Pathophysiology of Rotator Cuff Tears

1

Trevor P. Scott, Adam Z. Khan,
and Frank A. Petrigliano

Pearls and Pitfalls

Pearls

- Acute cuff tears are often amenable to repair, even if they are massive.
- The degeneration-microtrauma theory is most accepted conceptualization of cuff disease.
- The rotator cuff is the major stabilizer of the shoulder during normal ROM. Small tears do not affect this capability, but larger tears may.
- Investigation and further understanding of these fundamental mechanisms will not only lead to better diagnostic and prognostic capabilities but will also aid in the development of better treatment modalities and adjunctive therapies for massive rotator cuff tears.PitfallsMuscle atrophy and fatty degeneration are associated with high failure rates in massive rotator cuff repairs.
- The exact pathway of muscle degeneration and fatty atrophy is not known and remains an area of active research.
- The pain generator in the setting of rotator cuff tears is not yet known, and research is ongoing.
- The exact size of cuff tear which leads to loss of force coupling and normal shoulder biomechanics is not yet known.

T.P. Scott, MD
Department of Orthopedic Surgery, UCLA Santa Monica Orthopaedic Center, 1250 16th Street, Santa Monica, CA 90404, USA
e-mail: tscott@mednet.ucla.edu

A.Z. Khan, BS
Department of Orthopaedic Surgery, David Geffen School of Medicine at UCLA, 10833 Le Conte Avenue, Los Angeles, CA 90095, USA
e-mail: Akhan881@gmail.com

F.A. Petrigliano, MD (✉)
UCLA David Geffen School of Medicine, 10833 Le Conte Avenue, 76-143-CHS, Los Angeles, CA 90095, USA
e-mail: fpetrigliano@gmail.com

Introduction

Rotator cuff injury is a common cause of shoulder pain accounting for 4.5 million clinic visits annually in the United States [1]. Massive tears account for between 10 and 40 % of all tears [2]. There is currently no consensus on the definition of a massive rotator cuff tear. Among the more commonly used definitions is that of Cofield et al. who described a massive rotator cuff tear as a tear with a diameter greater than 5 cm [3]. Another widely used definition is that used by

L.V. Gulotta and E.V. Craig (eds.), *Massive Rotator Cuff Tears: Diagnosis and Management*,
DOI 10.1007/978-1-4899-7494-5_1,

Gerber et al. that a massive rotator cuff tear is complete detachment of two or more cuff tendons from the proximal humerus [4]. Burkhart also suggested that massive tears be defined as tears greater than 5 cm and then further classified by pattern and edge mobility [5]. Posterosuperior tears are much more common than anterosuperior tears that extend down to the [6–10].

Massive tears may be amenable to surgery, especially when they are acute and tissue compliance is well maintained, but unfortunately, cases such as this are in the minority. Adhesions, scarring, fibrosis, tendon retraction, and poor tendon quality may all conspire to create a technically challenging repair [4, 11]. Furthermore, multiple studies have shown the re-tear rates following the repair of massive rotator cuff tears to be much greater than for smaller cuff tears. The purpose of this chapter is to review the pathophysiology and biomechanical changes that occur in the setting of massive rotator cuff tears and to discuss the clinical relevance of these functional alterations [12–18].

Historical Overview

The first documented description of tears of the tendons about the shoulder was reported by J.G. Smith in the *London Medical Gazette* in 1834 [12]. The connection between shoulder pain and the subacromial bursa was identified by Jaravay, and for several years this was believed to be the primary source of posttraumatic shoulder pain and stiffness, which was called "periarthritis humoscapularis" [13]. However, it was not until 1934 that Codman published his monograph on the anatomy of the rotator cuff and in which he discussed rotator cuff tears [19]. He was likely the first to identify that tears in the supraspinatus accounted for both difficulty with humeral abduction and shoulder pain. He was a proponent of early operative treatment and may have performed the first cuff repair in 1909 [20]. After Codman, McLaughlin and several other prominent surgeons including Armstrong, Smith-Peterson, Moseley, and Watson-Jones spent the next several decades publishing on the etiology and management of rotator cuff tears and there was emerging recognition that acromial abrasion might be a cause of rotator cuff injury [14–18].

Etiology

The etiology of rotator cuff tendinopathy and tears is commonly divided into extrinsic and intrinsic factors. Extrinsic factors are generally understood to mean compression or friction on the cuff by other shoulder structures. As early as 1924, Meyer described what would later come to be known as extrinsic factors when he discussed his "attrition theory" of musculotendinous rupture in the shoulder. He believed that many injuries which today would be described as rotator cuff tears could be attributed to chronic normal daily wear secondary to friction, and he believed supraspinatus tears originated superficially [21]. The concept of impingement was discussed in detail and classified by Neer in 1972. He identified spurs on the underside anterior 1/3 of the acromion, and he attributed degenerative changes of the acromion to friction from the cuff and humeral head. He associated tears of the cuff as being secondary to those same impinging forces. He described three stages to tears. Stage 1 was edema and hemorrhage in patients under 25, stage 2 was fibrosis and tendonitis in the 24–40 age group, and stage 3 were tendon ruptures and bone spurs in patients over 40 [22, 23]. Neer noted good results for focal acromioplasty of the anterior 1/3 of the lateral acromion. He also was much more aggressive with immediate surgical treatment with large complete tears than smaller injuries, correctly surmising that tendon retraction would make nonoperative treatment less successful and late surgical treatment challenging. For incomplete tears, he recommended an extended 9-month trial of nonoperative treatment, and for isolated complete supraspinatus tears, he performed surgery after a 6-week trial of nonoperative treatment [23].

Neer's hypothesis that impingement caused extrinsic cuff degeneration was further explored by Bigliani who identified three acromial shapes—flat, curved, and hooked—and noted that full-thickness rotator cuff tears were associated with hooked acromial shape [24]. It also was recognized that impingement could occur against multiple surfaces, given the remarkable range of motion of the glenohumeral joint. Thus, it could

be due not only to acromial shape but also to arthritic changes of the acromioclavicular (AC) joint or the coracoacromial ligament [25]. Further compression of the cuff, biceps tendon, and/or subacromial bursa between the humeral head and the acromion, AC joint, or coracoacromial ligament all may be related to motion of the humeral head [25, 26]. Also, the relatively shallow glenohumeral joint puts the joint at risk for instability that can lead to increased humeral head translation. Translation, in turn, can initiate or exacerbate impingement [25, 27].

Many authors have suggested that if impingement on superior structures actually leads to tears, then the majority of tears should be on the bursal side of the cuff. Yet, multiple studies have suggested that the majority of cuff tears start on the articular surface [28, 29]. Those authors have suggested that arthritic AC changes, and morphologic changes of the acromion and the CA ligament, which were thought to cause cuff impingement via extrinsic compression, may in fact simply be correlated with age. It is also possible the impingement changes may actually be a secondary response to intrinsic tendon changes [28, 30, 31]. Moreover, studies by Neer and others have shown that many patients with tears never performed hard labor or vigorous overhead activity [22].

This, however, does not discount impingement as a major factor in cuff tears; intrinsic factors suggest that the cuff fails on the articular side because there is more fibrocartilage, which has a lower tensile strength, on the articular side which is the side that may also undergo more strain [29, 32]. These findings have helped give rise to the theory that it is actually internal impingement of the cuff on the humeral head which results in tears [33]. In all likelihood, degenerative cuff tears are secondary to extrinsic compression combined with intrinsic factors. A recent rat study showed the rats whose cuffs were subject to both compression and overuse, as opposed to one or the other alone, had much greater rates of tendinopathy [34].

The degeneration-microtrauma theory [35] is the most widely accepted conceptualization of the events resulting in the development of rotator cuff disease. It describes *intrinsic degeneration* of the rotator cuff tendon secondary to age-related changes such as changes in collagen-type synthesis, vascular changes, hypoxia, or oxidative stress. This degeneration makes the tendon more susceptible to damage; repetitive stresses cause micro-injuries— i.e., reduction in the number of functional fibers in the tendon puts increasing load on the remaining fibers—which are not given enough time to heal before further trauma occurs. It should be noted that most studies, which aim to elucidate the pathophysiology of rotator cuff degeneration and rupture, are in animal models, and it is important to recognize the anatomic, biologic, and functional limitations inherent to animal research model systems.

Pathophysiology

Degeneration of the rotator cuff tendon results from a variety of intrinsic factors including but not limited to age-related degeneration, inflammation, vascular changes, and oxidative stress. Among these elements, the key factor leading to rotator cuff weakness and degeneration is aging.

Epidemiologic studies indicate a positive correlation between patient age and rotator cuff tear incidence. An ultrasound study performed by Tempelhof and colleagues [36] screened more than 400 asymptomatic volunteers and found an increase in tear prevalence with increasing age. Cuff tear incidence increased from 13 % in the 50–59-year-old age group to 51 % in the 80–89-year-old age group. The high incidence of asymptomatic rotator cuff tears in the aging population brings about the question of whether rotator cuff degeneration is in fact a pathologic process or could be considered a part of the "normal" aging process. Furthermore, the clinically relevant question of how an asymptomatic cuff tear develops into a painful, function-limiting, symptomatic tear requires further investigation.

With increasing age, many histologic changes have been observed. A study by Hashimoto and colleagues [37] described 7 characteristic features of age-related degeneration (Fig. 1.1). Thinning and disorganization of collagen fibers, myxoid degeneration (connective tissue replaced by mucus), and hyaline degeneration were observed in all 80 patient samples in the study. Other degenerative changes observed were vascular proliferation

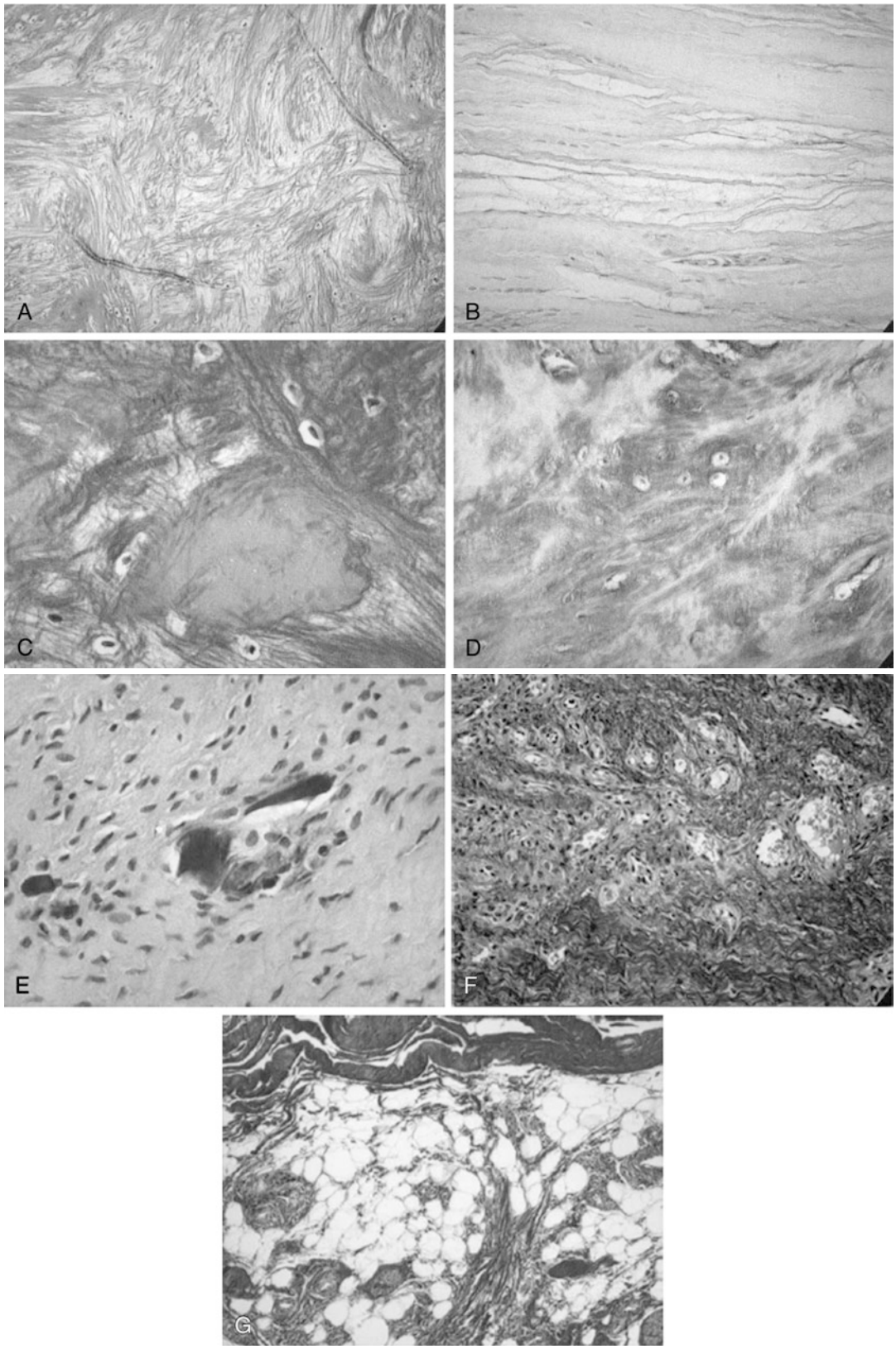

Fig. 1.1 (**a**) Thin and disorganized collagen fibers in the torn tendon (large tear, 10× magnification). (**b**) Split collagen fibers replaced with myxoid degeneration (large tear, 20×). (**c**) Hyaline degeneration; chondrocyte-like cells are visible near hyalines areas, (large tear, 20×). (**d**) Chondrocytes with lacunae, intracellular matrix

(34 %), fatty infiltration (33 %), chondroid metaplasia (21 %), and calcification (19 %).

