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REVIEW

Muscle Health & Fatty Infiltration with Advanced Rotator Cuff Pathology

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Abstract

Purpose of Review Fatty infiltration (FI) of the rotator cuff is a critical determinant of clinical outcomes following rotator cuff injuries and repairs. This review examines the natural history, pathophysiology, imaging evaluation, and treatment strategies for FI, highlighting recent insights into its cellular mechanisms and emerging therapeutic approaches.

Recent Findings Animal models demonstrate that FI begins shortly after tendon injury, progresses with muscle retraction and denervation, and is largely irreversible despite repair. Key cellular drivers include fibroadipogenic progenitor cells (FAPs), influenced by mechanical loading and inflammatory signaling pathways. Clinical studies show that FI is associated with advanced age, female sex, and full-thickness tears. Higher degrees of preoperative FI correlate with poorer functional outcomes and increased re-tear rates. Novel therapeutic targets, including pathways regulating FAP activity, TGF-β, and cell-based therapies, show promise in preclinical studies. Emerging strategies such as leukocyte-poor platelet-rich plasma (PRP) may mitigate FI progression in clinical settings.

Summary Fatty infiltration remains a significant barrier to successful rotator cuff repair and functional recovery. While surgical repair may slow FI progression, it is not consistently effective in reversing established muscle degeneration. Improved understanding of the molecular mechanisms driving FI has identified potential therapeutic targets, but their clinical applicability requires further validation. Future advances in regenerative medicine, including cell-based therapies and modulation of fibroadipogenic progenitors, offer hope for mitigating FI and improving long-term outcomes.

Keywords Fatty infiltration · Rotator cuff repair · Muscle degeneration · Epidemiology · Functional outcomes · Goutallier classification

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Introduction

Symptomatic rotator cuff tears are one of the most common musculoskeletal conditions, causing significant morbidity and financial burden due to lost productivity in economies across the world. Despite improvements in minimally invasive repair techniques and biomechanical constructs, the rate of recurrence for large to massive tears has remained as high as 50% in recent case series [1]. Accordingly, significant research has focused on biological augmentation of tendon-to-bone healing at the repaired enthesis. However, the fatty infiltration of the rotator cuff musculature is of paramount importance. Fatty infiltration (FI) has a significant impact on the outcomes of rotator cuff repair, even in the setting of a fully healed enthesis. Therefore, understanding the pathophysiology, imaging characteristics, natural history, potential for reversibility, and impact on outcomes with rotator cuff repair is critical for clinicians treating rotator cuff tears.

Epidemiology

The prevalence of rotator cuff tears in the general population has been estimated from cadaveric studies as well as radiographic studies of symptomatic and asymptomatic patients. Neer [2] reported a prevalence of 5% full-thickness rotator cuff tears during anatomic dissection of 500 cadaveric specimens, while Lehman et al. [3, 4]. found 17% of 235 specimens had full-thickness tears. Using ultrasound, Tempelhof et al. [1]. found an overall prevalence of asymptomatic rotator cuff tears of 23% in 411 volunteers. Within that cohort, 51% of patients older than 80 years of age had a tear.

The presence of fatty infiltration within injured rotator cuff muscle is closely linked to certain clinical factors and tear characteristics. Barry et al. [5] reported that prevalence of substantial fatty infiltration (≥ Goutallier grade 2) correlated with increasing patient age, female sex, and the presence of a full-thickness tendon tear. Furthermore, 41.4% of patients with complete tears exhibited fatty infiltration compared to 6.5% of patients with no tear. Melis and Walch et al. [6, 7] likewise reported found that fatty infiltration increased with longer duration of symptoms, with moderate supraspinatus fatty infiltration (grade 2) appearing at an average of 3 years after symptom onset, and severe fatty infiltration (grade 3–4) appearing roughly 5 years after symptom onset. In a cohort of 30 patients with glenohumeral arthritis who were indicated for total shoulder arthroplasty, the prevalence of grade 2 or greater fatty infiltration of at least one rotator cuff muscle was reported in 43% [8], suggesting that glenohumeral arthritis may be a risk factor for fatty infiltration of the rotator cuff even in the absence of a rotator cuff tendon tear.

Mechanisms/Pathophysiology

Fatty infiltration was initially thought to be due to a change in the pennation angle of muscle, which allowed epimuscular fat to infiltrate from the surrounding tissue into the muscle of the rotator cuff. Over the last decade, however, a more nuanced understanding of the intracellular sources of fatty infiltration has developed. Several animal and human studies have demonstrated the importance of fibroadipoprogenitor cells (FAPs) in the development of fatty infiltration [9]. In 2010, Uezemi and colleagues uncovered a previously unreported mesenchymal cell that had unique differentiation capabilities that they termed the *fibroadipoprogenitor cell*, *or FAP* [10]. In two elegant studies [10, 11], they found that this stem cell had a unique cell surface marker within muscle, PDGFRa, which allows researchers to track it over time, and when given the proper stimulus, was able to differentiate into several other cell types within muscle including adipocytes and fibroblasts (as well as osteocytes).

These cells have been found to have a central role in the regulation of muscle degeneration in several disease states including muscular dystrophy, amyotrophic lateral sclerosis (ALS), and aging [10–17]. FAPs have been found in animal models to proliferate at the time of rotator cuff injury, and directly contribute to the development of fatty infiltration through expression of white fat-associated genes including PPARy, CREB/P, and other fat-related genes [18–20]. This work was critical as it explained the relative lack of differentiation capabilities of the muscle stem cell (satellite cell) that has limited capability to differentiate, and the fact that other mesenchymal cell sources such as pericytes and bone marrow derived sources did not appear to be producing fatty infiltration. Over the past 15 years, a series of more elegant studies have expanded on the role of these critical cells as a key effector of development, injury, repair, and regeneration in muscle.

