Immunologic Contributions Following Rotator Cuff Injury and Development of Cuff Tear Arthropathy

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Abstract

» Rotator cuff tear arthropathy (RCTA) describes a pattern of glenohumeral degenerative changes following chronic rotator cuff tears that is characterized by superior humeral head migration, erosion of the greater tuberosity of the humeral head, contouring of the coracoacromial arch to create a socket for the humeral head, and eventual glenohumeral arthritis.

» Acute and chronic inflammatory changes following rotator cuff tears are thought to contribute to cartilage damage, muscle fibrosis, and fatty infiltration in the glenohumeral joint.

» In vitro animal studies targeting various inflammatory modulators, including macrophages, insulin-like growth factor-I, and transforming growth factor-beta pathways, provide promising therapeutic targets to improve healing after rotator cuff tears.

» The role of platelet-rich plasma in the treatment and prevention of RCTA has been investigated, with conflicting results.

Chronic shoulder pain is estimated to affect approximately 8% of Americans and ranks second only to chronic knee pain in musculoskeletal disease burden[1]. Rotator cuff pathology is the primary cause of shoulder disability that is seen by orthopaedic surgeons[1]. People who are >40 years of age are at the greatest risk for rotator cuff disease, and more than two-thirds of those treated with rotator cuff repair are of working age[1]. It is estimated that almost 60% of people who are >60 years age and 80% of those who are >80 years of age have rotator cuff tears (RCTs), resulting in a large economic and societal burden[2,3].

The rotator cuff is composed of the muscle bellies and the tendons of the supraspinatus, infraspinatus, teres minor, and subscapularis. The primary function of the rotator cuff is to provide dynamic stability to the shoulder by balancing the force couples about the glenohumeral joint in both the coronal and transverse planes[4]. Rotator cuff disease encompasses a spectrum of pathology ranging from bursitis and tendinopathy to partial-thickness and complete tears. The instability caused by chronic RCTs results in a predictable pattern of glenohumeral degenerative changes termed "rotator cuff tear arthropathy" (RCTA)[4]. Loss of dynamic support puts higher strain on the static stabilizers, such as the labrum, the joint capsule, and the glenohumeral ligaments, and results in glenoid erosion, cartilage wear, and humeral head deformity. Progression of RCTA is evidenced by superior migration of the humerus due to the unrestricted superior pull of the deltoid, resulting in erosion of the greater tuberosity of the humeral head and contouring of the coracoacromial arch, creating a socket for the humeral head[4,5].

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RCTA may ultimately lead to humeral head collapse, severe deformity, and end-stage glenohumeral arthritis.

Inflammation plays an important role in the development and progression of muscle and tendon injuries. This process involves a complex and precise coordination of multiple inflammatory cascades and immunologic factors that may ultimately dictate whether soft tissues, including rotator cuff tendons, heal or progress to chronic inflammation and RCTA. This review article highlights our current understanding of the immunologic contributions following rotator cuff injuries, their impact on RCTA, and novel therapeutic strategies to delay or prevent RCTA.

Pathomechanical Theories of RCTA Development

The exact cause of RCTA remains unknown; however, a variety of pathomechanical theories have been hypothesized. The force couple theory, as proposed by Burkhart in 1992, uses the general biomechanics of the shoulder to explain the cause of RCTA[6]. It states that massive RCTs cause uncoupling of the dynamic stabilizers, specifically the net inferior force of the rotator cuff muscles and the superiorly directed force of the deltoid[6,7]. This decoupling causes superior migration of the humeral head on the glenoid. These altered biomechanics result in instability, reduced motion, and eventual chondral loss[8].

The crystal-mediated theory was first described by Halverson et al. in 1981[9]. It speculates that the presence of intra-articular calcium phosphate crystals triggers an immunologic cascade, eventually resulting in proteolytic enzyme degradation of the rotator cuff. They believed that phagocytosis of the calcium phosphate crystals by synovial macrophage-like cells causes release of collagenase and proteinase, resulting in further tissue degradation, promoting release of additional crystals and a cycle of continued inflammation[7,9]. In support of this, more recent work by Antoniou et al. found elevated levels of apatite crystals in the synovial fluid of patients with large RCTs or glenohumeral arthritis[10]. While the pathophysiology of the crystal-mediated theory remains to be fully investigated and validated, it is still recognized as a potential cause of RCTA.

Initially developed in 1983, the Neer rotator cuff theory describes a combination of mechanical and nutritional factors causing degradation of the rotator cuff. Similar to the force couple theory, the mechanical pathway of the Neer model refers to the unbalanced forces across the shoulder joint, leading to acromial impingement and gradual wear of the cuff musculature and glenoid[7]. Loss of glenohumeral motion with periarticular damage was postulated to cause a loss of fluid pressure, thereby altering the chemical content of synovial fluid. These nutritional changes include a decrease in glycosaminoglycans that, in combination with recurrent hemorrhagic effusions, results in additional bone and soft-tissue destruction[8,11]. Additionally, the leakage of synovial fluid is theorized to disrupt the negative pressure within the glenohumeral joint, which serves as an important static stabilizer of the shoulder[7]. Decreased shoulder activity due to pain is thought to reduce the delivery of synovial nutrients and, thus, further accelerate articular cartilage degeneration and disuse osteopenia[7].

