Massive tear (*N* = 6)	25.4
Chronicity of symptoms (months)	13.5 ± 15.4

Small tear (< 1 cm), medium tear (1–3 cm), large tear (3–5 cm), massive tear (> 5 cm)

N number of subjects, *SD* standard deviation

Table 2 Relationships between %intramuscular fat and body mass index (BMI, kg/m^2) or age (years) for rotator cuff muscles across subjects in non-normalized and three normalized conditions: teres major, triceps, and teres minor

		Non-normalized	Normalized to teres major	Normalized to triceps	Normalized to teres minor
Supraspinatus					
Age (years) $N = 37$	r	0.61	0.29	0.36	0.14
	p value	< 0.001*	0.084	0.030*	0.424
BMI (kg/m^2) $N = 35$	r	0.42	0.17	0.10	− 0.05
	p value	0.012*	0.328	0.555	0.799
Infraspinatus/teres minor					
Age (years) $N = 37$	r	0.51	0.30	0.36	0.17
	p value	0.001*	0.068	0.028*	0.316
BMI (kg/m^2) $N = 35$	r	0.37	0.21	0.12	0.05
	p value	0.030*	0.217	0.491	0.755
Subscapularis					
Age (years) $N = 37$	r	0.58	0.18	0.23	− 0.10
	p value	< 0.001*	0.273	0.167	0.543
BMI (kg/m^2) $N = 35$	r	0.27	− 0.08	− 0.08	− 0.35
	p value	0.115	0.662	0.654	0.039*
Infraspinatus					
Age (years) $N = 37$	r	0.45	0.23	0.30	0.11
	p value	0.006*	0.162	0.075	0.530
BMI (kg/m^2) $N = 35$	r	0.39	0.21	0.13	0.09
	p value	0.022*	0.218	0.466	0.615

Values presented as Pearson correlation coefficient (r) and p value (*$p < 0.05$)