In animal models, fatty infiltration can be decreased through inhibition of several pathways, all of which appear to modulate the FAP response to injury. These include inhibition of TGF-β, retinoic acid, and PPARy [21–24]. In human studies, FAPs have been shown to proliferate at the time of rotator cuff injury and increase in number as tear size progresses, suggesting that these cells do not become exhausted with aging or injury [25]. Non-biased transcriptomic studies have shown that FAPs isolated from partial and larger tears behave differently, with FAPs from full-thickness tears more likely to express makers of adipogenesis.

Early transcriptomic studies demonstrated that FAPs represented a heterogeneous cell population capable of both regenerative and pathologic responses to muscle injury [26, 27]. Therefore, there stands to reason that there is a biologic role for the fatty infiltration within muscle during a time of rotator cuff injury. It has been noted that in some circumstances, FAPs expressed factors that were similar to beige and brown fat, particularly the protein UCP-1, or uncoupling protein-1, a protein that is related to mitochondria energy use and beige fat development [28]. Therefore, it is possible that FAPs could also have a regenerative phenotype when given the proper stimulus, which would then be a potential reservoir of latent endogenous stem cells within muscle that could be stimulated to promote muscle regeneration.

It has been noted that B-agonists such as mirabegron and amibegron are able to promote increased UCP-1 expression in beige fat [29]. Mouse and human FAPs treated in vitro with B-agonists have an increase in UCP-1 expression, and importantly, demonstrate a decrease in adipogenesis in vitro, suggesting a shunt away from white fat and towards a more beige fat phenotype. RT-PCR evaluation of FAPs that had undergone this treatment showed expression of several 'beige fat' markers including UCP-1, PRDM-16, as well as other factors associated with myogenic growth including IGF-1 and follistatin isoforms. Notably, similar gene expression with the same treatment in human FAP populations has been demonstrated. This initial work suggests that FAPs could have an alternative, pro-myogenic pathway has been termed beige-FAPs for their similarity to beige fat.

Several pre-clinical models support FAPs as having a regenerative phenotype in rotator cuff injury and repair. Beige-FAP differentiated cells transplanted into a rotator cuff model of injury were able to virtually eliminate fatty infiltration [30]. Pharmacologic administration a B-agonist is also able to promote muscle regeneration both after rotator cuff injury and repair, with elimination of rotator cuff fat and amelioration of atrophy. Using single cell RNA sequencing, recent studies suggest multiple possible mechanisms behind the FAP-mediated muscle recovery. Single-cell RNA sequencing of human FAPs from the rotator cuff revealed 6 distinct subpopulations of human FAPs, with one subpopulation demonstrating the presence of UCP1 + beige adipocytes with a distinct profile of BAT, mitochondrial, and extracellular vesicle-associated markers. Markers from these cells showed a high expression level of CD81, which is a marker of extracellular vesicle production. In vitro, highly purified FAP-EVs were able to differentiate both myotubes and fibroblasts into myotubes. In vivo, mice that were treated with EVs at the time of rotator cuff injury demonstrated markedly reduced muscle atrophy and fatty infiltration as compared with treatment with control EVs or phosphate-buffered saline [31]. Thus, EVs represent an appealing potential strategy to harness the regenerative potential of B-agonist treated human FAPs in a scalable strategy. Additionally, it has been shown that FAPs may mediate mitochondrial transfer to recovering cells following rotator cuff injury as a second potential pathway for recovery [32].

The differentiation of FAPs into fat cells is tightly regulated by complex signaling networks. Key pathways involved in this regulation include those critical for embryonic development, such as Wnt/β-catenin, which play a role in managing fat accumulation across various organ systems. In muscle tissue, overexpression of WNT5A and WNT7A has been shown to mitigate fatty infiltration following glycerol-induced injury [33, 34]. Additionally, cell cycle-related pathways, such as Akt/mTOR, work in conjunction with the white fat-associated gene PPARγ to modulate adipogenesis in FAPs. Akt/mTOR activation enhances PPARγ expression, which subsequently regulates adipogenic differentiation through a negative feedback loop [35]. Pharmacological inhibition of mTOR disrupts preadipocyte differentiation into mature adipocytes by targeting PPARγ [36]. However, complete inhibition of PPARγ also affects muscle stem cell proliferation and myogenesis, underscoring its vital role in both muscle recovery and adipogenesis.

Other signaling pathways also play significant roles in fat differentiation, though they are not fully understood. For example, NF-κB, which is pivotal in regulating inflammation and muscle atrophy, has been linked to fat differentiation. The NOTCH signaling pathway, influenced by Delta1, can prevent fatty differentiation of FAPs [37, 38]. However, in the absence of NF-κB, FAPs lose sensitivity to the anti-adipogenic effects of NOTCH signaling, indicating an interaction between NOTCH and NF-κB pathways [38].

Fibrosis pathways also play a crucial role in determining whether FAPs differentiate into adipocytes. Key regulators like TGF-β play a central role by promoting the myofibroblast differentiation of FAPs while also inhibiting adipogenesis [39, 40]. Notably, inhibition of TGF-β signaling results in reduced fibrosis, fatty infiltration, and muscle loss following injury, which is associated with a decrease in PPARy signaling [22]. However, this pathway is not yet fully understood. Moreover, TGF-β works in conjunction with MMP-13, which is a protease that breaks down collagen and is essential for modulating fibrogenic processes. In vitro experiments have demonstrated that MMP-13 knockout FAPs exhibited increased adipogenesis and reduced fibrogenesis compared to wild-type FAPs despite administration of TGF-β [41]. This suggests that TGF-β is an upstream regulator of MMP-13, highlighting their combined role in regulating fat differentiation and fibrosis.