Longo and colleagues [38] subsequently reevaluated the histology of rotator cuff tears. In the torn rotator cuff samples, they found increased waviness and disorganization (loss of parallel architecture) of collagen fibers and an increase in vascularity. Furthermore, rounding of tenocyte nuclei—normally flat and spindle shaped—to the point where they almost resembled chondrocytes was observed in the torn cuff samples.

In a rat model, overuse of the rotator cuff tendon led to downregulation of TGF-β1. Another study by Perry and colleagues [39] looked at rat model of repetitive microtrauma and found acute increases (peak at 3 days) in VEGF and subacute (8 weeks) increases in inducible cyclooxygenase (COX-2). The results of these studies not only support the repetitive microtrauma theory, but they imply the presence of acute inflammation as well as a central role for angiogenic mediators.

Oxidative stress and the production of reactive oxygen species (ROS) are implicated in the degeneration and pathologic destruction of a variety of different tissue types. One of the main mechanisms by which ROS are thought to contribute to tissue degeneration is through the activation of the intrinsic apoptotic pathway. Studies by Yuan and colleagues [40] exhibited an increase in apoptotic cells at the cuff tear edge (34 %) as compared with control (13 %). In addition to induction of apoptosis, oxidative stress has been shown to induce cuff degeneration through induction of two other auxiliary factors: c-Jun N-terminal protein kinase (JNK), a mitogen-induced protein kinase (MAPK) expressed intracellularly, and matrix metalloproteinase-1 (MMP-1), an enzyme present in the extracellular environment. In vivo, JNK and MMP-1 expression were increased in torn supraspinatus tendon specimens as well as in tendon specimens that were exposed to the ROS peroxide [41] (Fig. 1.2).

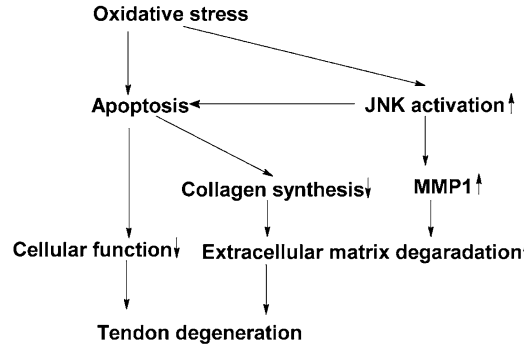

Fig. 1.2 Model of potential pathway of oxidative stress and apoptosis in rotator cuff degeneration (Wang et al. [41])

MMPs are responsible for maintaining the dynamic homeostasis of the extracellular matrix (ECM). They are in a delicate equilibrium with endogenous inhibitors of their activity: tissue inhibitors of MMPs (TIMPs) [42]. A disruption of balance in the expression and activity of MMP and TIMP is associated with pathologic change in overuse tendinopathies [43] as well as specifically rotator cuff tears [44]. MMP-1 is found to be in low concentration in normal tendon and increased in damaged supraspinatus tendon [45, 46], along with MMP-9 and MMP-13 [46]. MMPs and JNK secondary to oxidative stress are believed to contribute to the loss of tissue architecture and weakened structure in the rotator cuff.

Early histologic studies of injured rotator cuff showed little to no evidence of chronic inflammation [37, 47, 48]. Some studies have been able to show the expression of inflammatory cytokines and mediators [49–52], but many histologic studies are unable to demonstrate the presence of actual inflammatory cells [37, 47, 53–55]. A limitation to these studies is that samples were obtained in the later stages of rotator cuff tear progression. However, more recent data published by Millar and colleagues [56] demonstrated the first in vivo human evidence of an inflammatory infiltrate in early tendinopathy.

Fig. 1.1 (continued) stained with alcian blue (large tear 20×). (**e**) Calcific deposits in tendon between spindle-shaped fibroblasts and collagen fibers (massive tear, 40×). (**f**) Proliferation of small vessels in all tendon layers and edema (articular surface tear, 20×). (**g**) Fatty infiltration in the proximal tendon, distributed from middle to deep tissue layer (large tear, 10×). **a**, **c**, **f**, and **g** are stained with Masson trichrome; **b** and **e** are stained with hematoxylin and eosin; **d** is stained with alcian blue (Hashimoto et al. [37])

They found the subscapular tendons of patients with supraspinatus tears had an increased number of macrophages, mast cells, and T cells as well as a higher vessel density compared with the torn supraspinatus and control subscapularis tissue.

There exists some controversy with regard to the role that vascular changes play in the degeneration of the rotator cuff tendon. The traditional line of belief is that a "critical" zone of hypovascular tissue exists 10–15 mm from the insertion of the supraspinatus tendon, which makes this area more prone to tears [19, 57, 58]. Furthermore, via ultrasonography imaging, it is a well-documented phenomenon that blood supply to the rotator cuff decreases with age, especially past the age of 40 [59].

Yet, histologic data is more equivocal in regard to the significance of this hypovascular zone to cuff pathology. In the majority of histologic studies, hypervascular tissue is observed around the cuff tear site—a response to injury believed to proliferate from the subsynovial layer long after the original injury [37, 55]. Rathbun and colleagues [60] found that reduced perfusion to the rotator cuff is observed only when the arm is fully adducted. However, a histologic study by Brooks and colleagues [61] found a decrease in the degree of filling, size, and number of vessels in the proximal 15 mm to the supraspinatus insertion. Interestingly, they found this same pattern in the infraspinatus, which tears much less frequently.

Despite equivocal histologic and imaging data on the vascular changes that may occur during the development of rotator cuff pathology, there is some molecular data being uncovered that supports a role for local hypoxia in the development of rotator cuff pathology. Benson and colleagues [62] observed within the torn supraspinatus an increase in expression of BNip3, a proapoptotic cytokine of the BcL-2 family, as well as hypoxia-inducible factor-1α, indicating a connection between local hypoxia and inflammation-induced apoptosis. Furthermore, Millar and colleagues [50] showed that hypoxia, in addition to inducing apoptotic mediators, will induce a change in collagen synthesis—decreasing collagen I synthesis and increasing collagen III synthesis, as well as increasing key inflammatory mediators: monocyte chemotactic protein (MCP)-1, interleukin (IL)-6, and IL-8. Additionally, as will be discussed in a later section, local hypoxia may drive the differentiation of pluripotent cells to an adipocyte lineage.

A retrospective ultrasonographic study of patients evaluated for shoulder pain performed by Baumgarten and colleagues [63] found that a history of smoking is correlated with an increased risk of rotator cuff tears; they also observed a time-dependent and dose-dependent relationship between smoking and rotator cuff tear incidence. This observation may be due to microvascular disease; however, a causal relationship has not been well established.

Abboud and colleagues [64] found that increased total cholesterol, LDL, and triglycerides were all present in patients with rotator cuff pathology compared with controls. They also found lower HDL levels in patients with rotator cuff disease compared with control patients. Whether elevated cholesterol is actually an independent predictor of cuff pathology or simply an ancillary factor that accompanies advanced age is unclear.

Various studies have indicated that genetics may be involved in the pathogenesis of rotator cuff tears [65–68]. Although no specific gene mutations or abnormalities have been correlated with rotator cuff tear incidence, there is an epidemiologic data indicating a genetic component to rotator cuff disease. Harvie and colleagues [69] showed that siblings have a 2.42 relative risk of developing full-thickness tears compared with controls.

An interesting alternative theory compares rotator cuff degeneration to CNS damage. In the CNS, repeated stimulation and release of glutamate results in "excitotoxicity" and leads to apoptosis of neurons [70]. The neural theory of tendinopathy [71] follows a similar line of thinking: neural overstimulation, secondary to tendon overuse, results in recruitment of inflammatory cells and apoptosis. Hart and colleagues [72] have already documented this inflammatory cell recruitment, secondary to neural overstimulation, in vivo. The key molecules implicated driving degeneration are glutamate and substance P.

There is some evidence showing substance P overexpression association with rotator cuff pathology [73]. Furthermore, Molloy and colleagues [70] found an increase in various glutamate-signaling proteins in rat supraspinatus tendon following overuse. Further evidence in support of this theory is limited.

The development of symptoms related to rotator cuff pathology is poorly understood. Having an asymptomatic rotator cuff tear increases the risk of future symptomatic progression [74]. Yet many asymptomatic tears do not develop into symptomatic tears. There is also data correlating increasing tear size with symptomatic presentation; Yamaguchi and colleagues performed an ultrasonographic study of 588 patients and found that in patients with bilateral tears, the symptomatic tear was larger than the asymptomatic tear and in symptomatic shoulders the average cuff tear size is 30 % greater than in asymptomatic shoulders [75].

Definitive histologic evidence of inflammation within a degenerating rotator cuff is elusive, but many proinflammatory cytokines and inflammatory mediators such as COX-2, leukotriene B4, and PGE_2 are overexpressed in rotator cuff injuries. It is hypothesized the painful symptoms of rotator cuff disease could be mediated by COX-2 and PGE_2 [35, 76]. There is still limited data in support of these theories, and further investigation needs to be performed.

Muscle Degeneration

In orthopedic literature, the phenomenon of adipocyte accumulation in and around skeletal muscle is referred to by a variety of names: fatty infiltration, fatty degeneration, or fatty change. A histologic study, by Meyer and colleagues [77], showed normal-appearing muscle fibers with adipocyte infiltration, but no degeneration—suggesting fatty infiltration as the appropriate terminology. Itoigawa and colleagues [78], however, believe the "infiltrating" adipocytes to actually be differentiating from muscle stem cells and therefore believed fatty degeneration to be accurate. As this debate is ongoing, this chapter will use these terms interchangeably.

Muscle atrophy is commonly seen with disuse and the unloading of tensile force on the skeletal muscle. Yet, the rotator cuff is unique in that when injured, a fatty-fibrous degeneration, in addition to disuse atrophy, is observed. It is currently unclear if fatty degeneration of the rotator cuff is suggestive of a failed repair mechanism that predisposes to tears or if it is simply intrinsic to the normal degenerative process [79].

The tear of the rotator cuff tendon, detachment from the bone, and subsequent unloading of stress on the rotator cuff tendon and muscle lead to changes in the muscle and tendon structure. Structural changes include myofibril disorganization—decreased sarcomere length and number—followed by a reduction in muscle mass and volume rather than fiber death [80]. This disuse atrophy, resulting from an extended period of muscle retraction, leads to a pattern of progressive fibrosis and increased fat content that accumulated at intrafascicular, extrafascicular, and intratendinous sites within the muscle [77, 81, 82]. Fatty infiltration and muscle atrophy are seen throughout the tendon and muscle [79]. The degree of fatty infiltration and muscle atrophy progression in rotator cuff tears is positively correlated with patient age, tear size (length and width), location, full-thickness involvement [83], and chronicity [81] of the tear. Suprascapular neuropathy or denervation secondary to muscle retraction and resulting neuropraxia has also been implicated in contributing to the degree of these pathologic changes [84–89].