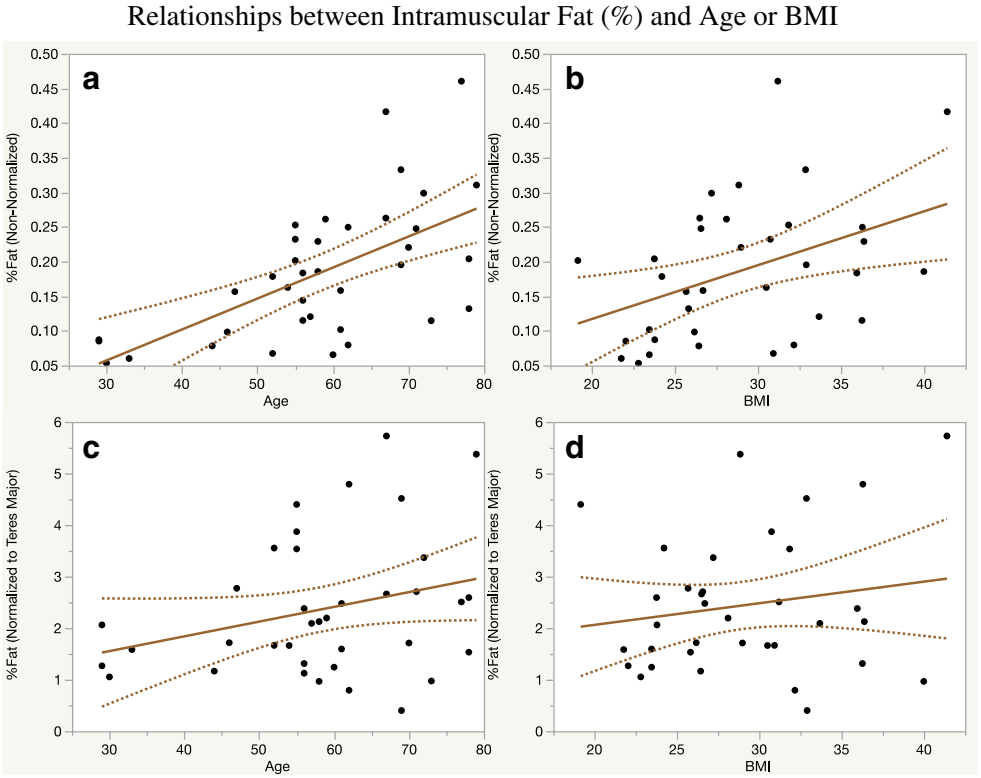

Fig. 2 Linear regression plots comparing %intramuscular fat and either age or BMI for supraspinatus muscle before and after normalization to teres major. **a** Relationship between age and %fat before normalization ($r = 0.61$, $p < 0.001$). **b** Relationship between BMI and %fat before normalization ($r = 0.42$, $p = 0.012$). **c** Relationship between age and %fat after normalization to teres major ($r = 0.29$, $p = 0.084$). **d** Relationship between BMI and %fat after normalization to teres major ($r = 0.17$, $p = 0.328$). Normalized values are expressed as a %fat ratio

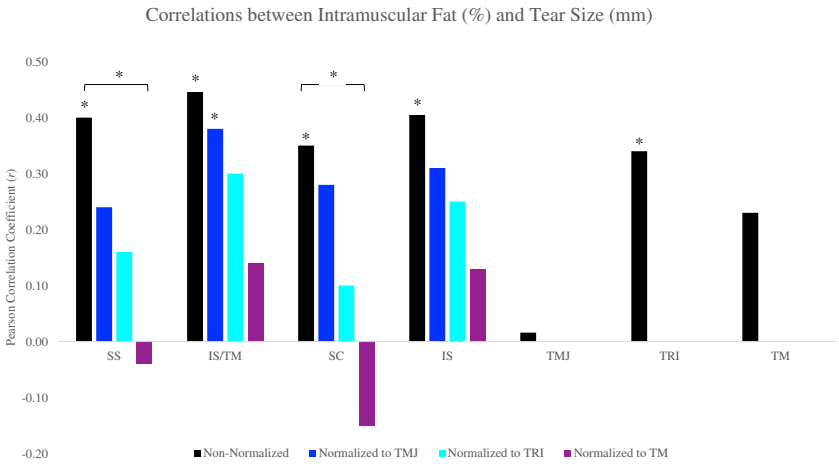

Fig. 3 Correlation coefficients (r) for relationships between %fat and tear size (*$p < 0.05$) across the non-normalized and three normalized conditions for supraspinatus (SS), combined infraspinatus/teres minor (IS/TM), subscapularis (SC), and infraspinatus (IS); SS: non-normalized ($p = 0.015$); IS/TM: non-normalized ($p = 0.005$), teres major-normalized ($p = 0.021$); SC: non-normalized ($p = 0.032$); IS: non-normalized ($p = 0.013$). Significant differences in Fisher-transformed %fat-tear size correlations across pre and post-normalized conditions are shown in brackets; SS (non-normalized)-TM: $p = 0.020$; SC (non-normalized)-TM: $p = 0.048$. Correlation coefficients are also shown for relationships between %intramuscular fat and tear size (*$p < 0.05$) among each of the three reference muscles used as controls for normalization: teres major (TMJ: $p = 0.925$), triceps (TRI: $p = 0.042$*), and teres minor (TM: $p = 0.17$)

teres minor demonstrated significance between %fat and BMI in one muscle (SC: $r = -0.35$, $p = 0.039$).