Pathophysiology

Multiple pathophysiologic and pathomechanical mechanisms have been proposed for the development of fatty infiltration of the rotator cuff. Meyer and Gerber et al. [42] analyzed longitudinal sections of muscle from sheep that underwent infraspinatus tendon release and compared to uninjured controls, and found the angle separating parallel fibers, termed the pennation angle, increased with tendon release. They concluded this increased interstitial space resulting from mechanical unloading of the muscle allowed space for fat cells and fibrous tissue to "infiltrate" between the remaining muscle fibers. In a follow-up study, Gerber et al. [43] used a sheep infraspinatus tear model to show that mechanical elongation of a previously retracted infraspinatus tendon led to arrest of fatty infiltration and partial reversal of muscle atrophy. Thus, mechanical unloading of an injured rotator cuff tendon is thought to play a role in the developing fatty infiltration, though further work is still needed to elucidate this process at the mechanoreceptor level.

In addition to mechanical unloading, denervation of the rotator cuff is thought to contribute to fatty infiltration. One proposed mechanism by which this denervation may occur is through traction on the suprascapular nerve, either at the level of the suprascapular notch [44] or at the level of the scapular spine [45]. Mallon et al. [46] demonstrated that in 8 patients with massive cuff tears, 100% demonstrated suprascapular neuropathy on EMG which was shown to be partially reversed in 2 patients (25%) who consented to EMG follow-up after surgical repair. A comparative study between patients with chronic rotator cuff tears without EMG evidence of suprascapular neuropathy and patients without rotator cuff tears who had abnormal suprascapular nerve function on EMG demonstrated different morphological patterns of fatty infiltration within the rotator cuff, suggesting that fatty infiltration resulting from chronic rotator cuff tears develops through a distinct process from isolated suprascapular neuropathy [47]. Clinical studies assessing the potential efficacy of suprascapular nerve decompression in the setting of rotator cuff repair have not yet shown a functional benefit of performing this procedure routinely in this setting [48].

Small animal models of rotator cuff tear have frequently combined a tendon unloading injury with direct injury to the suprascapular nerve in order to recapitulate the pathology found in the human rotator cuff following a chronic tear. Several of these studies concluded that the addition of suprascapular nerve injury increases the amount of fatty infiltration seen compared to tendon transection alone [49, 50] Wang et al. [28] found that reversal of suprascapular nerve compression in the mouse rotator cuff resulted in reinnervation of the supraspinatus and infraspinatus muscles in a process dependent on the expression of the gene uncoupling protein-1 (UCP1).

In summary, the pathogenesis of fatty infiltration in the rotator cuff is likely multifactorial and dependent upon both mechanical unloading as well as a secondary injury to the suprascapular nerve, though the exact interplay between these two mechanisms has yet to be fully elucidated.

Diagnosis and Staging

Physical Exam

Physical exam and imaging remain the mainstay of diagnosis in patients with advanced rotator cuff pathology. A standard examination of the shoulder begins with inspection and palpation of the supraspinatus and infraspinatus fossa to assess for rotator cuff atrophy. Comparison to the contralateral side may be helpful to assess for loss of muscle bulk. The presence of either supraspinatus or infraspinatus atrophy had a positive likelihood ratio (LR +) of 2.0 (95% CI: 1.5–2.7) for a rotator cuff tear [51]. In the setting of a massive rotator cuff tear, the humeral head can sometimes be appreciated to be abutting the acromion or to have escaped anterosuperiorly with passive elevation of the arm [52]. Aside from these maneuvers, over 25 special tests have been described for the examination of the rotator cuff. Strength tests were the most accurate for assessing a full-thickness rotator cuff tear, and included drop arm (LR +: 3.3, 95% CI: 1.0–11), external rotation lag sign (LR +: 7.2, 95% CI: 1.7–31), and internal rotation lag sign (LR +: 5.6, 95% CI: 2.6–12) [53]. The drop arm test assesses the supraspinatus and is positive when the patient immediately drops the arm from abducted position of 90° rather than slowly returning it to the side [54]. The positive external rotation lag sign is indicative of infraspinatus pathology and is positive when the patient is unable to maintain the position of full passive external rotation and 0° abduction of the shoulder [54]. The internal rotation lag test or passive lift off is positive when the patient is unable to maintain the position of full passive internal rotation with the hand lifted off the back and suggests a subscapularis tear [54]. Not surprisingly, the presence of these signs occur in advanced rotator cuff disease and are often associated with massive rotator cuff tears and pseudoparesis [52].

Imaging and Staging

Radiography is routinely used in the evaluation of the rotator cuff because imaging findings may indirectly suggest pathology or provide additional information that is critical to clinical management. A standard radiographic series of the shoulder

includes a Grashey view with and without weighted abduction, scapular Y, and an axillary lateral. These views may reveal irregularities of the greater tuberosity at the attachment site of the supraspintatus tendon, such as sclerosis, osteophytes, or subchondral cysts, which is indicative a full-thickness tear [55, 56]. Other information provided by radiographs includes the presence of inferior acromial sclerosis and lateral acromial spurring, which can be markers of subacromial impingement [57]. Calcifications along the rotator cuff insertion can also be visualized. Superior migration of the humeral head with narrowing of the acromiohumeral interval (AHI) and discontinuity of the scapulohumeral arch can be suggestive of a large or massive rotator cuff tear that has disrupted the force couples of the glenohumeral joint. Moreover, a decreased AHI has been shown to be associated with increased fatty degeneration of the rotator cuff muscles with 50–91% of Goutallier stage 3 or 4 tears having an AHI ≤ 6 mm [58–60]. Persistent cephalad migration of the humeral head can potentially lead to acetabularization of the acromion, superior glenohumeral joint space narrowing, and eventually humeral had collapse [61].