Muscle atrophy and fatty degeneration are progressive and often irreversible adverse histologic changes that occur throughout the tendon and muscle [82, 90, 91]. While surgical repair may prevent further progression of muscle atrophy and fatty degeneration, it often does not reverse established preoperative fatty degeneration and atrophy [90–94]. Many of the histologic changes noted in rotator cuff tendon are also reflected in the rotator cuff muscle. The ECM is extensively reorganized and remodeled by the same family of matrix metalloproteinases (MMPs) during the progression of muscle atrophy following a rotator cuff tear. MMP-2,

MMP-9, and MMP-13 overexpression has been associated with muscle atrophy [82, 90, 91]. It has also been hypothesized that the Akt-mammalian target of rapamycin (mTOR) pathway is central to the development of muscle atrophy [95]. Increased mTOR and Akt activity is associated with an inhibition of nuclear factor kappa B (NF-κB) and forkhead transcription factor (FOXO). Both NF-κB and FOXO regulate increased expression of proteins associated with muscle atrophy [96, 97]. In chronic human supraspinatus tears, these proteinases along with NF-κB were upregulated [98] (Fig. 1.3).

The exact source of the adipocytes that contribute to fatty degeneration of the rotator cuff is still not certain. The current hypotheses are (1) preexisting adipocytes are stimulated and proliferate within the muscle, (2) resident pluripotent stem cells are signaled to differentiate into mature adipocytes, and (3) adipocytes are recruited from extramuscular sources [78]. Of the three, the current molecular research indicates that the differentiation of local stem cells, known as mesenchymal stem cells (MSCs), appears to be the most likely source of adipocytes during fatty degeneration. Transcription factors of the MRF family implicated in the differentiation of myoblasts into mature myocytes are MYoD, Myf-5, myogenin, and MRF4 [100, 101]. Furthermore, two different families of transcription factors are believed to differentiate pre-adipocytes into mature adipocytes; these are CCAT/enhancer-binding proteins (C/EBPs) and peroxisome proliferator-activated receptors (PPARs) [78, 102, 103]. In an ovine model of rotator cuff tear, real-time PCR analysis identified increases in Myf-5 and PPARγ expression after tenotomy and subsequent increases in Myf-5 and C/EBPβ expression post repair [104]. Furthermore, the Wnt signaling pathway has also been identified to be central to adipogenesis of MSCs [78, 105–107]. More specifically, in vitro culture of a murine myogenic cell line (C2C12) in an adipogenic culture media resulted in diminished Wnt10b expression and increased expression of PPARγ and C/EBPα; this expression pattern was subsequently confirmed in vivo by gene expression analysis in a rotator cuff tear rat model [78].

Fatty degeneration predominates in the distal portion of the rotator cuff muscle near the musculotendinous junction [78, 88, 91, 108]; at this region of the cuff, there also exists a more sustained decrease in Wnt10b as well as an increase in PPARγ and C/EBPα [78]. Two mechanisms are implicated in driving these changes in protein signaling. The first is muscle retraction: mechanical stretching of muscle tissue was shown to increase Wnt10 signaling and inhibit adipogenesis [109]. Therefore, retraction of muscle tissue is thought to have the opposite effect on Wnt signaling and thus promotes adipocyte proliferation. The second mechanism is that local hypoxia can contribute to adipocyte proliferation through trans-differentiation of myoblasts [106]. This trans-differentiation is associated with increased PPARγ expression, which is also observed during hypoxic conditions [106]. Furthermore, two different studies have found increased expression of hypoxia-inducible factor 1 and VEGF to be associated with the development of fatty infiltration [62, 110].

Rotator Cuff Healing at the Bone-Tendon Junction

The normal insertion of tendon into the bone is comprised of four distinct zones: tendon, unmineralized fibrocartilage, mineralized fibrocartilage, and bone [111]. Following rotator cuff repair, the tendon-to-bone interface does not recapitulate the native enthesis but rather forms a reactive scar [112, 113].

One suggestion is that healing is affected by the vascular supply to the rotator cuff [114]. As described in the aforementioned histologic studies [37, 38], vascular proliferation is often noted in torn rotator cuff muscle. In contrast, Gamradt and colleagues [115] have found that the healing cuff tendon is fairly avascular and that a significant amount of the vascular supply to the healing cuff originates from the bone [46, 116].

Other than decreased vascular supply, it is also believed that poor cuff healing is a result of disorganized temporal expression of cytokines. Furthermore, slow and incomplete bony ingrowth

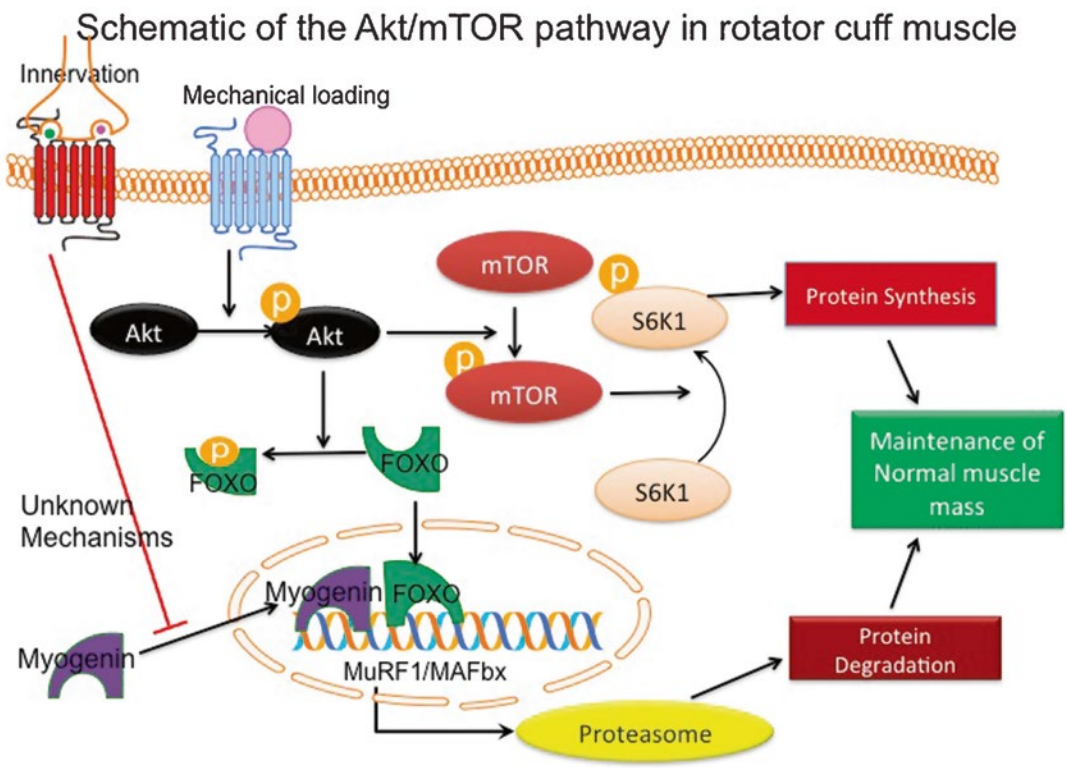

Fig. 1.3 Akt/mTOR signaling pathway in the rotator cuff muscle. A balance between protein degradation and synthesis maintains muscle mass. Akt-mTOR-S6K1 pathway stimulates protein synthesis secondary to normal mechanical loading of muscle tissue. Via an undetermined mechanism, normal muscle innervation inhibits MuRF-1/MAFbx overexpression through myogenin activation (Liu et al. [99])

into the tendon from the prepared tuberosity, inflammatory cells that precipitate scar formation at tendon-bone interface, and a scarce population of undifferentiated stem cells at the bone-tendon interface all may prevent proper healing [112].

Three stages are involved in the degeneration and healing of the rotator cuff: (1) inflammatory phase, (2) repair phase, and (3) remodeling phase [117]. Various cytokines are expressed throughout different time points within these three stages to facilitate proper tendon-to-bone healing. During the inflammatory phase, the fibrovascular scar tissue is produced in the rotator cuff following an infiltrate of mast cells and macrophages [56]. These macrophages will secrete signaling molecule such as transforming growth factor β1 (TGF-β1): a cytokine known to increase collagen formation and proteinase activity [118]. After the inflammatory phase, fibroblasts are activated within the repair phase. These activated fibroblasts express a variety of cytokines, which are described below.

PDGF-β is believed to play a central role in the repair of tendons and ligaments. It has been shown to promote chemotaxis, extracellular matrix production, surface integrin expression, cell proliferation, and revascularization in fibroblasts [119–122]. Improved mechanical properties stem from PDGF-β stimulating increased collagen I production. In an ovine model of rotator cuff repair, sheep treated with PDGF-β had improved histologic scores and load-to-failure rates [123]. The TGF-β family of proteins is integral to normal fetal development, modulation of scar tissue after a wound, and tendon-to-bone healing [112]. Varied expression levels of two different TGF-β isoforms modulate the amount of scar that forms at the tendon-bone healing site

[124, 125]. Treatment of the healing enthesis with TGF-β3 produces a more favorable collagen I to collagen III ratio to withstand increased tensile strength [126]. The BMP family, which is a subset of the TGF-β superfamily, also plays a role in healing of the enthesis via bony ingrowth. BMP-12, BMP-13, and BMP-14 are three cytokines [127], which contribute to the synthesis of fibrocartilage, induction of neotendon, and ligament formation. During the initial inflammatory phase of tendon healing, IGF-1 is activated. It contributes to chemotaxis as well as proliferation of fibroblasts and inflammatory cells to the site of injury [112]. In vivo, it increases cellular proliferation, enhances matrix synthesis, improves tendon mechanical properties, and reduces time to functional recovery [128–130]. FGF-1 and bFGF (also known as FGF-2) are both central modulators of angiogenesis and mesenchymal cell mitogenesis [112]. The more potent mitogen is bFGF, and during healing it helps initiate the formation of granulation tissue [131–133] and induction of fibroblast collagenase with a dose-dependent increase in type III collagen expression levels [134, 135]. Furthermore, bFGF expression by fibroblasts is also associated with improved tendon healing [134–137], cell proliferation, cell migration, collagen production, and angiogenesis [138–141]. Increased vascular supply is also central to proper rotator cuff healing. Vascular endothelial growth factor (VEGF) contributes to neovascularization and, in several models, has been observed at the site of the healing enthesis [142–145].

Just as rotator cuff pathology is a degenerative process resulting from a variety of influences, proper rotator cuff healing is also a multifactorial process. Therefore, rotator cuff repairs often fail through a combination of barriers to proper healing, which can be characterized into three broad categories: biologic factors, technical errors, and traumatic failure [114], of which the biologic factors may be the most pertinent. The biologic factors that underlie improper rotator cuff healing are the patient age, level of fatty degeneration, amount of muscle atrophy, cuff vascularity, and tear size. Furthermore, medical comorbidities such as diabetes, nicotine use, and NSAID use have also been found to be detrimental in rotator cuff healing.

Fatty degeneration and muscle atrophy are both independent predictors of poor functional outcomes following rotator cuff repair [90]. Increases in fatty infiltration and muscle atrophy can increase the tension applied to the repair site as these degenerative changes decrease the compliance of the musculotendinous unit. This phenomenon has been confirmed in both animal models and clinical studies [146]. Postoperative radiographic assessment demonstrates higher re-tear rates to be associated with an increased degree of fatty degeneration and muscle atrophy [90, 147, 148]. Although degenerative changes in the rotator cuff muscle are often irreversible [82, 90, 91], the further progression of these changes can be diminished by surgical repair [90–94]. Therefore, earlier repair can lead to greater recovery of muscle and tendon elasticity [149], lower re-tear rates, and improved clinical results [150].

As mentioned earlier, there is a positive correlation between patient age and cuff tear incidence. Several studies have found that increasing patient age is also correlated with decreased healing rates postoperatively [151–157]. One contributing factor could be insufficient postoperative vascular supply in elderly patients. Contrast-enhanced ultrasound suggests that blood supply to the tendon has an effect on healing [59, 114, 115], and diminished blood supply to the rotator cuff is observed with increasing age, especially in patients over 40 [59].