Recent studies have begun to appreciate the importance of the critical shoulder angle (CSA), measured between the plane of the glenoid fossa and a line from the inferior edge of the glenoid to the lateral edge of the acromion on an anterior oblique view with the patient rotated 35° to 45° to the affected side, also known as a Grashey-view radiograph[12,13] (Fig. 1). This radiographic parameter combines the measurements of glenoid inclination and the lateral extension of the acromion. A retrospective study by Moor et al. demonstrated that a cohort of asymptomatic shoulders with normal rotator cuffs and no osteoarthritis (OA) had a mean CSA of 33.3°, while patients with magnetic resonance imaging (MRI)-documented full-thickness RCTs without OA had higher CSAs that averaged 38°, and patients with primary OA and no RCTs had lower CSAs that averaged 28°[12]. Biomechanically, a larger CSA (>35°) with an upwardly sloped glenoid fossa and large acromial cover has been shown to increase glenohumeral shear forces, leading to supraspinatus tendon overload in order to preserve joint stability. This may be 1 contributing factor in the increased prevalence of RCTs in patients with a larger CSA that is seen clinically[14].

Despite these proposed theories, many from the early 1980s and 1990s, our understanding of RCTA remains poor. It is unclear why only some patients with massive RCTs progress to RCTA or why patients with similar radiographic findings can have widely variable clinical presentations. Furthermore, the cellular and immunologic contributions following rotator cuff injuries to the development of RCTA have only begun to be elucidated.

Elevated Acute Inflammation in the Shoulder Following RCTs

The acute phase of inflammation is characterized by increased blood flow and vascular permeability, resulting in accumulation of edema, leukocytes, and inflammatory mediators such as cytokines. Cytokines orchestrate the inflammatory response and are major determinants of cellular infiltration and activation, and are also the systemic response to inflammation.

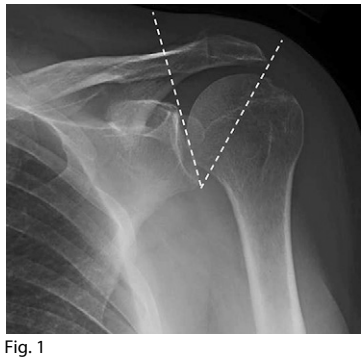

Fig. 1

Radiograph of a patient with RCTA showing the assessment of the CSA as measured between a line from the inferior to the superior border of the glenoid fossa and another line from the inferior border of the glenoid to the most inferolateral point of the acromion, as described by Moor et al.[12].

Proinflammatory acute-phase cytokines include interleukin-1 (IL-1), tumor necrosis factor-alpha (TNF-α), IL-6, IL-11, and IL-8. These cytokines have been found at elevated levels in the synovial fluid of patients with acute rotator cuff pathology[15].

Gotoh et al. demonstrated substantially higher concentrations of inflammatory cytokines, particularly IL-1β, in synovial tissue samples from glenohumeral joints of patients with full-thickness RCTs compared with those with partial-thickness or nonperforating tears at the time of surgery[16]. Histologic examination and reverse transcription-polymerase chain reaction (RT-PCR) analysis demonstrated increased expression of IL-1β mRNA within synovial lining cells, infiltrating mononuclear cells, and synovial fibroblasts in shoulders with perforating full-thickness tears. Okamura et al. used enzyme-linked immunosorbent assays (ELISA) to analyze IL-1β, IL-6, and IL-8 levels in synovial fluid samples from patients with symptomatic RCTs[17]. They found that elevated synovial IL-8 concentration correlated with both increased resting pain and increased levels of IL-6 and IL-1β[17]. In a similar study, Osawa et al. obtained intraoperative synovial fluid samples from patients with RCTs and control samples from patients with non-rotator-cuff shoulder pathology, such as impingement syndrome, superior labral anterior-posterior (SLAP) lesions, and anterior instability[18]. Those with RCTs showed higher levels of IL-1β, matrix metalloproteinase-2 (MMP-2), and MMP-13 compared with the control samples. They further demonstrated that samples from patients with full-thickness tears had substantially higher levels of MMP-13 and IL-1β than those with partial-thickness tears[18]. Notably, MMPs are known to induce proteolytic activity that leads to the pathologic destruction of cartilage in arthritis[19,20].

Various inflammatory cells also have been shown to play an important role following acute rotator cuff injury. Millar et al. examined samples of subscapularis tendon at the time of arthroscopic surgery in patients undergoing rotator cuff repair as well as a control sample of those undergoing shoulder stabilization surgery with an intact rotator cuff[21]. Histologic and immunohistochemical analysis of the tendon samples showed significantly greater macrophage, mast cell, and T-cell concentrations in the RCT group compared with the control subscapularis tendons. This study provided evidence of inflammatory cell infiltration, particularly involving the innate immune pathways, in early mild-to-moderate tendinopathy[21]. In another study, Abrams et al. performed histological analysis of the level of synovitis in patients with full-thickness RCTs and compared them with patients without rotator cuff pathology[22]. They showed that synovitis scores were significantly higher in the RCT group compared with the control synovial samples ($p < 0.001$). Additionally, the RCT group showed elevated levels of inflammatory mediators, specifically MMP-3, IL-6, and specialized macrophage lines ($CD45^+$ and $CD68^+$)[22]. Together, these findings of elevated acute phase cytokines, glenohumeral synovitis, and inflammatory cell infiltration following RCTs have been proposed as contributors to the development of glenohumeral arthropathy[16].