Computed tomography (CT) has a limited role in the evaluation of a suspected rotator cuff tear. However, Goutallier et al. initially classified the degree of fatty infiltration of the rotator cuff muscle after tendon rupture using axial CT images (Fig. 1) [62]. The classification system is based on the amount of intramuscular fat tissue compared with the amount of muscle tissue and is graded from 0 to 4. Stage 0 corresponds to completely normal muscle; stage 1 represents some fatty streaks; stage 2 has more muscle than fat; stage 3 has an equal amount of muscle and fat; and stage 4 has more fat than muscle. The intraobserver agreement of this classification system on CT scans varied from 0.61 to 0.69, which indicates good agreement [63, 64]. Conversely, the interobserver reliability ranged from 0.40 to 0.50, which indicates poor-to-moderate agreement [63, 64]. To limit variability, the Goutallier classification has been modified from a 5-tiered system into a 3-tiered system (normal: stages 0 and 1; moderately pathologic: stage 2; advanced degeneration: stages 3 and 4) [65]. This improved intraobserver reliability to 0.71 – 0.77 and interobserver reliability to 0.48 – 0.59 [63]. CT images demonstrating Goutallier Grade 4 fatty infiltration of the infraspinatus muscle on (A) axial and (B) sagittal views.

Magnetic resonance imaging (MRI) has become a popular modality to evaluate the rotator cuff due to excellent soft tissue resolution and a global assessment of all shoulder structures. A full-thickness rotator cuff tear can be diagnosed with 92.1% sensitivity and 92.9% specificity on MRI [66]. Administration of intraarticular contrast can further improve the diagnostic accuracy of a full-thickness rotator cuff tear to a sensitivity of 95.4% and a specificity of 98.9% [66]. Other critical information about the rotator cuff obtained with MRI is the degree of tendon retraction, severity of muscular atrophy, and the amount of muscle fatty degeneration. Sagittal T1-weighted MRI has largely supplanted CT scans as the preferred imaging modality for the assessment of fatty infiltration due to avoidance of ionizing radiation and higher intraobserver and interobserver agreement [64, 65]. Fuchs described an MRI method of grading the degree of fatty infiltration using the most lateral parasagittal image in which the scapular spine was in contact with the scapular body (Fig. 2) [65]. In this method, the amount of intramuscular fat is scored using either the 5-level or 3-level Goutallier classification. The interobserver agreement of fatty degeneration according to the Fuchs method ranged from 0.61 to 1.0, respectively [65].

Recently, multiple MRI techniques have been developed to quantify the fat content of rotator cuff muscles, including single-voxel MR spectroscopy, spectroscopic gradient-echo imaging, fat-selective imaging, and water-fat imaging [67–69]. One method, the iterative decomposition of echoes of asymmetric length (IDEAL), has been shown to be highly reproducible and correlated to the Goutallier classification with over 90% agreement (Fig. 3) [70]. By using this

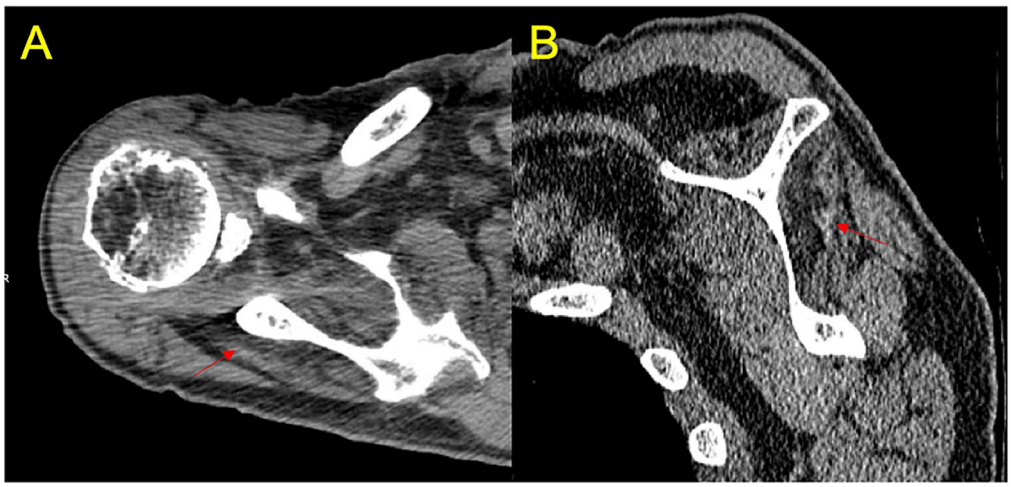

Fig. 1 CT images demonstrating Goutallier Grade 4 fatty infiltration of the infraspinatus muscle on (**A**) axial and (**B**) sagittal views