There are multiple factors intrinsic to the cuff tear itself that can also contribute to poor outcomes following repair. These include the number of cuff tendons torn [154], the quality of the cuff tendon, as well as the initial tear size [152, 154–157]. A study by Nho and colleagues [157] established that with each centimeter increase in tear size, there is a twofold increase in risk of persistent tear or re-tear following repair. Finally, postoperative NSAID (indomethacin and celecoxib) administration in a rat model has been demonstrated to effect tendon-to-bone healing. Animals treated with NSAIDs showed decreased collagen organization and maturation as well as a

decreased load-to-failure ratio at 4- and 8-week time points following rotator cuff repair [158]. However, there have been no clinical studies to confirm the detrimental effects of NSAID use on rotator cuff healing.

Biomechanics of Rotator Cuff Tear

The effect of a massive rotator cuff tear on the biomechanics of the shoulder can only be understood in the context of normal shoulder biomechanics. The purpose of the shoulder is to position the hand in space, and the glenohumeral joint has the greatest range of motion of any joint to accomplish this function. The design of the shoulder provides a balance between motion, force transmission, and stability: the rotator cuff contributes to all three.

Shoulder motion is complex, but a reasonable understanding of it can be gained by considering the shoulder through the lens of planar and 3D motion. Planar motion consists of spinning, sliding, and rolling. Spinning is essentially rotation of the humeral head on the fixed glenoid; the instantaneous center of rotation is at the center of the humeral head. Sliding is translation of the humerus on the glenoid, and the instantaneous center of the rotation is at the center of glenoid curvature. Finally rolling is a motion between moving and fixed segments where the contact points are constantly changing [159]. The shoulder is essentially a spherical spinning joint with a small amount of translation [160] (Fig. 1.4). Alternately shoulder motion can be thought of in terms of Eulerian angles as along the x axis (along the humeral shaft), y axis (lateral to the scapular plane), and the z axis (perpendicular to the scapula). Shoulder motion can be described by angular motion in those planes and is known to be sequence dependent [159, 161] (Fig. 1.5).

The exact contribution of each aspect of the cuff to shoulder motion remains a subject of great debate. In general, however, what is known is that the supraspinatus assists the deltoid in some capacity to elevate the humerus, and it also externally rotates the arm [162–166]. Whether this is primarily after the first 30° of abduction as postulated remains undetermined, many authors have argued that in fact the supraspinatus is likely most important in the first 30° of abduction as that is where its mechanical advantage is greatest [162, 164, 167]. The subscapularis internally rotates the humerus, and the infraspinatus and teres minor externally rotate the humerus [166]. The subscapularis, infraspinatus, and teres minor also may elevate or depress the humerus depending on the position of the humerus. The inferior cuff likely contributes to some aspect of abduction though this is probably as a stabilizer [164, 168].

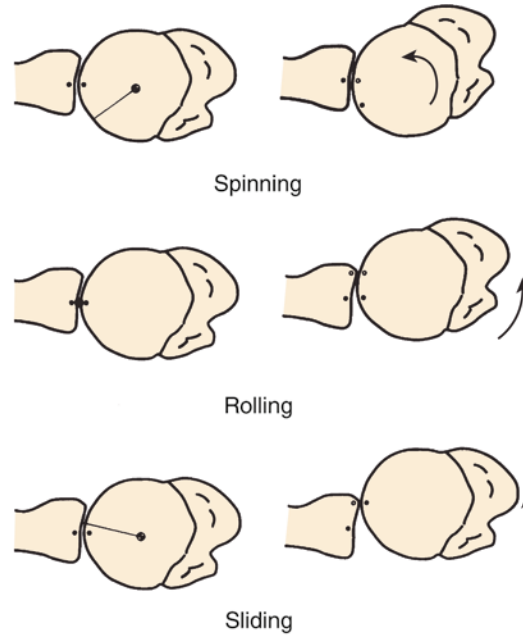

Fig. 1.4 The three planar types of motion (spinning, rolling, and sliding) all occur in the glenohumeral joint (Itoi et al. [161])

The rotator cuff also provides a significant contribution to the stability of the glenohumeral joint. Stability of the glenohumeral joint is provided by a combination of static and dynamic stabilizers. The static stabilizers primarily contribute to stability at the extremes of joint motion and consist of both soft tissue and bony components; but they are mostly independent of the cuff. The glenoid itself provides some stability via approximately 25–30 % contact with humeral head, which is increased to 33 % by an intact labrum.

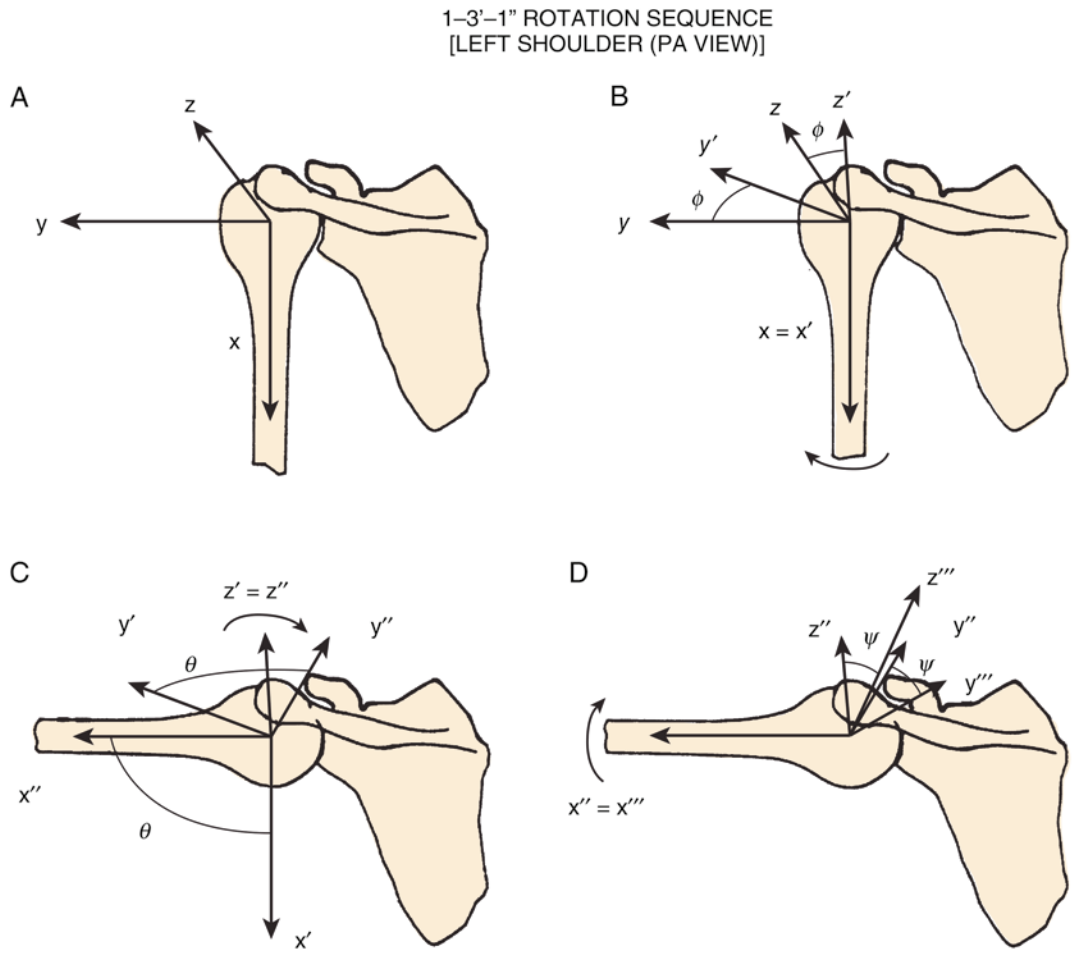

Fig. 1.5 Glenohumeral motion in three dimensions as described by the Eulerian system. (**a**) Neutral position, (**b**) First rotation ϕ: axial rotation about x axis represents the plane of elevation, (**c**) Second rotation θ: rotation about z' axis represents arm elevation, (**d**) Third rotation ψ: axial rotation about x'' axis represents humeral rotation (Itoi et al. [161])

The glenohumeral articulation, even when the labrum is included, is shallow and relatively unstable, but stability at the extremes of motion is greatly increased by the ligamentocapsular structures. The coracoacromial ligament is a key superior stabilizer of the shoulder; the superior glenohumeral ligament prevents inferior subluxation; the middle glenohumeral ligament blends with the subscapular tendon and provides anterior stability especially in mid-abduction and external rotation; the inferior glenohumeral ligament functions as a primary anterior-posterior stabilizer in abduction. The inferior glenohumeral ligament's anterior band contributes stability in flexion or external rotation, whereas its posterior band is the key ligamentous stabilizer in extension [169]. Finally negative intra-articular pressure prevents subluxation, especially inferiorly [170, 171].

While these structures are important to stability of the shoulder, especially at the extremes of motion, the cuff is an important component of dynamic shoulder stabilization. In fact, it is probably the major stabilizer in normal shoulder range of motion. All muscles of the shoulder, especially the rotator cuff, provide passive resistance to humeral displacement, which is demonstrated by

the fact that muscle removal but not cuff paralysis significantly increased the range of motion of the joint [164, 172]. The muscles of the rotator cuff also provide stability through a barrier effect. The anterior barrier to subluxation is provided by subscapularis, and superiorly the supraspinatus provides a spacer between the head and acromion [173, 174].

Most important, though, is contraction of the cuff musculature, which is probably essential in creating joint compression via the "compression-contracture" model of stability. The contraction of the cuff musculature both centers the head and compresses the head against the glenoid concavity which in turn prevents lateral translation [42, 164]. The balanced compression of the anterior and posterior aspects of the cuff leads to the idea of force coupling first suggested in the work of Inman and later Saha [175, 176]. The long head of the biceps tendon, often abnormal in the setting of rotator cuff injury, may help compress the head and likely help compensate for the loss of stability with cuff injury [177]. Overall the muscles of the rotator cuff are key to glenohumeral stability and allow the other muscles of the shoulder to move the stabilized glenohumeral joint.

The final component of shoulder biomechanics that bears examination is the force generated by the muscles across the glenohumeral joint. Joint reaction forces are greatest at 90° of abduction, as are joint contact pressure, though only in the setting of an intact cuff creating normal force coupling [178, 179]. Massive cuff tears decrease this effect, but small isolated tears of the supraspinatus do not appear to have a major effect (Fig. 1.6) [178].

Multiple studies have attempted to determine the activity of the cuff muscles in various arm functions aside from generation of force coupling. Duchenne's earliest studies used galvanic measures, but more recent studies have primarily utilized EMG. The majority of studies have examined the relative importance of the supraspinatus and the deltoid to arm abduction. It remains subject to debate, but the supraspinatus is likely most essential at the generation of abduction, though if this is due more to stabilization as part of the cuff or due to its moment arm giving it a mechanical advantage is unclear. It also is likely a key centralizer of the humeral head due to the location of its moment arm [180]. Meanwhile the infraspinatus and teres minor work as humeral head depressors, but as noted above that is position dependent [164]. However, overall it seems that the cuff is most important for stabilization as in vivo EMG studies suggest that the cuff musculature is activated prior to other muscles in shoulder motion [181].