Chronic Inflammation, Fatty Infiltration, and Muscle Fibrosis Following RCTs

Large RCTs that are left untreated or fail repair may progress to the development of atrophy of the rotator cuff musculature, accumulation of fat within and around the muscle fibers, and fibrosis of the rotator cuff complex. Chronic inflammation is responsible for muscle atrophy and degeneration in numerous pathologies, including muscular dystrophy, sarcopenia, and chronic obstructive pulmonary disease[23-25]. The role of chronic inflammation in rotator cuff muscle atrophy, degeneration, and fibrosis after massive RCTs has only recently been investigated.

Using an established rat model, Davies et al. found significantly increased rotator cuff RhoA signaling at 2 weeks following massive tendon and nerve injury ($p < 0.05$)[26]. RhoA is a small GTPase that activates RhoA kinase (ROCK), which increases actin cytoskeleton turnover and monocyte transendothelial tissue migration[27]. This increased RhoA signaling in injured rotator cuff tissue was associated with significantly elevated expression of inflammatory markers, including TNF-α and transforming growth factor-beta 1 (TGF-β1), at 6 weeks after injury. Furthermore, RhoA signaling was associated with monocyte infiltration, which in turn worsened rotator cuff fatty infiltration, atrophy, and fibrosis.

Gumucio et al. investigated the induction of various RNA molecules 30 days after massive supraspinatus and infraspinatus tears in a rat model[28]. These RNA molecules included peroxisome proliferator-activated receptor gamma (PPARγ), perilipin-1 (PLIN1), MMP-2, and MMP-14, which regulate atrophy, fibrosis, lipid accumulation, inflammation, and macrophage recruitment. Tissue samples from the supraspinatus and infraspinatus muscles showed a 40% to 50% reduction in mass relative to controls[28]. Gene expression analysis also revealed upregulation of cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX). COX-2 catalyzes the formation of proinflammatory prostaglandins that inhibit muscle stem-cell proliferation and muscle regeneration, while 5-LOX converts arachidonic acid into proinflammatory leukotrienes[29-31].

It has been proposed that specific muscle-resident progenitor cells, $Tie2^+$ mesenchymal progenitors and platelet-derived growth factor receptor alpha-positive ($PDGFR\alpha^+$) fibro-adipogenic progenitor (FAP) cells, are the major source of fibroblasts and adipocytes in rotator cuff muscle fatty infiltration, respectively[32]. FAP cells are resident in normal muscle and are typically quiescent in healthy tissue. Joe et al. demonstrated that these cells proliferate in

response to cellular damage and enhance the rate of differentiation of primary myogenic progenitors[33]. FAPs have also been shown to generate ectopic white fat when implanted within damaged muscle in the setting of elevated inflammation, further supporting their role as the source of fat production and fatty infiltration after RCTs[33].

Fibrosis, or deposition of fibrous tissue, is considered to be an irreversible change to the structure and function of injured muscles, including the rotator cuff. Fibrosis following RCT has been demonstrated to increase the stiffness of the muscle, increasing tension at the repair site, and potentially decreasing repairability and healing potential[34]. Despite the important deleterious effects of fibrosis following RCTs, little is known about the underlying etiology. Work by Liu et al. demonstrated that increases in fibrosis after RCT in an animal model were associated with concomitant increases in TGF-β gene and protein expression at both 2 and 6 weeks[32]. This upregulation of TGF-β signaling was further marked by increased collagen I, collagen III, and alpha-smooth muscle actin (α-SMA), downstream markers that are all related to increased tissue fibrosis. As highlighted previously, macrophages appear to be the dominant cell type contributing to fibrosis following RCTs through RhoA signaling[26].

Cartilage Damage Following RCTs

While mechanical theories of RCTA have focused on the loss of the rotator cuff force couples that lead to abnormal joint kinematics, the exact pathophysiology of cartilage deterioration in the shoulder remains poorly understood[35]. It has been well documented that injury to the joint or surrounding soft tissue results in the production of damage-associated molecular patterns, including cartilage extracellular matrix (ECM) breakdown products[36]. Early work by Homandberg and Hui suggested that ECM breakdown products could promote inflammation and cartilage loss[37]. Specifically, in vitro studies demonstrated that the addition of fibronectin (a ubiquitous ECM glycoprotein) fragments to human articular cartilage induced the production of TNF-α, IL-1α, IL-1β, MMP-1, and MMP-3, which are implicated in chondrolysis[37]. Furthermore, when these fibronectin fragments were injected into the knees of adolescent rabbits in vivo, substantial and rapid cartilage damage was observed, with up to a 70% loss in total cartilage proteoglycan at 7 days after injection[38]. Numerous other ECM products, including cartilage oligomeric matrix protein, fibromodulin, aggrecan, and osteoadherin, have also been shown to activate complement, which may directly induce chondrolysis or indirectly activate downstream proinflammatory and cartilage catabolic pathways[36]. Proinflammatory cytokines have further been shown to alter cartilage homeostasis, inhibiting normal anabolic processes and promoting further catabolic mechanisms[39,40]. Together, these data highlight the detrimental impact that a proinflammatory milieu may have on cartilage health.