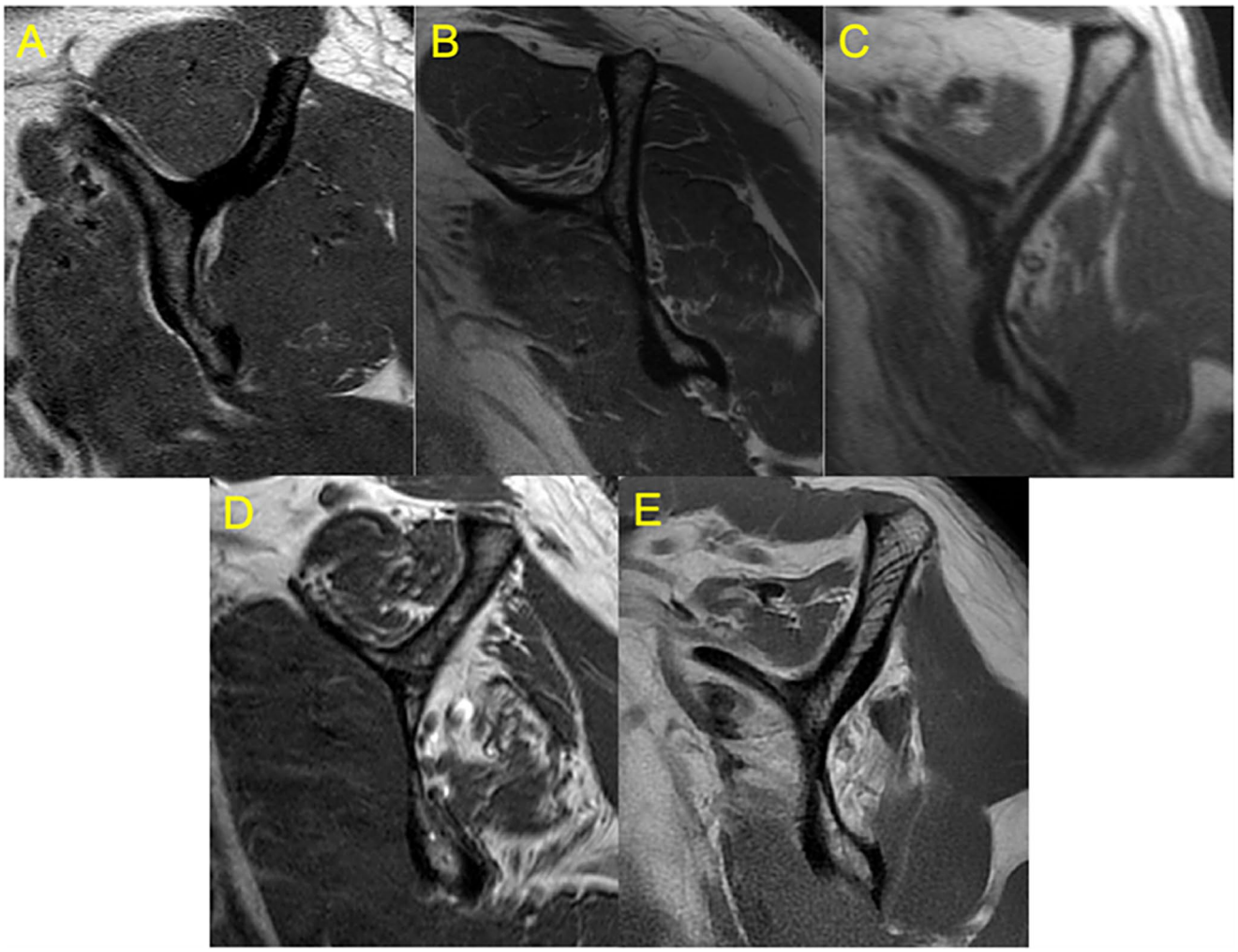

Fig. 2 Fuchs modification of the Goutallier classification using sagittal MRI. (**A**) Grade 0, (**B**) Grade 1, (**C**) Grade 2, (**D**) Grade 3, and (**E**) Grade 4 fatty infiltration of the infraspinatus muscle

technique, continuous measurements of the percentage of intramuscular fat can be determined in any region of interest, allowing for improved evaluation of muscular changes compared to the semi-quantitative Goutallier scores [71]. The fat fraction measurements obtained from IDEAL sequences is also sensitive enough to detect the subtle progression of fatty infiltration of the rotator cuff muscle before and 6-months after repair [71]. Moreover, the IDEAL preoperative fat fraction can also predict outcome scores and retears after rotator cuff repair [72].

Ultrasound (US) evaluation of the rotator cuff has become more widespread over the past several decades due to advances in technology, increased portability, and decreased costs [73]. With a trained operator, a full-thickness rotator cuff tear can be diagnosed with a sensitivity of 92.3% and specificity of 94.4% on US and is comparable to the accuracy of MRI [66]. In addition, US can be used to assess the degree of fatty degeneration based on the echogenicity and architecture of the muscle [74]. Strobel classified the severity of fatty degeneration based on a 3-point system. Grade 0 was considered normal and corresponded to muscle that was isoechoic to the deltoid or trapezius. There was clearly visible intramuscular tendon and muscle pennate pattern. Grade 1 and 2 were abnormal and consisted of muscle with increasing echogenicity and loss of a visible intramuscular tendon and muscle pennate pattern. This system had a substantial interobserver reliability of 0.71 [75]. Furthermore, the percentage agreement between US and MRI ranged from 87.5 −92.5% [75].

Natural History of Rotator Cuff Fatty Infiltration

Fatty infiltration (FI) has a significant impact on the outcomes of rotator cuff repair, even in the setting a successful healing of the enthesis. Therefore, understanding the natural history of FI is critical to ensure treatment before