Relationships to tear size

As shown in Fig. 3, %fat in all rotator cuff muscles before normalization showed a positive linear relationship with tear size (SS: $r = 0.40$, $p = 0.015$; IS/TM: $r = 0.46$, $p = 0.005$; SC: $r = 0.35$, $p = 0.032$; IS: $r = 0.41$, $p = 0.013$). After normalization to teres major, %fat was significantly related to tear size in the IS/TM muscle ($r = 0.38$, $p = 0.021$) and demonstrated trends in the IS ($r = 0.31$, $p = 0.061$) and SC ($r = 0.28$, $p = 0.096$). In contrast, there were no statistically significant relationships between %fat and tear size in all four muscles after normalization to triceps (SS: $r = 0.16$, $p = 0.331$; IS/TM: $r = 0.30$, $p = 0.069$; SC: $r = 0.10$, $p = 0.551$; IS: $r = 0.25$, $p = 0.129$) and teres minor (SS: $r = -0.04$, $p = 0.799$; IS/TM: $r = 0.14$, $p = 0.392$; SC: $r = -0.15$, $p = 0.391$; IS: $r = 0.13$, $p = 0.451$).

Analyses using Fisher transformations of each correlation were used to determine whether normalized %fat-tear size relationships significantly differed from those before normalization. Non-normalized relationships were shown to be significantly different from teres minor-normalized relationships in two muscles (SS: $p = 0.020$; SC: $p = 0.048$). In contrast, the non-normalized relationships between %fat and tear size did not significantly deviate from these relationships after normalization to teres major (SS: $p = 0.204$, IS/TM: $p = 0.451$, SC: $p = 0.677$, IS: $p = 0.318$) or triceps (SS: $p = 0.075$, IS/TM: $p = 0.197$, SC: $p = 0.080$, IS: $p = 0.187$).

Also depicted in Fig. 3 are the relationships between RC tear size and %fat in the three reference muscles. Tear size was shown to be significantly related to %fat in triceps ($r = 0.34$, $p = 0.042$), whereas no significant relationships were characterized between tear size and %fat in either teres major ($r = 0.02$, $p = 0.925$) or teres minor ($r = 0.23$, $p = 0.170$). Means and standard deviation for %fat measurements of reference muscles were as follows: teres major (0.092 ± 0.076), triceps (0.061 ± 0.031), and teres minor (0.115 ± 0.122).

Discussion

In this preliminary study, we examined whether normalization methods can isolate fatty infiltration in rotator cuff muscles attributed specifically to a RC tear by controlling for individual factors, such as age and BMI and other unknown confounders. For normalization to be successful, we expected relationships between RC %fat and both age and BMI to weaken after normalization procedures. We see this after normalization to each reference muscle (teres major, triceps, teres minor). There are several findings in this pilot study, however, that make teres major more suitable than triceps or teres minor as a reference muscle for normalization.

The first is the finding that normalization to teres major eliminated all relationships between %fat and age or BMI, while normalization to triceps and teres minor maintained several confounding relationships between age and BMI, respectively. This suggests that normalization to teres major best isolated the confounding effects of age and BMI on %fat. This is important because the degree to which each reference muscle (i.e., normalization method) could eliminate relationships involving age and BMI represented its ability to account for

confounding individual factors in %fat quantification. The second finding is that normalization with teres major was the only normalization condition to maintain a significant %fat-tear size relationship in any rotator cuff muscle (exhibited in IS/TM). We believe the reduction in strength of this relationship following normalization can be accounted for by individual systemic differences, including BMI and age—not to mention a variety of other possible health co-morbidities that may impact intramuscular %fat and thus accounted for through normalization. In contrast to teres major, normalization with triceps and teres minor eliminated all significant relationships between %fat and tear size. The elimination of these relationships is problematic because %fat is believed to be an independent indicator of tear size after controlling for independent factors like BMI and age [16]. Furthermore, Fisher transformations showed that normalization to teres minor significantly altered the relationship between %fat and tear size in SS and SC, making teres minor a particularly poor candidate for normalization procedures. Finally, %fat in triceps showed a significant relationship to tear size, so using it as a muscle for normalization may paradoxically obscure the %fat-RC tear size relationship that we hope to isolate. This stands in contrast to %fat in teres major, which was itself shown unrelated to tear size. Overall, these results suggest triceps and teres minor are less suitable than teres major as reference muscles for normalization of %fat in rotator cuff muscles.