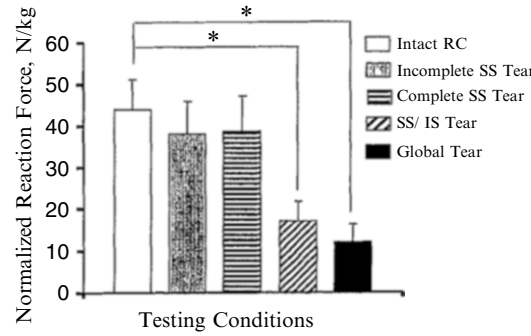

Fig. 1.6 The glenohumeral force normalized for the weight of the arm in each of the above testing conditions demonstrates a decrease in joint reaction force in large tears (Parsons et al. [178])

Pathological Effect of a Rotator Cuff Tear on Shoulder Biomechanics

The exact etiology of massive rotator cuff tears and their natural history remain undetermined. Most models suggest that the tears initiate in the anterior supraspinatus insertion and then spread posteriorly [25, 182]. Once initiated, a tear results in greater stress across the remaining fibers at the edge. When the force on the remaining fibers exceeds maximal tensile strength, this scenario can lead to propagation of the tear. The edges of the tear have compromised blood flow and are exposed to the lytic enzymes present in synovial fluid, both of which impede healing [20]. Once a tear has become large enough, activation of the deltoid may actually create a significant amount of shear stress that can damage the joint or even propagate the tear further [179]. This may also lead to further cuff degeneration as the remaining

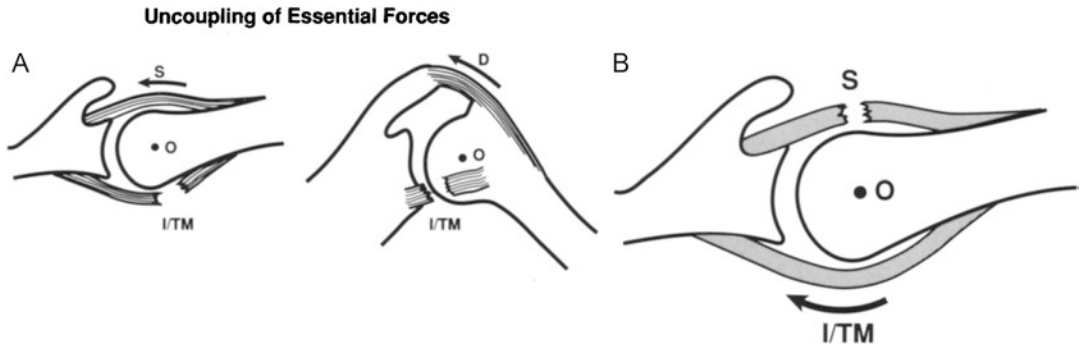

Fig. 1.7 Transverse plane force coupling is disrupted by massive tears of the posterior rotator cuff, including the infraspinatus and teres minor (**a**). Loss of force plane coupling transversely due to a tear of the subscapularis (**b**). *O* center of rotation, *S* subscapularis, *D* deltoid, *I* infraspinatus, *TM* teres minor (Burkhart et al. [186])

superior cuff may be compressed between the elevated humeral head and the acromion. Erosion of the superior glenoid rim may also hamper the remaining shoulder musculature's ability to stabilize the humeral head against the glenoid [174].

Massive Rotator Cuff Tears and Shoulder Biomechanics

Patients with rotator cuff tears, even massive tears, have a wide range of clinical symptoms; many are even asymptomatic (though they frequently develop symptoms over time) [183]. As a result, the exact function of the rotator cuff and the subsequent effect of cuff tears have remained a subject of great debate.

As discussed previously, the glenohumeral joint functions primarily as a spherical joint with a small amount of translation to allow that motion [184, 185]. Within that context, the cuff maintains concavity compression to stabilize the joint so that it may be moved by other shoulder girdle muscles; it also functions to steer and rotate the joint [164, 176, 181]. This data implies that the major function of the rotator cuff is to maintain dynamic stability of the glenohumeral joint, which in turn helps position the hand in space. Probably less importantly, the cuff also functions to move the joint [181].

Small tears isolated to the supraspinatus have a minimal effect on shoulder biomechanics in cadaver and computer models where pain is not a relevant issue. Massive tears, on the other hand, disrupt the stabilizing mechanism of the rotator cuff. However, if there is normal force coupling, then the shoulder can potentially function normally, even in the setting of a large tear. Burkhart and his coauthors suggested that if the subscapularis and posterior cuff engage in transverse force coupling in the transverse plane and the inferior cuff and deltoid are balanced coronally, then the humerus can rotate in a stable fashion [186] (Fig. 1.7). This led them to recommend partial repair without complete closure of massive tears if force coupling could be established. Moreover, a subsequent study indicated that an intact teres minor and subscapsularis were key to good function after surgery [186, 187]. As Burkhart and other authors have noted, patients can often tolerate a tear of the supraspinatus and superior half of the infraspinatus, but a tear of the inferior half of the infraspinatus may lead to a loss of balanced force coupling and functional impairment [5, 178, 188, 189]. If the tear becomes large enough that the force coupling is lost, then the deltoid becomes a destabilizing force that pulls the humeral head superiorly. A boutonniere deformity can develop where the inferior cuff actually becomes the humeral head elevator. This can also damage the superior glenoid and labrum, further destabilizing the glenohumeral joint [174].

Rotator cuff tears can also result in the loss of the barrier effect of the supraspinatus, and

potentially other cuff muscles, which can also allow abnormal head kinematics, especially superior head migration. The loss of the barrier, in concert with destabilizing effect of the deltoid, may be what causes massive cuff tears to progress to cuff tear arthropathy [174]. The effect of tears on the joint reaction forces remains unclear. Parsons et al. found that joint reactive force was decreased in complete tears of the supraspinatus; but Hansen found the joint-reactive force to be increased at early abduction. If joint reactive force is decreased, it could indicate at least partial loss of the stabilizing contraction compression mechanism [160, 178].

The question of when a large tear begins to alter the biomechanics of the shoulder was further addressed by a recent cadaver study by Oh et al. The authors found that it was necessary for a rotator cuff tear to include the entire supraspinatus and one-half of the infraspinatus to result in superior and posterior migration of the humeral head. This finding was in agreement with that of most other authors and reemphasizes the necessity of force coupling for the stabilization that allows the shoulder to function. This study was unique in that the superficial shoulder muscles were left intact, and they found that the head was stabilized by activation of the pectoralis major and latissimus dorsi [164, 182, 186–188]. A similar cadaver study by Hansen et al., in which the humeral head was stabilized, demonstrated that increasing force in the remaining cuff muscles and a less significant increase at the deltoid were required to abduct the arm, but that at least until the tear was 7 cm in length, this increased force requirement was well within the physiological range an average person could generate in vivo [71]. Interestingly, this study also showed that massive rotator cuff tears increased the force requirements for the remaining musculature, most notably at the initiation of abduction. For the largest 8 cm tears, the force required was beyond what the deltoid could likely generate in a fatigued state [71].

It is important to note that the aforementioned cadaveric studies are limited by the fact that even when fatigue is factored in, the studies do not take into account the significant pain patients often experience, which may limit muscle activation. Such pain can cause a reflex inhibition of the cuff musculature that could change shoulder biomechanics. Thus, even small tears can alter shoulder biomechanics in vivo, despite models suggesting that the effect should be minimal. Kelly and colleagues performed a study that compared patients with symptomatic and asymptomatic cuff tears (determined by pain level and range of motion after tear confirmed on MRI) as well as patients with no cuff pathology (determined by MRI). Electromyographical (EMG) analysis of these three patient populations during various functional tests (i.e., internal rotation, lifting weight onto an overhead shelf, etc.) showed statistically significant differences in muscle firing patterns, although sample size was low. The activation of the supraspinatus muscle during all functional tests was greatest in the symptomatic rotator cuff tear patient population and least in the control patient population (no cuff pathology). Asymptomatic patients had an activation level of the supraspinatus muscle that was between that of symptomatic and control patients [190].

Other factors not considered in most biomechanical studies include the fact that chronic tears also develop tendon retraction and fatty infiltration that further decrease the force that a muscle can generate. Those effects may change the pennation angles of individual muscle fibers. These changes can cause further loss of normal shoulder biomechanics [146, 191, 192].

For patients who are poor candidates for rotator cuff repair, physical therapy programs which focus on anterior deltoid strengthening have produced some success in increasing shoulder elevation and abduction and reducing pain. These programs focus on the anterior deltoid and the teres minor which together may reapproximate force coupling. Furthermore, the anterior portion of the deltoid allows elevation without the shearing effect that activation of the middle portion of the deltoid may cause [193, 194]. While these studies suggest that physical rehabilitation focused on strengthening the remaining musculature may allow elderly and low demand patient to maintain quasi-normal biomechanics, they are likely not able to reestablish the stabilizing effect of the intact rotator cuff, especially in very large rotator cuff tears.

Summary

The development of rotator cuff pathology is multifactorial in nature; resulting from a combination of intrinsic and extrinsic factors. Age-related degeneration, oxidative stress, vascular changes, and inflammation are all potential contributors to the intrinsic pathology of the rotator cuff. Of the variety of cellular and morphologic changes that are observed in the setting of massive rotator cuff tears, two changes—muscle atrophy and fatty degeneration—are strongly correlated with high repair failure rates and worsening functional outcomes. Yet, the precise molecular basis for these changes is largely unknown.

Massive tears of the rotator cuff prevent the cuff from stabilizing the humeral head on the glenoid to allow other muscles to generate motion across the joint. It is unclear exactly how large a tear must be to cause a loss of the force coupling effect of the rotator cuff and normal shoulder biomechanics. Another major question, still unanswered, is the mechanism behind the evolution of subjective pain in the setting of rotator cuff pathology as many cuff tears are asymptomatic. Investigation and further understanding of these fundamental mechanisms will not only lead to better diagnostic and prognostic capabilities but will also aid in the development of better treatment modalities and adjunctive therapies for massive rotator cuff tears.

References

1. Oh LS, Wolf BR, Hall MP, Levy BA, Marx RG. Indications for rotator cuff repair: a systematic review. Clin Orthop Relat Res. 2007;455:52–63.
2. Bedi A, Dines J, Warren RF, Dines DM. Massive tears of the rotator cuff. J Bone Joint Surg Am. 2010;92:1894–908.
3. Cofield RH, Parvizi J, Hoffmeyer PJ, Lanzer WL, Ilstrup DM, Rowland CM. Surgical repair of chronic rotator cuff tears. A prospective long-term study. J Bone Joint Surg Am. 2001;83-A:71–7.
4. Gerber C, Fuchs B, Hodler J. The results of repair of massive tears of the rotator cuff. J Bone Joint Surg Am. 2000;82:505–15.
5. Burkhart SS. Arthroscopic treatment of massive rotator cuff tears. Clinical results and biomechanical rationale. Clin Orthop Relat Res. 1991;(265):45–56.
6. Harryman 2nd DT, Hettrich CM, Smith KL, Campbell B, Sidles JA, Matsen 3rd FA. A prospective multipractice investigation of patients with full-thickness rotator cuff tears: the importance of comorbidities, practice, and other covariables on self-assessed shoulder function and health status. J Bone Joint Surg Am. 2003;85-A:690–6.
7. Habermeyer P, Krieter C, Tang KL, Lichtenberg S, Magosch P. A new arthroscopic classification of articular-sided supraspinatus footprint lesions: a prospective comparison with Snyder's and Ellman's classification. J Shoulder Elbow Surg. 2008;17:909–13.
8. Ellman H, Kay SP, Wirth M. Arthroscopic treatment of full-thickness rotator cuff tears: 2- to 7-year follow-up study. Arthroscopy. 1993;9:195–200.
9. Ellman H, Hanker G, Bayer M. Repair of the rotator cuff. End-result study of factors influencing reconstruction. J Bone Joint Surg Am. 1986;68:1136–44.
10. Kreuz PC, Remiger A, Erggelet C, Hinterwimmer S, Niemeyer P, Gachter A. Isolated and combined tears of the subscapularis tendon. Am J Sports Med. 2005;33:1831–7.
11. Goutallier D, Postel JM, Gleyze P, Leguilloux P, Van Driessche S. Influence of cuff muscle fatty degeneration on anatomic and functional outcomes after simple suture of full-thickness tears. J Shoulder Elbow Surg. 2003;12:550–4.
12. Smith JG. The classic: pathological appearances of seven cases of injury of the shoulder-joint: with remarks. 1834. Clin Orthop Relat Res. 2010;468:1471–5.
13. Jarjavay JF. Sur la luxation du tendon de la longue portion du muscle biceps humeral; sur la luxation des tendons des muscles peroniers lateraux. Gazette Hebdomadaire de Médecine et de Chir. 1867;21:325.
14. Mclaughlin H, McLaughlin HL, Asherman EG. Lesions of the musculotendinous cuff of the shoulder IV: some observations based upon the results of surgical repair. J Bone Joint Surg. 1951;33:76–86.
15. Armstrong JR. Excision of the acromion in treatment of the supraspinatus syndrome; report of 95 excisions. J Bone Joint Surg Br. 1949;31B:436–42.
16. Watson-Jones R. The classic: "Fractures and Joint Injuries" by Sir Reginald Watson-Jones, taken from "Fractures and Joint Injuries," by R. Watson-Jones, Vol. II, 4th ed., Baltimore, Williams and Wilkins Company, 1955. Clin Orthop Relat Res. 1974;(105):4–10.
17. Mosely H. Shoulder lesions. Edinburgh: F & S Livingstone; 1969.
18. S-P MN. Useful surgical procedures for rheumatoid arthritis involving joints of the upper extremity. Arch Surg. 1943;46:764–70.
19. Codman EA. The shoulder; rupture of the supraspinatus tendon and other lesions in or about the subacromial bursa. Boston: T. Todd company; 1934.
20. Matsen FA. The shoulder. In: Rockwood CAM, Frederick A, editors. Philadelphia: Saunders Elsevier; 2009.
21. Meyer AW. Use destruction in the human body. Cal West Med. 1937;47:375–83.