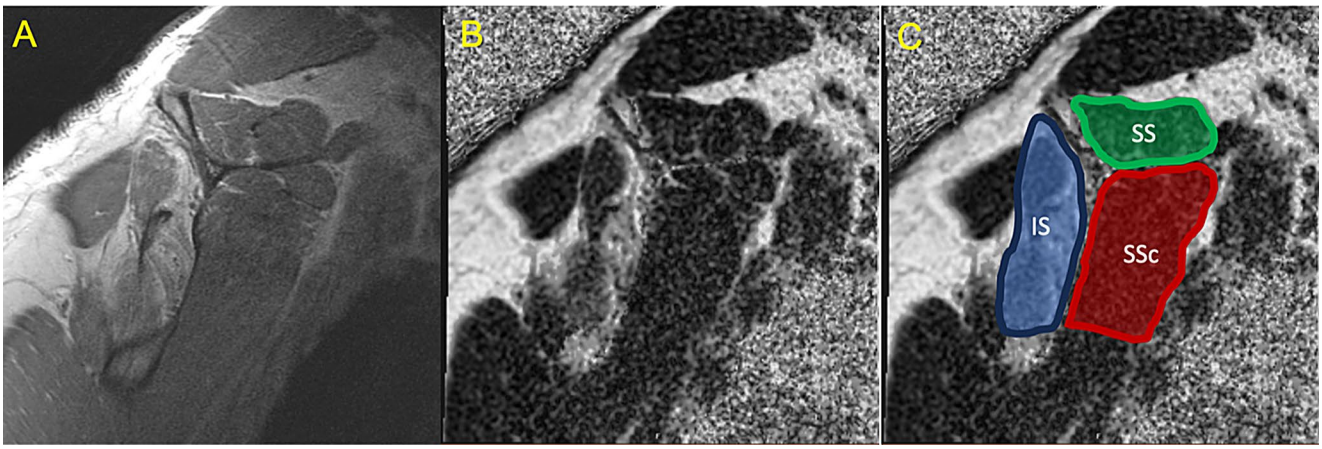

Fig. 3 Sagittal (**A**) T1-weighted and (**B**) IDEAL MRI sequences demonstrating fatty infiltration of infraspinatus muscle. (**C**) Fat fraction measurements of the supraspinatus, infraspinatus, and subscapularis muscles were 9.9%, 35.6%, and 9.8%, respectively. SS, supraspinatus; IS, infraspinatus; SSc, subscapularis

irreversible, pathological changes compromise clinical outcomes. FI is the irreversible progression of muscle degeneration, with several factors influencing the rate and severity of infiltration and concomitant muscle atrophy.

Animal models have demonstrated that FI begins shortly after injury to the rotator cuff and progressively worsens over time if not treated. In a rabbit model of massive rotator cuff tears in a supraspinatus transection model, Bjorkenheim [76] identified fatty degeneration of the muscle interspace and atrophy of muscle fibers as early as 4 weeks post-injury, which progressed to greatest prominence at 6 weeks. Similarly, Rubino et al. [77] found in a different rabbit rotator cuff tear model that FI was present at 6 weeks post-transection and increased over time until the last time point of one year. The FI was most prominent near the supraspinatus and progressed from the musculotendinous junction toward the muscle origin.

In a sheep model, Gerber et al. [78] simulated a chronic rotator cuff tear releasing the infraspinatus and allowing it to retract for forty weeks before repairing the tendon and evaluating changes thirty-five weeks after repair. The authors found that the infraspinatus muscle continually degenerated with progressive atrophy and accumulation of intrafascicular and intrafascicular fat after tendon release. The degree of FI was related to the amount of musculotendinous retraction, with higher retraction leading to a greater amount of FI. Additionally, FI was irreversible with repair and remained constant even after repair. However, muscular atrophy was at least partially reversed with successful repair. Taken together, these translation animal models have all acknowledged the progressive worsening nature of FI and demonstrate that without intervention, FI will impair the physiological properties of the muscle to a degree where functional recovery is not possible.

Investigations on the natural history of FI and atrophy in humans have demonstrated similar results in nonoperative outcomes of rotator cuff tear patients. In a large retrospective study, Melis et al. [7] evaluated 1688 patients with rotator cuff tears of varying severity to determine the degree of FI and muscular atrophy. The authors found that in small tears, FI was minimal or absent. Moderate FI of the supraspinatus was present on average three years after the onset of shoulder symptoms, with traumatic RC tears presenting with FI earlier than chronic tears. Severe FI was present on average around five years after the onset of symptoms. FI progression was faster when rotator cuff tears were traumatic in nature and involved more than one tendon. Furthermore, increased time between symptom onset and diagnosis was significantly associated with greater muscular changes. Ultimately, the authors concluded that rotator cuff repair should be completed before FI reaches Goutallier stage 2 to prevent poor outcomes following surgical treatment. Another study by Naimark et al. described the tangent sign on a sagittal MRI and noted significantly inferior outcomes in patients with a positive tangent sign, signifying Goutallier stage 2 or greater atrophy of the supraspinatus muscle belly [79].

To further demonstrate the insidious progression of FI in rotator cuff tears, a study by Maman et al. [80] evaluated non-operative treatment of symptomatic rotator cuff tears in 59 shoulders with the use of MRI. All patients received MRI scans six months or more after the initial MRI. The results corroborated those reported by Melis et al. [7] No partial-thickness tear demonstrated supraspinatus atrophy, and 24% of full-thickness tears demonstrated atrophy. Most importantly, tear progression was significantly more common in shoulders with fatty infiltration (70%) than those shoulders without fatty infiltration (24%). Additionally, factors found

to be associated with rotator cuff tear progression were age greater than 60, full-thickness tears, and the presence of FI.

Interestingly, FI can exist even in the absence of rotator cuff tears or severe tendinopathy. Gueniche et al. [81] reported the presence of FI in shoulders lacking rotator cuff tendinopathy. A retrospective review of 210 patients with intact rotator cuffs found that FI progressively increased with age, with significant increases after 40 years of age. Furthermore, a Goutallier grade 2 was commonly found in patients of advanced age. 17% of patients aged 50–60, 50% of patients aged 60–70, and 76% of patients over 70 demonstrated grade 2 FI on CT scan. This is important to note as patients may have an underlying prior history of FI, especially if they present later in life. This could certainly impact outcomes of surgical management in the setting of a subsequent rotator cuff tendon injury.