Prior studies have elucidated relationships between RC %fat and tear size [16], but not all individual factors can be accounted for with current methods. Moreover, %fat has been shown to be related to many individual factors; these include age and BMI [16], but also perhaps a variety of other health comorbidities (cardiovascular disease, hyperlipidemia, diabetes) [16, 25, 26, 35]. All of these may serve as potential confounders in the %fat-tear size relationship and normalization has not been previously explored or validated as a solution. We believe normalization to teres major can better isolate the true relationships between %fat and tear size or other variables by eliminating confounding individual differences.

There were several strengths to this preliminary study. The creation of a normalization standard has the potential to allow for greater accuracy in quantitative %fat measurements by eliminating possible confounding variables. Whereas prior work has used statistical corrections for these confounders with group data [16], normalization to teres major allows for evaluation of %fat in RC muscles attributed to the tear in an individual patient. Furthermore, this proposed method is subject-specific to capture variables beyond age and BMI, such as other health co-morbidities that may impact fatty infiltration. Future work may allow for the development of a quantitative %fat threshold to allow for greater diagnostic accuracy than the Goutallier scale in evaluating rotator cuff muscle quality related to tear size to optimize timing of surgical treatment recommendations. Another strength unique to this study includes the segmentation method that allowed 3D quantification of fat of each rotator cuff muscle from the glenoid to the medial border of the scapula. This is an improvement over most %fat quantification studies that limit sagittal oblique segmentation to lateral scapular images surrounding the Y-view [16, 21]. The examination of the entire muscle body accounts for potential intramuscular differences in fatty infiltration [36]. Moreover, teres minor and infraspinatus were manually segmented in two ways (distinct from one another and combined) to best facilitate comparisons to prior studies that have approached their segmentation in different ways.

This pilot study should be interpreted with an understanding of its limitations. First of all, the sample size consisted of 37 patients with a predominance of small to medium-sized tears and the majority comprised of male subjects (65%). As such, we believe our data is most generalizable to this population, who may benefit the most from monitoring RC disease progression when managed non-operatively. Moreover, other specific factors believed to influence fat infiltration beyond age and BMI (including activity level, insulin resistance, hypercholesterolemia, dyslipidemia, cardiovascular conditions, or chronicity of tear), were not included in the study to further validate the extent of normalization under each condition. It should also be noted that our analysis did not take into account the possibility of racial differences in fat infiltration [37]. We believe these would be valuable areas of future study. Another potential limitation of this study is that we cannot determine whether RC muscles and potential reference muscles (e.g., teres major) demonstrate similar patterns of baseline muscle aging; prior studies have differentiated RC muscles based on temporal patterns of fatty infiltration [38]. It may also be noted that possible biomechanical effects, such as underuse atrophy or compensatory hypertrophy, from our use of an ipsilateral reference muscle could alter %fat in muscle following RC tear. Our use of ipsilateral normalization methods, however, is clinically applicable and could be integrated into future imaging protocols without additional imaging needed. We also assessed for a possible confounding effect by testing for the presence of relationships between %fat in the reference muscles to tear size. This effect was only found significant in the triceps muscle. Nonetheless, future research involving normalization with bilateral shoulder imaging may be valuable to further validate current study preliminary results.

Normalization procedures using MRI-based %fat quantification methods may more effectively account for fat infiltration related to individual co-morbidities (specifically BMI and age), and may have utility to quantify %fat in muscle attributed specifically to a RC tear. Results of this pilot study support the use of teres major for ipsilateral normalization of RC fat infiltration and, furthermore, discourage the use of triceps or teres minor. Accounting for within-patient confounders can facilitate accurate understanding of RC intramuscular degenerative progression that can be more isolated to RC tear alone with monitoring of disease progression.

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Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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