22. Neer CS. Impingement lesions. Clin Orthop Relat Res. 1983;173:70–7.
23. Neer 2nd CS. Anterior acromioplasty for the chronic impingement syndrome in the shoulder: a preliminary report. J Bone Joint Surg Am. 1972;54:41–50.
24. Bigliani LU, Ticker JB, Flatow EL, Soslowsky LJ, Mow VC. Relationship of acromial architecture and diseases of the rotator cuff. Orthopade. 1991;20: 302–9.
25. Mehta S, Gimbel JA, Soslowsky LJ. Etiologic and pathogenetic factors for rotator cuff tendinopathy. Clin Sports Med. 2003;22:791–812.
26. Uhthoff HK, Hammond DI, Sarkar K, Hooper GJ, Papoff WJ. The role of the coracoacromial ligament in the impingement syndrome. A clinical, radiological and histological study. Int Orthop. 1988;12:97–104.
27. Mayerhoefer ME, Breitenseher MJ, Wurnig C, Roposch A. Shoulder impingement: relationship of clinical symptoms and imaging criteria. Clin J Sport Med. 2009;19:83–9.
28. Ozaki J, Fujimoto S, Nakagawa Y, Masuhara K, Tamai S. Tears of the rotator cuff of the shoulder associated with pathological changes in the acromion. A study in cadavera. J Bone Joint Surg Am. 1988;70:1224–30.
29. Nakajima T, Rokuuma N, Hamada K, Tomatsu T, Fukuda H. Histologic and biomechanical characteristics of the supraspinatus tendon: reference to rotator cuff tearing. J Shoulder Elbow Surg. 1994;3:79–87.
30. Worland RL, Lee D, Orozco CG, SozaRex F, Keenan J. Correlation of age, acromial morphology, and rotator cuff tear pathology diagnosed by ultrasound in asymptomatic patients. J South Orthop Assoc. 2003;12:23–6.
31. Ogata S, Uhthoff HK. Acromial enthesopathy and rotator cuff tear. A radiologic and histologic postmortem investigation of the coracoacromial arch. Clin Orthop Relat Res. 1990;254:39–48.
32. Reilly P, Amis AA, Wallace AL, Emery RJ. Mechanical factors in the initiation and propagation of tears of the rotator cuff. Quantification of strains of the supraspinatus tendon in vitro. J Bone Joint Surg Br. 2003;85:594–9.
33. Edelson G, Teitz C. Internal impingement in the shoulder. J Shoulder Elbow Surg. 2000;9:308–15.
34. Soslowsky LJ, Thomopoulos S, Esmail A, et al. Rotator cuff tendinosis in an animal model: role of extrinsic and overuse factors. Ann Biomed Eng. 2002;30:1057–63.
35. Nho SJ, Yadav H, Shindle MK, Macgillivray JD. Rotator cuff degeneration: etiology and pathogenesis. Am J Sports Med. 2008;36:987–93.
36. Tempelhof S, Rupp S, Seil R. Age-related prevalence of rotator cuff tears in asymptomatic shoulders. J Shoulder Elbow Surg. 1999;8:296–9.
37. Hashimoto T, Nobuhara K, Hamada T. Pathologic evidence of degeneration as a primary cause of rotator cuff tear. Clin Orthop Relat Res. 2003;(415):111–20.
38. Longo UG, Franceschi F, Ruzzini L, et al. Histopathology of the supraspinatus tendon in rotator cuff tears. Am J Sports Med. 2008;36:533–8.
39. Perry SM, McIlhenny SE, Hoffman MC, Soslowsky LJ. Inflammatory and angiogenic mRNA levels are altered in a supraspinatus tendon overuse animal model. J Shoulder Elbow Surg. 2005;14:79S–83.
40. Yuan J, Murrell GA, Trickett A, Wang MX. Involvement of cytochrome c release and caspase-3 activation in the oxidative stress-induced apoptosis in human tendon fibroblasts. Biochim Biophys Acta. 2003;1641:35–41.
41. Wang F, Murrell GA, Wang MX. Oxidative stress-induced c-Jun N-terminal kinase (JNK) activation in tendon cells upregulates MMP1 mRNA and protein expression. J Orthop Res. 2007;25:378–89.
42. Birkedal-Hansen H, Yamada S, Windsor J, et al. Matrix metalloproteinases. Curr Protoc Cell Biol. 2008; Chapter 10: Unit 10.8.
43. Lo IK, Marchuk LL, Hollinshead R, Hart DA, Frank CB. Matrix metalloproteinase and tissue inhibitor of matrix metalloproteinase mRNA levels are specifically altered in torn rotator cuff tendons. Am J Sports Med. 2004;32:1223–9.
44. Magra M, Maffulli N. Matrix metalloproteases: a role in overuse tendinopathies. Br J Sports Med. 2005;39:789–91.
45. Gotoh M, Hamada K, Yamakawa H, Tomonaga A, Inoue A, Fukuda H. Significance of granulation tissue in torn supraspinatus insertions: an immunohistochemical study with antibodies against interleukin-1 beta, cathepsin D, and matrix metalloprotease-1. J Orthop Res. 1997;15:33–9.
46. Rodeo SA, Kawamura S, Kim HJ, Dynybil C, Ying L. Tendon healing in a bone tunnel differs at the tunnel entrance versus the tunnel exit: an effect of graft-tunnel motion? Am J Sports Med. 2006;34: 1790–800.
47. Astrom M, Rausing A. Chronic Achilles tendinopathy. A survey of surgical and histopathologic findings. Clin Orthop Relat Res. 1995;(316):151–64.
48. Maffulli N, Wong J, Almekinders LC. Types and epidemiology of tendinopathy. Clin Sports Med. 2003;22:675–92.
49. Fu SC, Wang W, Pau HM, Wong YP, Chan KM, Rolf CG. Increased expression of transforming growth factor-beta1 in patellar tendinosis. Clin Orthop Relat Res. 2002;(400):174–83.
50. Millar NL, Wei AQ, Molloy TJ, Bonar F, Murrell GA. Cytokines and apoptosis in supraspinatus tendinopathy. J Bone Joint Surg Br. 2009;91:417–24.
51. Tsuzaki M, Guyton G, Garrett W, et al. IL-1 beta induces COX2, MMP-1, −3 and −13, ADAMTS-4, IL-1 beta and IL-6 in human tendon cells. J Orthop Res. 2003;21:256–64.
52. Yang G, Im HJ, Wang JH. Repetitive mechanical stretching modulates IL-1beta induced COX-2, MMP-1 expression, and PGE2 production in human patellar tendon fibroblasts. Gene. 2005;363: 166–72.
53. Kannus P, Jozsa L. Histopathological changes preceding spontaneous rupture of a tendon. A controlled study of 891 patients. J Bone Joint Surg Am. 1991; 73:1507–25.

54. Khan KM, Cook JL, Bonar F, Harcourt P, Astrom M. Histopathology of common tendinopathies. Update and implications for clinical management. Sports Med. 1999;27:393–408.
55. Uhthoff HK, Sano H. Pathology of failure of the rotator cuff tendon. Orthop Clin North Am. 1997;28:31–41.
56. Millar NL, Hueber AJ, Reilly JH, et al. Inflammation is present in early human tendinopathy. Am J Sports Med. 2010;38:2085–91.
57. Lohr JF, Uhthoff HK. The microvascular pattern of the supraspinatus tendon. Clin Orthop Relat Res. 1990;(254):35–8.
58. Miniaci A, Dowdy PA, Willits KR, Vellet AD. Magnetic resonance imaging evaluation of the rotator cuff tendons in the asymptomatic shoulder. Am J Sports Med. 1995;23:142–5.
59. Rudzki JR, Adler RS, Warren RF, et al. Contrast-enhanced ultrasound characterization of the vascularity of the rotator cuff tendon: age- and activity-related changes in the intact asymptomatic rotator cuff. J Shoulder Elbow Surg. 2008;17:96S–100.
60. Rathbun JB, Macnab I. The microvascular pattern of the rotator cuff. J Bone Joint Surg Br. 1970;52: 540–53.
61. Brooks CH, Revell WJ, Heatley FW. A quantitative histological study of the vascularity of the rotator cuff tendon. J Bone Joint Surg Br. 1992;74:151–3.
62. Benson RT, McDonnell SM, Knowles HJ, Rees JL, Carr AJ, Hulley PA. Tendinopathy and tears of the rotator cuff are associated with hypoxia and apoptosis. J Bone Joint Surg Br. 2010;92:448–53.
63. Baumgarten KM, Gerlach D, Galatz LM, et al. Cigarette smoking increases the risk for rotator cuff tears. Clin Orthop Relat Res. 2010;468:1534–41.
64. Abboud JA, Kim JS. The effect of hypercholesterolemia on rotator cuff disease. Clin Orthop Relat Res. 2010;468:1493–7.
65. Chaudhury S, Carr AJ. Lessons we can learn from gene expression patterns in rotator cuff tears and tendinopathies. J Shoulder Elbow Surg. 2012;21: 191–9.
66. Lippi G, Longo UG, Maffulli N. Genetics and sports. Br Med Bull. 2010;93:27–47.
67. Longo UG, Lamberti A, Maffulli N, Denaro V. Tendon augmentation grafts: a systematic review. Br Med Bull. 2010;94:165–88.
68. Longo UG, Lamberti A, Maffulli N, Denaro V. Tissue engineered biological augmentation for tendon healing: a systematic review. Br Med Bull. 2011;98:31–59.
69. Harvie P, Ostlere SJ, Teh J, et al. Genetic influences in the aetiology of tears of the rotator cuff. Sibling risk of a full-thickness tear. J Bone Joint Surg Br. 2004;86:696–700.
70. Molloy TJ, Kemp MW, Wang Y, Murrell GA. Microarray analysis of the tendinopathic rat supraspinatus tendon: glutamate signaling and its potential role in tendon degeneration. J Appl Physiol. 2006;101:1702–9.
71. Rees JD, Wilson AM, Wolman RL. Current concepts in the management of tendon disorders. Rheumatology (Oxford). 2006;45:508–21.
72. Hart DA Frank CB, Bray RC. Inflammatory processes in repetitive motion and overuse syndromes: potential role of neurogenic mechanisms in tendons and ligaments. In: Gordon SL, Blair SJ, Fine LJ, National Institute of Arthritis and Musculoskeletal and Skin Diseases (U.S.), editors. Repetitive motion disorders of the upper extremity. 1st ed. Rosemont: American Academy of Orthopaedic Surgeons; 1995, xxii, 565 p.
73. Gotoh M, Hamada K, Yamakawa H, Inoue A, Fukuda H. Increased substance P in subacromial bursa and shoulder pain in rotator cuff diseases. J Orthop Res. 1998;16:618–21.
74. Yamaguchi K, Tetro AM, Blam O, Evanoff BA, Teefey SA, Middleton WD. Natural history of asymptomatic rotator cuff tears: a longitudinal analysis of asymptomatic tears detected sonographically. J Shoulder Elbow Surg. 2001;10:199–203.
75. Yamaguchi K, Ditsios K, Middleton WD, Hildebolt CF, Galatz LM, Teefey SA. The demographic and morphological features of rotator cuff disease. A comparison of asymptomatic and symptomatic shoulders. J Bone Joint Surg Am. 2006;88:1699–704.
76. Gotoh M, Hamada K, Yamakawa H, et al. Interleukin-1-induced glenohumeral synovitis and shoulder pain in rotator cuff diseases. J Orthop Res. 2002;20: 1365–71.
77. Meyer DC, Hoppeler H, von Rechenberg B, Gerber C. A pathomechanical concept explains muscle loss and fatty muscular changes following surgical tendon release. J Orthop Res. 2004;22:1004–7.
78. Itoigawa Y, Kishimoto KN, Sano H, Kaneko K, Itoi E. Molecular mechanism of fatty degeneration in rotator cuff muscle with tendon rupture. J Orthop Res. 2011;29:861–6.
79. Chaudhury S, Dines JS, Delos D, Warren RF, Voigt C, Rodeo SA. Role of fatty infiltration in the pathophysiology and outcomes of rotator cuff tears. Arthritis Care Res (Hoboken). 2012;64:76–82.
80. Steinbacher P, Tauber M, Kogler S, Stoiber W, Resch H, Sanger AM. Effects of rotator cuff ruptures on the cellular and intracellular composition of the human supraspinatus muscle. Tissue Cell. 2010;42:37–41.
81. Melis B, DeFranco MJ, Chuinard C, Walch G. Natural history of fatty infiltration and atrophy of the supraspinatus muscle in rotator cuff tears. Clin Orthop Relat Res. 2010;468:1498–505.
82. Nakagaki K, Ozaki J, Tomita Y, Tamai S. Fatty degeneration in the supraspinatus muscle after rotator cuff tear. J Shoulder Elbow Surg. 1996; 5:194–200.
83. Kim HM, Dahiya N, Teefey SA, Keener JD, Galatz LM, Yamaguchi K. Relationship of tear size and location to fatty degeneration of the rotator cuff. J Bone Joint Surg Am. 2010;92:829–39.
84. Kim HM, Galatz LM, Lim C, Havlioglu N, Thomopoulos S. The effect of tear size and nerve