Various factors can also contribute to the rate at which FI develops. Giri et al. [82] found that among the MOON and ROW cohorts, being overweight carried a 2.3 times increased odds of FI in the setting of rotator cuff tears, and obesity carried a 3.28 times increased odds of FI. Furthermore, women were 4.9 times more likely to have FI when compared to men. These variables are important to consider when counseling patients on prognosis after surgery and contemplating surgical options for management. Some patients may be more susceptible to developing FI and, thus, may be treated more aggressively to prevent accelerating FI progression.

Treatment or Reversibility of FI

Given the progressive nature of FI, any intervention that can mitigate or reverse progression are of paramount importance. However, the consensus remains mixed on whether rotator cuff repair can halt or reverse previously established FI. One cohort study evaluating 38 patients found that after rotator cuff repair and follow-up with MRI at 1-year postoperatively, a successful repair demonstrated minimal FI progression with no muscle degeneration reversal or improvement [83]. Additionally, failed repairs demonstrated significantly more FI progression.

Jo and Shin [84] evaluated pre-operative and 3-day postoperative MRIs of 101 patients who received arthroscopic rotator cuff repairs and found that in the short-term postoperative period, Goutallier grades improved by at least 1 grade in 50%, 75%, and 95.8% of patients with pre-operative Goutallier grades of 2,3, and 4 respectively. Hamano et al. [85] obtained MRI studies in 94 patients fourteen days after rotator cuff repair and then follow-up MRIs at 1-year and 2-years postoperatively to evaluate the progression of FI and muscle atrophy. Contrary to other studies that demonstrated stable or worsening FI after repair [83, 86], FI significantly improved at both follow-up time points, and FI improved the most in the large to massive tear group. Muscle atrophy was found to improve in partial tears and small to medium tears, whereas it did not improve in the large to massive tear group.

Another study evaluated medium-to-large rotator cuff tears in 41 patients managed with arthroscopic repair or nonoperative treatment and rehabilitation [87]. Follow-up with MRI and clinical outcome measures were completed at an average of 55 months. For patients who received arthroscopic repair, no significant progression of FI or muscle atrophy was observed when compared to the non-operative group that demonstrated significantly increased tear size, degree of tendon retraction, and amount of FI and muscle atrophy at follow-up. While muscle atrophy did improve in 23.5% of patients, the majority showed no improvement of muscle atrophy or FI.

Given the mixed results of multiple studies, it is still unclear whether FI progression is halted with surgery. It appears progression is at least slowed with rotator cuff repair, which emphasizes the potential importance of surgical intervention. With nonoperative management, it has been demonstrated rotator cuff tear size and FI will both progress over time.

Effect of Fatty Infiltration on Outcomes After Rotator Cuff Repair

While rates of structural healing for repair of large to massive tears are rather modest, surgical management provides an opportunity to halt the natural history of FI and prevent further worsening. This is important because the effect of FI on patient outcomes after rotator cuff repair is well documented.

Gladstone et al. [83] noted that muscular atrophy and FI of the rotator cuff, especially of the infraspinatus, have a significant influence as independent predictors of functional outcome. In a study of two hundred shoulders after rotator cuff repair, Goutallier et al. [88] found that 36% experienced recurrent tears and the retears were significantly more common in patients with presurgical fatty degeneration. Furthermore, a higher presurgical fatty degeneration index score was associated with a lower mean postoperative Constant score. Raman et al. [89] found that fatty infiltration has a significant negative effect on the outcomes after rotator cuff repair with an odds ratio of 9.3.

A recent systemic review and meta-analysis evaluated sixteen studies investigating the effect of preoperative fatty infiltration on functional outcomes and retear rates after rotator cuff repair [90]. Meta-analysis showed that

preoperative FI led to significantly higher rates of re-tear (odds ratio of 4.6) and significantly lower Constant scores when compared to patients with no fatty infiltration. However, the authors found no statistical difference in patient-reported ASES and UCLA scores between groups, respectively.

Although a few studies have analyzed the effect of FI on outcomes following rotator cuff repair, there remains a paucity of high-quality large studies evaluating the effects of FI in patients. Two randomized, controlled trials evaluated for correlation between preoperative Goutallier classification scores and postoperative Constant Scores. Milano et al. [91] found that lower Goutallier grades were associated with higher Constant scores at an average of 2 years follow-up in a series of 101 patients. Grasso et al. [92], however, found no correlation between preoperative FI grades and postoperative Constant scores. Given that these were both high-quality studies with mixed results, future studies need to be completed to further define the influence FI has on patient-reported outcomes after surgical repair. The literature does appear to support an increased rate of tear recurrence in patients who have elevated fatty infiltration in the preoperative stage.

Further research is needed to identify possible treatments to more constantly halt or reverse the natural history of fatty degeneration. Emerging therapies such as platelet-rich plasma (PRP) may offer improved outcomes in patients with fatty infiltration. Zhang et al. [93] demonstrated in an RCT of 104 patients the potential to reverse fatty infiltration using leukocyte-poor PRP injected into the muscle. The authors compared standard control rotator cuff repair patients to those who received a total of 3 PRP injections within 2 weeks postoperative with follow-up over 2 years. Although no difference in outcome scores was observed, the patients who received PRP had a significantly lower re-tear rate and decreased Goutallier score. This suggests that possible adjuvant therapies during and after the immediate post-op phase may be positive for preventing retears, allowing enhanced healing, and reducing existing fatty infiltration.