There are few in vivo studies that have evaluated the effect of inflammation on cartilage damage following rotator cuff injury. In 2013, Kramer et al. examined cartilage damage in rats with either a massive RCT in the form of a supraspinatus or infraspinatus tenotomy or a suprascapular nerve transection to denervate the muscles without opening the joint capsule[41]. The 2 treatment groups demonstrated similar levels and patterns of cartilage degeneration, suggesting that mechanical factors, such as loss of force couples, rather than nutritional deficiencies from loss of synovial fluid, are primarily responsible for the cartilage damage seen after rotator cuff injury. While this study demonstrated that mechanical factors play a major role in the development of RCTA, it did not rule out the contribution of inflammatory factors in cartilage loss since no synovial fluid or synovial tissue samples were examined for inflammatory mediators. Future studies examining the effects of inflammatory mediators on cartilage loss would be invaluable in our understanding of the development of RCTA.

Immunomodulating Therapies in Tendon Healing

Healing after rotator cuff repair is a well-known clinical challenge, with studies demonstrating failure rates ranging from 20% to 94%[42,43]. The physiologic tendon-bone enthesis consists of tendon, noncalcified cartilage, calcified cartilage, and bone[44]. These 4 layers are not regenerated upon repair of a damaged insertion site. Rather, they heal with a fibrovascular scar interface with a higher ratio of type-III to type-I collagen, which lacks the same biomechanical properties of the native physiologic enthesis[45,46]. Recurrent RCTs continue to be a noteworthy postoperative complication and, thus, various treatment options have been investigated to improve the outcomes following rotator cuff repair. Structural repair strategies include patch augmentation and superior capsule reconstruction for patients who are too young for reverse total shoulder arthroplasty[8,47,48]. In addition to these structural augmentation strategies, recent studies have also investigated targeted inflammatory modulation techniques to improve tendon healing[46].

Macrophages are an important cellular component of the inflammatory response following rotator cuff injury and are thought to play an important role in fibrovascular scar formation following rotator cuff repair[45]. The potential for macrophages to be a target of immunomodulating therapies in tendon healing was investigated in a rat model of anterior cruciate ligament (ACL) reconstruction[45]. Using liposomal clodronate, a bisphosphonate that induces macrophage apoptosis, Hays et al. demonstrated decreased macrophage and TGF-β accumulation at the tendon-bone interface at all time points up to 28 days following ACL reconstruction. Those receiving liposomal clodronate had a greater degree of interface remodeling between tendon

and bone, increased osteoid formation and mineral apposition rates, and greater increases in load to failure and stiffness than the control group[45].

Insulin-like growth factor-I (IGF-I) is a major mediator at all stages of wound-healing, inflammation, and tendon repair. Work by Kurtz et al. investigated the benefits of IGF-I treatment following Achilles tendon transection in rats[49]. The rats were randomized into groups of sham surgery, Achilles tendon transection alone, and transection plus IGF-I augmentation. The rats underwent a functional evaluation preoperatively and postoperatively until day 15. Those treated with IGF-I had a significantly smaller functional deficit immediately postoperatively and decreased time to functional recovery than the control group, with no significant difference in Achilles tendon load to failure after postoperative day 15[49].

Inhibiting or reversing muscle fibrosis provides another promising target to improve outcomes following muscle injury and repair. Many molecules have been shown to inhibit the TGF-β pathway, such as decorin, suramin, relaxin, and gamma interferon, with decreases in fibrosis but with substantial and unacceptable side effects such as severe nausea, vomiting, diarrhea, dizziness, and drowsiness[50]. The use of angiotensin II receptor blockers (ARBs), however, has been shown to modulate TGF-β and reduce fibrosis in several tissues, including skeletal muscle, with a less severe side-effect profile[51]. In an animal model of gastrocnemius lacerations, Bedair et al. demonstrated that systemic treatment with an ARB resulted in dose-dependent histologic improvement in muscle regeneration and a measurable reduction in fibrous tissue formation compared with controls at 3 and 5 weeks after injury[50]. Hydroxymethylglutaryl (HMG) coenzyme A (CoA) reductase inhibitors, or "statins," have also been shown to markedly reduce fibrosis in an animal model of supraspinatus tears[52]. Statins are thought to achieve this through direct downregulation of type-I collagen expression and may also indirectly regulate the ECM content of tissues by modulating MMP expression and activity level.