injury on rotator cuff muscle fatty degeneration in a rodent animal model. J Shoulder Elbow Surg. 2012;21:847–58.
85. Liu X, Laron D, Natsuhara K, Manzano G, Kim HT, Feeley BT. A mouse model of massive rotator cuff tears. J Bone Joint Surg Am. 2012;94:e41.
86. Liu X, Manzano G, Kim HT, Feeley BT. A rat model of massive rotator cuff tears. J Orthop Res. 2011;29:588–95.
87. Mallon WJ, Wilson RJ, Basamania CJ. The association of suprascapular neuropathy with massive rotator cuff tears: a preliminary report. J Shoulder Elbow Surg. 2006;15:395–8.
88. Rowshan K, Hadley S, Pham K, Caiozzo V, Lee TQ, Gupta R. Development of fatty atrophy after neurologic and rotator cuff injuries in an animal model of rotator cuff pathology. J Bone Joint Surg Am. 2010;92:2270–8.
89. Shah AA, Butler RB, Sung SY, Wells JH, Higgins LD, Warner JJ. Clinical outcomes of suprascapular nerve decompression. J Shoulder Elbow Surg. 2011;20:975–82.
90. Gladstone JN, Bishop JY, Lo IK, Flatow EL. Fatty infiltration and atrophy of the rotator cuff do not improve after rotator cuff repair and correlate with poor functional outcome. Am J Sports Med. 2007;35:719–28.
91. Rubino LJ, Sprott DC, Stills Jr HF, Crosby LA. Fatty infiltration does not progress after rotator cuff repair in a rabbit model. Arthroscopy. 2008;24:936–40.
92. Yamaguchi H, Suenaga N, Oizumi N, Hosokawa Y, Kanaya F. Will preoperative atrophy and Fatty degeneration of the shoulder muscles improve after rotator cuff repair in patients with massive rotator cuff tears? Adv Orthop. 2012;2012:195876.
93. Goutallier D, Postel JM, Bernageau J, Lavau L, Voisin MC. Fatty muscle degeneration in cuff ruptures. Pre- and postoperative evaluation by CT scan. Clin Orthop Relat Res. 1994;(304):78–83.
94. Mellado JM, Calmet J, Olona M, et al. Surgically repaired massive rotator cuff tears: MRI of tendon integrity, muscle fatty degeneration, and muscle atrophy correlated with intraoperative and clinical findings. AJR Am J Roentgenol. 2005;184: 1456–63.
95. Laron D, Samagh SP, Liu X, Kim HT, Feeley BT. Muscle degeneration in rotator cuff tears. J Shoulder Elbow Surg. 2012;21:164–74.
96. Senf SM, Dodd SL, Judge AR. FOXO signaling is required for disuse muscle atrophy and is directly regulated by Hsp70. Am J Physiol Cell Physiol. 2010;298:C38–45.
97. Senf SM, Dodd SL, McClung JM, Judge AR. Hsp70 overexpression inhibits NF-kappaB and Foxo3a transcriptional activities and prevents skeletal muscle atrophy. FASEB J. 2008;22:3836–45.
98. Schmutz S, Fuchs T, Regenfelder F, Steinmann P, Zumstein M, Fuchs B. Expression of atrophy mRNA relates to tendon tear size in supraspinatus muscle. Clin Orthop Relat Res. 2009;467:457–64.
99. Liu X, et al. Evaluation of Akt/mTOR activity in muscle atrophy after rotator cuff tears in a rat model. J Orthop Res. 2012;30:1440–6.
100. Perry RL, Rudnick MA. Molecular mechanisms regulating myogenic determination and differentiation. Front Biosci. 2000;5:D750–67.
101. Sabourin LA, Rudnicki MA. The molecular regulation of myogenesis. Clin Genet. 2000;57:16–25.
102. Otto TC, Lane MD. Adipose development: from stem cell to adipocyte. Crit Rev Biochem Mol Biol. 2005;40:229–42.
103. Rosen ED, Walkey CJ, Puigserver P, Spiegelman BM. Transcriptional regulation of adipogenesis. Genes Dev. 2000;14:1293–307.
104. Frey E, Regenfelder F, Sussmann P, et al. Adipogenic and myogenic gene expression in rotator cuff muscle of the sheep after tendon tear. J Orthop Res. 2009;27:504–9.
105. Bennett CN, Hodge CL, MacDougald OA, Schwartz J. Role of Wnt10b and C/EBPalpha in spontaneous adipogenesis of 243 cells. Biochem Biophys Res Commun. 2003;302:12–6.
106. Itoigawa Y, Kishimoto KN, Okuno H, Sano H, Kaneko K, Itoi E. Hypoxia induces adipogenic differentiation of myoblastic cell lines. Biochem Biophys Res Commun. 2010;399:721–6.
107. Park JR, Jung JW, Lee YS, Kang KS. The roles of Wnt antagonists Dkk1 and sFRP4 during adipogenesis of human adipose tissue-derived mesenchymal stem cells. Cell Prolif. 2008;41:859–74.
108. Safran O, Derwin KA, Powell K, Iannotti JP. Changes in rotator cuff muscle volume, fat content, and passive mechanics after chronic detachment in a canine model. J Bone Joint Surg Am. 2005;87: 2662–70.
109. Akimoto T, Ushida T, Miyaki S, et al. Mechanical stretch inhibits myoblast-to-adipocyte differentiation through Wnt signaling. Biochem Biophys Res Commun. 2005;329:381–5.
110. Lakemeier S, Reichelt JJ, Patzer T, Fuchs-Winkelmann S, Paletta JR, Schofer MD. The association between retraction of the torn rotator cuff and increasing expression of hypoxia inducible factor 1alpha and vascular endothelial growth factor expression: an immunohistological study. BMC Musculoskelet Disord. 2010;11:230.
111. Woo SL, An K-N, Arnoczky SP, et al. Anatomy, biology, and biomechanics of tendon, ligament, and meniscus. In: Simon SR, American Academy of Orthopaedic Surgeons, editors. Orthopaedic basic science. Rosemont: American Academy of Orthopaedic Surgeons; 1994, xvi, 704 p.
112. Bedi A, Maak T, Walsh C, et al. Cytokines in rotator cuff degeneration and repair. J Shoulder Elbow Surg. 2012;21:218–27.
113. Gulotta LV, Rodeo SA. Growth factors for rotator cuff repair. Clin Sports Med. 2009;28:13–23.
114. Montgomery SR, Petrigliano FA, Gamradt SC. Failed rotator cuff surgery, evaluation and decision making. Clin Sports Med. 2012;31:693–712.

115. Gamradt SC, Gallo RA, Adler RS, et al. Vascularity of the supraspinatus tendon three months after repair: characterization using contrast-enhanced ultrasound. J Shoulder Elbow Surg. 2010;19:73–80.
116. Gerber C, Schneeberger AG, Perren SM, Nyffeler RW. Experimental rotator cuff repair. A preliminary study. J Bone Joint Surg Am. 1999;81:1281–90.
117. Carpenter JE, Thomopoulos S, Flanagan CL, DeBano CM, Soslowsky LJ. Rotator cuff defect healing: a biomechanical and histologic analysis in an animal model. J Shoulder Elbow Surg. 1998; 7:599–605.
118. Hays PL, Kawamura S, Deng XH, et al. The role of macrophages in early healing of a tendon graft in a bone tunnel. J Bone Joint Surg Am. 2008;90: 565–79.
119. Harwood FL, Goomer RS, Gelberman RH, Silva MJ, Amiel D. Regulation of alpha(v)beta3 and alpha5beta1 integrin receptors by basic fibroblast growth factor and platelet-derived growth factor-BB in intrasynovial flexor tendon cells. Wound Repair Regen. 1999;7:381–8.
120. Nakamura N, Shino K, Natsuume T, et al. Early biological effect of in vivo gene transfer of platelet-derived growth factor (PDGF)-B into healing patellar ligament. Gene Ther. 1998;5:1165–70.
121. Nakamura N, Timmermann SA, Hart DA, et al. A comparison of in vivo gene delivery methods for antisense therapy in ligament healing. Gene Ther. 1998;5:1455–61.
122. Yoshikawa Y, Abrahamsson SO. Dose-related cellular effects of platelet-derived growth factor-BB differ in various types of rabbit tendons in vitro. Acta Orthop Scand. 2001;72:287–92.
123. Hee CK, Dines JS, Dines DM, et al. Augmentation of a rotator cuff suture repair using rhPDGF-BB and a type I bovine collagen matrix in an ovine model. Am J Sports Med. 2011;39:1630–9.
124. Campbell BH, Agarwal C, Wang JH. TGF-beta1, TGF-beta3, and PGE(2) regulate contraction of human patellar tendon fibroblasts. Biomech Model Mechanobiol. 2004;2:239–45.
125. Klein MB, Yalamanchi N, Pham H, Longaker MT, Chang J. Flexor tendon healing in vitro: effects of TGF-beta on tendon cell collagen production. J Hand Surg Am. 2002;27:615–20.
126. Kovacevic D, Fox AJ, Bedi A, et al. Calcium-phosphate matrix with or without TGF-beta3 improves tendon-bone healing after rotator cuff repair. Am J Sports Med. 2011;39:811–9.
127. Wolfman NM, Hattersley G, Cox K, et al. Ectopic induction of tendon and ligament in rats by growth and differentiation factors 5, 6, and 7, members of the TGF-beta gene family. J Clin Invest. 1997; 100:321–30.
128. Abrahamsson SO, Lundborg G, Lohmander LS. Recombinant human insulin-like growth factor-I stimulates in vitro matrix synthesis and cell proliferation in rabbit flexor tendon. J Orthop Res. 1991;9:495–502.
129. Dahlgren LA, van der Meulen MC, Bertram JE, Starrak GS, Nixon AJ. Insulin-like growth factor-I improves cellular and molecular aspects of healing in a collagenase-induced model of flexor tendinitis. J Orthop Res. 2002;20:910–9.
130. Kurtz CA, Loebig TG, Anderson DD, DeMeo PJ, Campbell PG. Insulin-like growth factor I accelerates functional recovery from Achilles tendon injury in a rat model. Am J Sports Med. 1999;27:363–9.
131. Canalis E, Centrella M, McCarthy T. Effects of basic fibroblast growth factor on bone formation in vitro. J Clin Invest. 1988;81:1572–7.
132. Gospodarowicz D, Neufeld G, Schweigerer L. Molecular and biological characterization of fibroblast growth factor, an angiogenic factor which also controls the proliferation and differentiation of mesoderm and neuroectoderm derived cells. Cell Differ. 1986;19:1–17.
133. Ide J, Kikukawa K, Hirose J, et al. The effect of a local application of fibroblast growth factor-2 on tendon-to-bone remodeling in rats with acute injury and repair of the supraspinatus tendon. J Shoulder Elbow Surg. 2009;18:391–8.
134. Chan BP, Chan KM, Maffulli N, Webb S, Lee KK. Effect of basic fibroblast growth factor. An in vitro study of tendon healing. Clin Orthop Relat Res. 1997;(342):239–47.
135. Chan BP, Fu S, Qin L, Lee K, Rolf CG, Chan K. Effects of basic fibroblast growth factor (bFGF) on early stages of tendon healing: a rat patellar tendon model. Acta Orthop Scand. 2000;71:513–8.
136. Takahasih S, Nakajima M, Kobayashi M, et al. Effect of recombinant basic fibroblast growth factor (bFGF) on fibroblast-like cells from human rotator cuff tendon. Tohoku J Exp Med. 2002; 198:207–14.
137. Tang JB, Cao Y, Zhu B, Xin KQ, Wang XT, Liu PY. Adeno-associated virus-2-mediated bFGF gene transfer to digital flexor tendons significantly increases healing strength: an in vivo study. J Bone Joint Surg Am. 2008;90:1078–89.
138. Chang J, Most D, Thunder R, Mehrara B, Longaker MT, Lineaweaver WC. Molecular studies in flexor tendon wound healing: the role of basic fibroblast growth factor gene expression. J Hand Surg Am. 1998;23:1052–8.
139. Khan U, Occleston NL, Khaw PT, McGrouther DA. Differences in proliferative rate and collagen lattice contraction between endotenon and synovial fibroblasts. J Hand Surg Am. 1998;23:266–73.
140. Thomopoulos S, Harwood FL, Silva MJ, Amiel D, Gelberman RH. Effect of several growth factors on canine flexor tendon fibroblast proliferation and collagen synthesis in vitro. J Hand Surg Am. 2005; 30:441–7.
141. Tsuzaki M, Brigman BE, Yamamoto J, et al. Insulin-like growth factor-I is expressed by avian flexor tendon cells. J Orthop Res. 2000;18:546–56.
142. Bidder M, Towler DA, Gelberman RH, Boyer MI. Expression of mRNA for vascular endothelial