Future Treatments

Based on current preclinical data, there are several potential therapeutic targets that could promote muscle regeneration following rotator cuff injury. Preclinical models have shown that targeting the PPARγ, retinoic acid, and akt/mTOR pathways may have beneficial effects on both fatty infiltration and muscle regeneration [23, 94, 95]. Targeted therapies towards TGF-B and BMPs may also help promote muscle regeneration as well, but are limited by the complicated systemic effects that may be challenging to overcome [22, 96]. B-agonist strategies that help promote 'browning' of white fat and phenotypic alterations in FAPs have not been tested in clinical trials, but are promising from a mechanistic standpoint in pre-clinical models [32, 97].

Cell based therapies, while not approved in the United States, could hold promise as well due to the arthroscopic approach and ability to directly treat muscle at the time of rotator cuff repair. Theoretically, cell based strategies that either directly stimulate endogenous FAPs and satellite cells, modulate the local immune system, or deliver cell based therapies could promote muscle regeneration in a manner similar to what has been proposed by volumetic muscle loss techniques, but technically easier due to an intact muscle structure [98].

Conclusions

The presence of fatty infiltration within injured rotator cuff muscle is common and correlates with increasing patient age, female sex, and the presence of a full-thickness tendon tear. Several animal and human studies have demonstrated the importance of fibroadipoprogenitor cells (FAPs) in the development of fatty infiltration. Early transcriptomic studies demonstrated that FAPs represented a heterogeneous cell population capable of both regenerative and pathologic responses to muscle injury. These cells have been found to have a central role in the regulation of muscle degeneration in several disease states including muscular dystrophy, amyotrophic lateral sclerosis (ALS), and aging. Mechanical loading and denervation of the rotator cuff are thought to contribute to fatty infiltration. Despite the initial classification of fatty infiltration on Goutallier et al. on axial CT images, magnetic resonance imaging (MRI) has become the modality of choice to evaluate the rotator cuff tendon and musculature due to excellent soft tissue resolution and a global assessment of all shoulder structures. Animal models have demonstrated that FI begins shortly after injury to the rotator cuff and progressively worsens over time if not treated. While it appears progression is at least slowed with rotator cuff repair, the results are mixed on whether rotator cuff repair can halt or reverse previously established FI. Clinical studies indicate that preoperative is associated with significantly higher rates of re-tear and significantly lower Constant scores when compared to patients with no fatty infiltration. Future research into pathways to promote muscle regeneration and inhibit fatty infiltration as well as new pluripotent, cell-based therapies will be promising for potential treatment.

Key References

32. Chi HM, Davies MR, Garcia SM, Montenegro C, Sharma S, Lizarraga M, et al. Defining Endogenous Mitochondrial Transfer in Muscle After Rotator Cuff Injury. Am J Sports Med. 2024;52:451–60.

- This study investigates mitochondrial transfer in muscle after rotator cuff injury, finding that FAPs do not fuse with injured fibers but instead contribute their mitochondria. Given the role of mitochondrial dysfunction's role in fatty infiltration and muscle atrophy, these findings could provide novel insights into muscle degeneration and therapeutic strategies.

31. Davies MR, Garcia S, Liu M, Chi H, Kim HT, Raffai RL, et al. Muscle-Derived Beige Adipose Precursors Secrete Promyogenic Exosomes That Treat Rotator Cuff Muscle Degeneration in Mice and Are Identified in Humans by Single-Cell RNA Sequencing. Am J Sports Med. 2022;50:2247–57.

- This study finds that beige adipose precursors can secrete factors that promote muscle regeneration. This could be a critical mechanism in reversing or preventing fatty infiltration after rotator cuff tears. By mediating pro-myogenic effects, this is a possible therapeutic target for treating muscle degeneration.

72. Lansdown DA, Morrison C, Zaid MB, Patel R, Zhang AL, Allen CR, et al. Preoperative IDEAL (Iterative Decomposition of Echoes of Asymmetrical Length) magnetic resonance imaging rotator cuff muscle fat fractions are associated with rotator cuff repair outcomes. J Shoulder Elbow Surg. 2019;28:1936–41.

- This study advances traditional subjective MRI grading by providing the IDEAL MRI fat fraction, a quantitative pre-operative predictor of rotator cuff repair outcomes. Higher fat fractions are associated with worse healing rates and functional recovery. This allows for improved risk stratification, enabling surgeons to identify patients at higher risk of poor outcomes and tailor treatment strategies, such as considering alternative surgical techniques or enhanced rehabilitation protocols.

81. Gueniche J, Bierry G. Rotator cuff muscles fatty infiltration increases with age: retrospective review of 210 patients with intact cuff on computed tomography arthrography. J Shoulder Elbow Surg. 2019;28:617–24.

- This study identifies the presence of fatty infiltration in rotator cuff muscles naturally increases with age, even without tendon tears. It offers important insights into age-related changes in muscle quality that can impact the risk of rotator cuff tears and the success of surgical outcomes in older adults. This is particularly important as FI class 2 is a common threshold for surgical indication, yet it is commonly found in patients over 70 without rotator cuff tears.

93. Zhang C, Cai Y-Z, Wang Y. Injection of Leukocyte-Poor Platelet-Rich Plasma for Moderate-to-Large Rotator Cuff Tears Does Not Improve Clinical Outcomes but Reduces Retear Rates and Fatty Infiltration: A Prospective, Single-Blinded Randomized Study. Arthrosc J Arthrosc Relat Surg. 2022;38:2381–2388.e1.

- This study was included because it evaluates a popular biologic, PRP, and its potential to address key challenges in rotator cuff repair, such as reducing retear rates and fatty infiltration. While it does not improve short-term clinical outcomes, it provides insight into how biologics like PRP may influence tendon healing and muscle preservation in moderate-to-large tears.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Competing Interests Dr. Asheesh Bedi - Arthrex, Inc.

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