Additional investigation is needed to evaluate the benefits of such immunomodulating therapies, specifically following rotator cuff injuries; however, these early studies provided promising avenues for such treatment modalities in promoting tendon healing and preventing fibrosis. One particular difficulty with cytokine therapy lies in maintaining effective concentrations for extended periods of time; therefore, implantable slow-release devices and gene therapy may provide improvements in cytokine delivery[53]. Unfortunately, application of single exogenous factors such as liposomal clodronate or IGF-I cannot recreate the complicated spatial and temporal expressions of the myriad growth factors and inflammatory cells that are involved in the inflammation, proliferation, and remodeling phases of tendon healing[54]. Many of these growth factors that are involved are stored in platelet alpha-granules, however, which provides the rationale for the theoretical benefit of platelet-rich plasma (PRP)[55].

Controversies Regarding PRP Treatment

PRP is an autologous derivative of whole blood, containing high concentrations of growth factors and platelets. When these platelets are activated, they release various cytokines and growth factors that have positive effects on cell proliferation, angiogenesis, cell chemotaxis, and matrix synthesis[54-57]. The various growth factors include TGF-β, fibroblast growth factor, PDGF, vascular endothelial growth factor, IGF-I, epithelial growth factor, and connective tissue growth factor[44,54]. The goal of PRP is to provide damaged tissue with higher concentrations of these cytokines and growth factors that promote physiologic healing.

While the basic science regarding PRP is compelling, clinical outcome studies on the efficacy of PRP in rotator cuff tendon repair have provided conflicting evidence[58]. In a study by Jo et al., 74 patients with medium-to-large RCTs were randomly assigned conventional repair or PRP-augmented repair to determine the effect of PRP on the speed and quality of healing[59]. While the authors did not observe any effect of PRP on the speed of healing, patients who were treated with PRP-augmented repair demonstrated increased supraspinatus muscle bulk at 1 year postoperatively, suggesting improved quality of healing. Additionally, a prospective, double-blinded study by Randelli et al. randomized 53 patients with complete RCTs into either repair augmented with PRP and an autologous thrombin component or a standard repair control group. No significant difference in healing rate was demonstrated overall; however, long-term results of subgroups with low-grade tears showed borderline significant improvements ($p = 0.08$) in healing at 2 years when measured by MRI[54].

Some studies, however, have shown less-impressive results regarding postoperative tendon healing. Rodeo et al. performed a double-blinded randomized controlled trial using platelet-rich fibrin matrix (PRFM) to augment rotator cuff repair, predicting that PRFM would provide sustained release of cytokines over time[55]. Seventy-nine patients received either standard rotator cuff repair or PRFM augmentation, and the study found no significant differences between the groups in tendon-to-bone healing or tendon vascularity when assessed on ultrasound[55]. Similarly, in another double-blinded randomized controlled trial by Ruiz-Moneo et al., 69 patients underwent conventional rotator cuff repair or repair augmented with plasma rich in growth factors. That study also found no significant difference between the 2 groups with regard to structural outcomes as measured by MRI[44].

There have also been conflicting data regarding the rate of rotator cuff retears following PRP-augmented

rotator cuff repair. Sánchez Márquez et al. assessed differences in retear rates of patients with massive RCTs who were randomized to repair supplemented with PRP with a high fibrin content or a control group. They found no significant differences in the number of retears on MRI between the 2 groups[60]. Jo et al., however, showed that there was a significantly lower retear rate in their PRP group compared with the conventional group[59].

In addition to its questionable effects on structural outcomes, PRP also has not demonstrated consistent benefit in clinical and patient-reported outcome (PRO) measures following rotator cuff repair. All of the above-mentioned studies evaluated PROs with the Constant score, a visual analog scale for pain, the University of California at Los Angeles (UCLA) score, shoulder symptoms, overall patient satisfaction, and/or internal or external rotation strength. There were no significant differences between the treatment group and the control group in any of these studies with regard to the measured clinical outcomes[44,54,55,59,60].

Various hypotheses exist to explain the differences in studied outcomes of PRP therapy. The individual growth factors have maximum activity at different stages of the healing process, so timing of the injection could affect the benefits of PRP[44]. Additionally, the variety of preparation methods in combination with differences in overall blood chemistry among individuals can lead to different final concentrations of platelets, leukocytes, anticoagulants, growth factors, and other PRP components. Moreover, the overall dosage and concentration of individual components that optimize healing has not yet been determined[55]. Finally, the optimal delivery medium (a thrombin clot, fibrin matrix, or simple injection of plasma) is yet to be elucidated; each medium results in variability in factor availability over time[55]. Thus, despite the promising theoretical value of PRP, studies have yet to demonstrate convincing and reproducible clinical benefits.

Overview

The development of RCTA involves mechanical factors including loss of force coupling as well as a complex immunologic cascade that results from the initial RCT. While parts of this inflammatory response have been elucidated, much of the complicated interplay between the various inflammatory cytokines and growth factors remains unknown. There have been promising results with regard to immunomodulation improving tendon healing, particularly in animal models; however, further investigation is needed to determine the optimal timing, dosage, and combination of inflammatory components that provide the best tendon-healing potential.