growth factor at the repair site of healing canine flexor tendon. J Orthop Res. 2000;18:247–52.
143. Boyer MI, Watson JT, Lou J, Manske PR, Gelberman RH, Cai SR. Quantitative variation in vascular endothelial growth factor mRNA expression during early flexor tendon healing: an investigation in a canine model. J Orthop Res. 2001;19:869–72.
144. Petersen W, Pufe T, Unterhauser F, Zantop T, Mentlein R, Weiler A. The splice variants 120 and 164 of the angiogenic peptide vascular endothelial cell growth factor (VEGF) are expressed during Achilles tendon healing. Arch Orthop Trauma Surg. 2003;123:475–80.
145. Petersen W, Unterhauser F, Pufe T, Zantop T, Sudkamp NP, Weiler A. The angiogenic peptide vascular endothelial growth factor (VEGF) is expressed during the remodeling of free tendon grafts in sheep. Arch Orthop Trauma Surg. 2003;123:168–74.
146. Hersche O, Gerber C. Passive tension in the supraspinatus musculotendinous unit after long-standing rupture of its tendon: a preliminary report. J Shoulder Elbow Surg. 1998;7:393–6.
147. Gerber C, Schneeberger AG, Hoppeler H, Meyer DC. Correlation of atrophy and fatty infiltration on strength and integrity of rotator cuff repairs: a study in thirteen patients. J Shoulder Elbow Surg. 2007;16:691–6.
148. Liem D, Lichtenberg S, Magosch P, Habermeyer P. Magnetic resonance imaging of arthroscopic supraspinatus tendon repair. J Bone Joint Surg Am. 2007;89:1770–6.
149. Coleman SH, Fealy S, Ehteshami JR, et al. Chronic rotator cuff injury and repair model in sheep. J Bone Joint Surg Am. 2003;85-A:2391–402.
150. Bassett RW, Cofield RH. Acute tears of the rotator cuff. The timing of surgical repair. Clin Orthop Relat Res. 1983;(175):18–24.
151. Boileau P, Brassart N, Watkinson DJ, Carles M, Hatzidakis AM, Krishnan SG. Arthroscopic repair of full-thickness tears of the supraspinatus: does the tendon really heal? J Bone Joint Surg Am. 2005;87:1229–40.
152. Cole BJ, McCarty 3rd LP, Kang RW, Alford W, Lewis PB, Hayden JK. Arthroscopic rotator cuff repair: prospective functional outcome and repair integrity at minimum 2-year follow-up. J Shoulder Elbow Surg. 2007;16:579–85.
153. DeFranco MJ, Bershadsky B, Ciccone J, Yum JK, Iannotti JP. Functional outcome of arthroscopic rotator cuff repairs: a correlation of anatomic and clinical results. J Shoulder Elbow Surg. 2007;16:759–65.
154. Gazielly DF, Gleyze P, Montagnon C. Functional and anatomical results after rotator cuff repair. Clin Orthop Relat Res. 1994;(304):43–53.
155. Harryman 2nd DT, Mack LA, Wang KY, Jackins SE, Richardson ML, Matsen 3rd FA. Repairs of the rotator cuff. Correlation of functional results with integrity of the cuff. J Bone Joint Surg Am. 1991;73:982–9.
156. Keener JD, Wei AS, Kim HM, et al. Revision arthroscopic rotator cuff repair: repair integrity and clinical outcome. J Bone Joint Surg Am. 2010;92:590–8.
157. Nho SJ, Brown BS, Lyman S, Adler RS, Altchek DW, MacGillivray JD. Prospective analysis of arthroscopic rotator cuff repair: prognostic factors affecting clinical and ultrasound outcome. J Shoulder Elbow Surg. 2009;18:13–20.
158. Cohen DB, Kawamura S, Ehteshami JR, Rodeo SA. Indomethacin and celecoxib impair rotator cuff tendon-to-bone healing. Am J Sports Med. 2006;34:362–9.
159. An KN, Chao EY. Kinematic analysis of human movement. Ann Biomed Eng. 1984;12:585–97.
160. Hansen ML, Otis JC, Johnson JS, Cordasco FA, Craig EV, Warren RF. Biomechanics of massive rotator cuff tears: implications for treatment. J Bone Joint Surg Am. 2008;90:316–25.
161. Itoi E. Biomechanics of the shoulder. In: Rockwood C, Matsen F, editors. The shoulder. Philadelphia: Saunders Elsevier; 2009.
162. Bechtol CO. Biomechanics of the shoulder. Clin Orthop Relat Res. 1980:37–41.
163. Markhede G, Monastyrski J, Stener B. Shoulder function after deltoid muscle removal. Acta Orthop Scand. 1985;56:242–4.
164. Thompson WO, Debski RE, Boardman 3rd ND, et al. A biomechanical analysis of rotator cuff deficiency in a cadaveric model. Am J Sports Med. 1996;24:286–92.
165. Itoi E, Minagawa H, Sato T, Sato K, Tabata S. Isokinetic strength after tears of the supraspinatus tendon. J Bone Joint Surg Br. 1997;79:77–82.
166. Kuechle DK, Newman SR, Itoi E, Niebur GL, Morrey BF, An KN. The relevance of the moment arm of shoulder muscles with respect to axial rotation of the glenohumeral joint in four positions. Clin Biomech (Bristol, Avon). 2000;15:322–9.
167. Howell SM, Imobersteg AM, Seger DH, Marone PJ. Clarification of the role of the supraspinatus muscle in shoulder function. J Bone Joint Surg Am. 1986;68:398–404.
168. Sharkey NA, Marder RA, Hanson PB. The entire rotator cuff contributes to elevation of the arm. J Orthop Res. 1994;12:699–708.
169. O'Brien SJ, Schwartz RS, Warren RF, Torzilli PA. Capsular restraints to anterior-posterior motion of the abducted shoulder: a biomechanical study. J Shoulder Elbow Surg. 1995;4:298–308.
170. Kumar VP, Balasubramaniam P. The role of atmospheric pressure in stabilising the shoulder. An experimental study. J Bone Joint Surg Br. 1985;67:719–21.
171. Gibb TD, Sidles JA, Harryman 2nd DT, McQuade KJ, Matsen 3rd FA. The effect of capsular venting on glenohumeral laxity. Clin Orthop Relat Res. 1991;(268):120–7.
172. Howell SM, Kraft TA. The role of the supraspinatus and infraspinatus muscles in glenohumeral kinematics of anterior should instability. Clin Orthop Relat Res. 1991;(263):128–34.

173. Turkel SJ, Panio MW, Marshall JL, Girgis FG. Stabilizing mechanisms preventing anterior dislocation of the glenohumeral joint. J Bone Joint Surg Am. 1981;63:1208–17.
174. Longo UG, Berton A, Papapietro N, Maffulli N, Denaro V. Biomechanics of the rotator cuff: European perspective. Med Sport Sci. 2012;57:10–7.
175. Inman VT, Saunders JB, Abbott LC. Observations of the function of the shoulder joint. Clin Orthop Relat Res. 1944;1996:3–12.
176. Saha AK. Dynamic stability of the glenohumeral joint. Acta Orthop Scand. 1971;42:491–505.
177. Kido T, Itoi E, Konno N, Sano A, Urayama M, Sato K. The depressor function of biceps on the head of the humerus in shoulders with tears of the rotator cuff. J Bone Joint Surg Br. 2000;82:416–9.
178. Parsons IM, Apreleva M, Fu FH, Woo SL. The effect of rotator cuff tears on reaction forces at the glenohumeral joint. J Orthop Res. 2002;20:439–46.
179. Poppen NK, Walker PS. Forces at the glenohumeral joint in abduction. Clin Orthop Relat Res. 1978;(135):165–70.
180. Yanagawa T, Goodwin CJ, Shelburne KB, Giphart JE, Torry MR, Pandy MG. Contributions of the individual muscles of the shoulder to glenohumeral joint stability during abduction. J Biomech Eng. 2008;130:021024.
181. David G, Magarey ME, Jones MA, Dvir Z, Turker KS, Sharpe M. EMG and strength correlates of selected shoulder muscles during rotations of the glenohumeral joint. Clin Biomech (Bristol, Avon). 2000;15:95–102.
182. Oh JH, Jun BJ, McGarry MH, Lee TQ. Does a critical rotator cuff tear stage exist?: a biomechanical study of rotator cuff tear progression in human cadaver shoulders. J Bone Joint Surg Am. 2011;93:2100–9.
183. Mall NA, Kim HM, Keener JD, et al. Symptomatic progression of asymptomatic rotator cuff tears: a prospective study of clinical and sonographic variables. J Bone Joint Surg Am. 2010;92:2623–33.
184. McMahon PJ, Debski RE, Thompson WO, Warner JJ, Fu FH, Woo SL. Shoulder muscle forces and tendon excursions during glenohumeral abduction in the scapular plane. J Shoulder Elbow Surg. 1995;4:199–208.
185. Graichen H, Stammberger T, Bonel H, Karl-Hans E, Reiser M, Eckstein F. Glenohumeral translation during active and passive elevation of the shoulder – a 3D open-MRI study. J Biomech. 2000;33:609–13.
186. Burkhart SS, Nottage WM, Ogilvie-Harris DJ, Kohn HS, Pachelli A. Partial repair of irreparable rotator cuff tears. Arthroscopy. 1994;10:363–70.
187. Gartsman GM. Massive, irreparable tears of the rotator cuff. Results of operative debridement and subacromial decompression. J Bone Joint Surg Am. 1997;79:715–21.
188. Su WR, Budoff JE, Luo ZP. The effect of anterosuperior rotator cuff tears on glenohumeral translation. Arthroscopy. 2009;25:282–9.
189. Burkhart SS. Fluoroscopic comparison of kinematic patterns in massive rotator cuff tears. A suspension bridge model. Clin Orthop Relat Res. 1992;(284):144–52.
190. Kelly BT, Williams RJ, Cordasco FA, et al. Differential patterns of muscle activation in patients with symptomatic and asymptomatic rotator cuff tears. J Shoulder Elbow Surg. 2005;14:165–71.
191. Warner JJ. Management of massive irreparable rotator cuff tears: the role of tendon transfer. Instr Course Lect. 2001;50:63–71.
192. Burkhart SS, Barth JR, Richards DP, Zlatkin MB, Larsen M. Arthroscopic repair of massive rotator cuff tears with stage 3 and 4 fatty degeneration. Arthroscopy. 2007;23:347–54.
193. Ainsworth R. Physiotherapy rehabilitation in patients with massive, irreparable rotator cuff tears. Musculoskeletal Care. 2006;4:140–51.
194. Levy O, Mullett H, Roberts S, Copeland S. The role of anterior deltoid reeducation in patients with massive irreparable degenerative rotator cuff tears. J Shoulder Elbow Surg. 2008;17:863–70.