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References

1. Weber S, Chahal J. Management of Rotator Cuff Injuries. J Am Acad Orthop Surg. 2020 Mar 1;28(5):e193-201.

2. Milgrom C, Schaffler M, Gilbert S, van Holsbeeck M. Rotator-cuff changes in asymptomatic adults. The effect of age, hand dominance and gender. J Bone Joint Surg Br. 1995 Mar;77(2):296-8.

3. Ferguson DP, Lewington MR, Smith TD, Wong IH. Graft Utilization in the Augmentation of Large-to-Massive Rotator Cuff Repairs: A Systematic Review. Am J Sports Med. 2016 Nov; 44(11):2984-92.

4. Eajazi A, Kussman S, LeBedis C, Guermazi A, Kompel A, Jawa A, Murakami AM. Rotator Cuff Tear Arthropathy: Pathophysiology, Imaging Characteristics, and Treatment Options. AJR Am J Roentgenol. 2015 Nov; 205(5):W502-11.

5. Hamada K, Yamanaka K, Uchiyama Y, Mikasa T, Mikasa M. A radiographic classification of massive rotator cuff tear arthritis. Clin Orthop Relat Res. 2011 Sep;469(9):2452-60.

6. Burkhart SS. Fluoroscopic comparison of kinematic patterns in massive rotator cuff tears. A suspension bridge model. Clin Orthop Relat Res. 1992 Nov;(284):144-52.

7. Nam D, Maak TG, Raphael BS, Kepler CK, Cross MB, Warren RF. Rotator cuff tear arthropathy: evaluation, diagnosis, and treatment: AAOS exhibit selection. J Bone Joint Surg Am. 2012 Mar 21;94(6):e34.

8. Rugg CM, Gallo RA, Craig EV, Feeley BT. The pathogenesis and management of cuff tear arthropathy. J Shoulder Elbow Surg. 2018 Dec; 27(12):2271-83.

9. Halverson PB, Cheung HS, McCarty DJ, Garancis J, Mandel N. "Milwaukee shoulder"—association of microspheroids containing hydroxyapatite crystals, active collagenase, and neutral protease with rotator cuff defects. II. Synovial fluid studies. Arthritis Rheum. 1981 Mar;24(3):474-83.

10. Antoniou J, Tsai A, Baker D, Schumacher R, Williams GR, Iannotti JP. Milwaukee shoulder: correlating possible etiologic variables. Clin Orthop Relat Res. 2003 Feb;(407):79-85.

11. Visotsky JL, Basamania C, Seebauer L, Rockwood CA, Jensen KL. Cuff tear arthropathy: pathogenesis, classification, and algorithm for treatment. J Bone Joint Surg Am. 2004;86-A(Suppl 2):35-40.

12. Moor BK, Bouaicha S, Rothenfluh DA, Sukthankar A, Gerber C. Is there an association between the individual anatomy of the scapula and the development of rotator cuff tears or osteoarthritis of the glenohumeral joint?: A radiological study of the critical shoulder angle. Bone Joint J. 2013 Jul;95-B(7):935-41.

13. Li X, Olszewski N, Abdul-Rassoul H, Curry EJ, Galvin JW, Eichinger JK. Relationship Between the Critical Shoulder Angle and Shoulder Disease. JBJS Rev. 2018 Aug;6(8):e1.

14. Gerber C, Snedeker JG, Baumgartner D, Viehöfer AF. Supraspinatus tendon load during abduction is dependent on the size of the critical shoulder angle: A biomechanical analysis. J Orthop Res. 2014 Jul;32(7):952-7.

15. Feghali CA, Wright TM. Cytokines in acute and chronic inflammation. Front Biosci. 1997 Jan 1;2:d12-26.

16. Gotoh M, Hamada K, Yamakawa H, Nakamura M, Yamazaki H, Ueyama Y, Tamaoki N, Inoue A, Fukuda H. Perforation of rotator cuff increases interleukin 1beta production in the synovium of glenohumeral joint in rotator cuff diseases. J Rheumatol. 2000 Dec;27(12): 2886-92.

17. Okamura K, Kobayashi T, Yamamoto A, Shitara H, Osawa T, Ichinose T, Takagishi K. Shoulder pain and intra-articular interleukin-8 levels in patients with rotator cuff tears. Int J Rheum Dis. 2017 Feb;20(2):177-81.

18. Osawa T, Shinozaki T, Takagishi K. Multivariate analysis of biochemical markers in synovial fluid from the shoulder joint for diagnosis of rotator cuff tears. Rheumatol Int. 2005 Aug;25(6):436-41.

19. Tetlow LC, Adlam DJ, Woolley DE. Matrix metalloproteinase and proinflammatory cytokine production by chondrocytes of human osteoarthritic cartilage: associations with degenerative changes. Arthritis Rheum. 2001 Mar;44(3):585-94.

20. Yoshihara Y, Nakamura H, Obata K, Yamada H, Hayakawa T, Fujikawa K, Okada Y. Matrix

metalloproteinases and tissue inhibitors of metalloproteinases in synovial fluids from patients with rheumatoid arthritis or osteoarthritis. Ann Rheum Dis. 2000 Jun;59(6): 455-61.

21. Millar NL, Hueber AJ, Reilly JH, Xu Y, Fazzi UG, Murrell GA, McInnes IB. Inflammation is present in early human tendinopathy. Am J Sports Med. 2010 Oct;38(10):2085-91.

22. Abrams GD, Luria A, Carr RA, Rhodes C, Robinson WH, Sokolove J. Association of synovial inflammation and inflammatory mediators with glenohumeral rotator cuff pathology. J Shoulder Elbow Surg. 2016 Jun; 25(6):989-97.

23. De Paepe B, De Bleecker JL. Cytokines and chemokines as regulators of skeletal muscle inflammation: presenting the case of Duchenne muscular dystrophy. Mediators Inflamm. 2013; 2013:540370.

24. Londhe P, Guttridge DC. Inflammation induced loss of skeletal muscle. Bone. 2015 Nov; 80:131-42.

25. Argilés JM, Busquets S, Stemmler B, López-Soriano FJ. Cachexia and sarcopenia: mechanisms and potential targets for intervention. Curr Opin Pharmacol. 2015 Jun; 22:100-6.

26. Davies MR, Lee L, Feeley BT, Kim HT, Liu X. Lysophosphatidic acid-induced RhoA signaling and prolonged macrophage infiltration worsens fibrosis and fatty infiltration following rotator cuff tears. J Orthop Res. 2017 Jul;35(7): 1539-47.

27. Mu X, Usas A, Tang Y, Lu A, Wang B, Weiss K, Huard J. RhoA mediates defective stem cell function and heterotopic ossification in dystrophic muscle of mice. FASEB J. 2013 Sep; 27(9):3619-31.

28. Gumucio JP, Korn MA, Saripalli AL, Flood MD, Phan AC, Roche SM, Lynch EB, Claflin DR, Bedi A, Mendias CL. Aging-associated exacerbation in fatty degeneration and infiltration after rotator cuff tear. J Shoulder Elbow Surg. 2014 Jan;23(1):99-108.

29. Mendias CL, Tatsumi R, Allen RE. Role of cyclooxygenase-1 and -2 in satellite cell proliferation, differentiation, and fusion. Muscle Nerve. 2004 Oct;30(4):497-500.

30. Shen W, Li Y, Tang Y, Cummins J, Huard J. NS-398, a cyclooxygenase-2-specific inhibitor, delays skeletal muscle healing by decreasing regeneration and promoting fibrosis. Am J Pathol. 2005 Oct;167(4):1105-17.

31. Stables MJ, Gilroy DW. Old and new generation lipid mediators in acute inflammation and resolution. Prog Lipid Res. 2011 Jan;50(1):35-51.

32. Liu X, Ning AY, Chang NC, Kim H, Nissenson R, Wang L, Feeley BT. Investigating the cellular origin of rotator cuff muscle fatty infiltration and fibrosis after injury. Muscles Ligaments Tendons J. 2016 May 19;6(1):6-15.

33. Joe AW, Yi L, Natarajan A, Le Grand F, So L, Wang J, Rudnicki MA, Rossi FM. Muscle injury activates resident fibro/adipogenic progenitors that facilitate myogenesis. Nat Cell Biol. 2010 Feb;12(2):153-63.

34. Sato EJ, Killian ML, Choi AJ, Lin E, Esparza MC, Galatz LM, Thomopoulos S, Ward SR. Skeletal muscle fibrosis and stiffness increase after rotator cuff tendon injury and neuromuscular compromise in a rat model. J Orthop Res. 2014 Sep;32(9):1111-6.

35. Neer CS 2nd, Craig EV, Fukuda H. Cuff-tear arthropathy. J Bone Joint Surg Am. 1983 Dec; 65(9):1232-44.

36. Sokolove J, Lepus CM. Role of inflammation in the pathogenesis of osteoarthritis: latest findings and interpretations. Ther Adv Musculoskelet Dis. 2013 Apr;5(2):77-94.

37. Homandberg GA, Hui F. Association of proteoglycan degradation with catabolic cytokine and stromelysin release from cartilage cultured with fibronectin fragments. Arch Biochem Biophys. 1996 Oct 15;334(2):325-31.

38. Homandberg GA, Meyers R, Williams JM. Intraarticular injection of fibronectin fragments causes severe depletion of cartilage proteoglycans in vivo. J Rheumatol. 1993 Aug; 20(8):1378-82.

39. Goldring MB, Fukuo K, Birkhead JR, Dudek E, Sandell LJ. Transcriptional suppression by interleukin-1 and interferon-gamma of type II collagen gene expression in human chondrocytes. J Cell Biochem. 1994 Jan;54(1):85-99.

40. Saklatvala J. Tumour necrosis factor alpha stimulates resorption and inhibits synthesis of proteoglycan in cartilage. Nature. 1986 Aug 7-13;322(6079):547-9.

41. Kramer EJ, Bodendorfer BM, Laron D, Wong J, Kim HT, Liu X, Feeley BT. Evaluation of cartilage degeneration in a rat model of rotator cuff tear arthropathy. J Shoulder Elbow Surg. 2013 Dec;22(12):1702-9.

42. Galatz LM, Ball CM, Teefey SA, Middleton WD, Yamaguchi K. The outcome and repair integrity of completely arthroscopically repaired large and massive rotator cuff tears. J Bone Joint Surg Am. 2004 Feb;86(2): 219-24.

43. Rhee YG, Cho NS, Yoo JH. Clinical outcome and repair integrity after rotator cuff repair in patients older than 70 years versus patients younger than 70 years. Arthroscopy. 2014 May; 30(5):546-54.

44. Ruiz-Moneo P, Molano-Muñoz J, Prieto E, Algorta J. Plasma rich in growth factors in arthroscopic rotator cuff repair: a randomized, double-blind, controlled clinical trial. Arthroscopy. 2013 Jan;29(1):2-9.

45. Hays PL, Kawamura S, Deng XH, Dagher E, Mithoefer K, Ying L, Rodeo SA. The role of macrophages in early healing of a tendon graft in a bone tunnel. J Bone Joint Surg Am. 2008 Mar;90(3):565-79.

46. Wu G, Xu PC, Wu P, Hu K, Sun Y, Cheng B, Lu Y. Advances in the treatment of rotator cuff lesions by cytokines. Front Biosci (Landmark Ed). 2017 Jan 1;22:516-29.

47. Lacheta L, Horan MP, Goldenberg BT, Dornan GJ, Higgins B, Millett PJ. Minimum 2-year clinical outcomes after superior capsule reconstruction compared with reverse total shoulder arthroplasty for the treatment of irreparable posterosuperior rotator cuff tears in patients younger than 70 years. J Shoulder Elbow Surg. 2020 Dec;29(12):2514-22.

48. Altintas B, Scheidt M, Kremser V, Boykin R, Bhatia S, Sajadi KR, Mair S, Millett PJ. Superior Capsule Reconstruction for Irreparable Massive Rotator Cuff Tears: Does It Make Sense? A Systematic Review of Early Clinical Evidence. Am J Sports Med. 2020 Nov;48(13):3365-75.

49. 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 May-Jun;27(3):363-9.

50. Bedair HS, Karthikeyan T, Quintero A, Li Y, Huard J. Angiotensin II receptor blockade administered after injury improves muscle regeneration and decreases fibrosis in normal skeletal muscle. Am J Sports Med. 2008 Aug; 36(8):1548-54.

51. Gardner T, Kenter K, Li Y. Fibrosis following Acute Skeletal Muscle Injury: Mitigation and Reversal Potential in the Clinic. J Sports Med (Hindawi Publ Corp). 2020 Sep 1;2020:7059057.

52. Davis ME, Korn MA, Gumucio JP, Harning JA, Saripalli AL, Bedi A, Mendias CL. Simvastatin reduces fibrosis and protects against muscle weakness after massive rotator cuff tear. J Shoulder Elbow Surg. 2015 Feb;24(2):280-7.

53. Evans CH. Cytokines and the role they play in the healing of ligaments and tendons. Sports Med. 1999 Aug;28(2):71-6.

54. Randelli P, Arrigoni P, Ragone V, Aliprandi A, Cabitza P. Platelet rich plasma in arthroscopic rotator cuff repair: a prospective RCT study, 2-year follow-up. J Shoulder Elbow Surg. 2011 Jun;20(4):518-28.

55. Rodeo SA, Delos D, Williams RJ, Adler RS, Pearle A, Warren RF. The effect of platelet-rich fibrin matrix on rotator cuff tendon healing: a prospective, randomized clinical study. Am J Sports Med. 2012 Jun;40(6):1234-41.

56. Goldenberg BT, Lacheta L, Dekker TJ, Spratt JD, Nolte PC, Millett PJ. Biologics to Improve Healing in Large and Massive Rotator Cuff Tears: A Critical Review. Orthop Res Rev. 2020 Oct 13; 12:151-60.

57. Greenspoon JA, Moulton SG, Millett PJ, Petri M. The Role of Platelet Rich Plasma (PRP) and Other Biologics for Rotator Cuff Repair. Open Orthop J. 2016 Jul 21;10:309-14.

58. Warth RJ, Dornan GJ, James EW, Horan MP, Millett PJ. Clinical and structural outcomes after arthroscopic repair of full-thickness rotator cuff tears with and without platelet-rich product supplementation: a meta-analysis and meta-regression. Arthroscopy. 2015 Feb;31(2): 306-20.

59. Jo CH, Shin JS, Shin WH, Lee SY, Yoon KS, Shin S. Platelet-rich plasma for arthroscopic repair of medium to large rotator cuff tears: a randomized controlled trial. Am J Sports Med. 2015 Sep;43(9):2102-10.

60. Sánchez Márquez JM, Martínez Díez JM, Barco R, Antuña S. Functional results after arthroscopic repair of massive rotator cuff tears; influence of the application platelet-rich plasma combined with fibrin. Rev Esp Cir Ortop Traumatol (English Edition). 2011;55(4):282-7.