Chapter 8
Regenerative Medicine for the Shoulder

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Tendinopathy in the Shoulder: The Rotator Cuff and Proximal Biceps Tendon

The rotator cuff (RTC) is a group of scapulohumeral muscles primarily involved in shoulder motion and stabilization. It is comprised of the supraspinatus, infraspinatus, teres minor, and subscapularis. Injury to one or more of the RTC muscles can be both painful and a cause significant impairment in daily functions and overhead tasks.

Rotator Cuff Tendinopathy

When evaluating RTC tendinopathies, it is important to be able to differentiate between the underlying subtypes in order to best manage the injury. Historically, RTC tendinopathies have often been referred to as "RTC tendonitis," although this term remains controversial as most histopathological studies have shown little to no evidence for inflammatory cells in the tendon of people who have underdone arthroscopic tendon repair [1]. Rotator cuff tendinosis on the other hand is thought to stem from the repetitive overuse of a previously injured tendon that had not had adequate time to heal [2]. Calcific tendinopathy of the RTC refers to an unexplained buildup of calcium deposits on one or more of the RTC tendons, resulting in pain and limitations with range of motion [3].

Identifying which muscle of the RTC is injured begins with a proper physical examination of the shoulder. After evaluating active and passive range of motion

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of the shoulder, provocative testing can help decipher which muscle of the RTC is affected. The goal of each test is to isolate the muscle and assess for pain and/or weakness. The provocative tests have varying sensitivities and specificities but collectively allow for a more accurate assessment and diagnosis.

The supraspinatus muscle is primarily a shoulder abductor and can be tested for pathology using multiple provocative tests in order to increase overall sensitivity and specificity. The gold standard test, however, is the "empty can" test which evaluates for pain and weakness during shoulder abduction [4].

The infraspinatus muscle is the primary external rotator of the shoulder and is best tested with the patient's elbow flexed to 90 degrees, adducted against the patient's waist, and the humerus medially rotated 45 degrees. A positive test would be pain and/or weakness with resisted external rotation of the shoulder in this position [5].

The teres minor muscle is also an external rotator and is best isolated with the patient's arm raised to 90 degrees in the scapular plane and the forearm flexed to 90 degrees. A positive test would be pain and/or weakness with resisted external rotation of the shoulder. This is known as a positive Hornblower's sign [6].

The subscapularis muscle is primarily an internal rotator of the shoulder. Gerber's "lift off" test will assess the subscapularis by placing the patient's arm in internal rotation behind the patient's back and having the patient to push off posteriorly against resistance. Pain or weakness is a sign of subscapularis pathology [5].

Rotator Cuff Tears

The prevalence of RTC tears increases with age and are present in about 20.7% of the population, many of whom may be asymptomatic [7]. Tears can be classified based on their size, location, and attachment of the tendon relative to the humeral head. If there is a "through and through" tear of a RTC tendon but the tendon is still well attached to the humeral head, it is considered a "full-thickness" tear. When the tendon tear involves complete detachment from the humeral head, the tear is more serious and is considered a "complete" tear [4]. A RTC tear is considered "partial thickness" when the tear does not involve the entire tendon. Partial-thickness tears are graded based on the percentage of the tendon which is torn. Grade I <25%; Grade II 25% to <50%; Grade III >50% [7]. Partial-thickness tears are further classified as either bursal-sided (outer portion of tendon) or articular-sided (inner portion of tendon) based on tear location. If the tear is located in the middle layers of the tendon and does not involve the inner/outer layers, then the tear is considered an intrasubstance tear [7].

Treatment of RTC tendinopathies often depends on the severity and chronicity of the injury. While strong evidence is lacking for the treatment of RTC tendinopathies, approach to treatment generally begins conservatively. In addition to rest after an acute injury, cryotherapy is one of the first recommended treatments followed by a period of rest and 7–10-day course of nonsteroidal anti-inflammatory drugs (NSAIDs). If cryotherapy is not available, ice may also be used in the early stages. Efficacy and evidence for the use of NSAIDs in acute injuries are controversial but generally remain a part of the initial standard of care used by most physicians. Both acute and chronic RTC tendinopathies can benefit from a comprehensive rehabilitation program that focuses on the shoulder girdle, emphasizing strength, range of motion, and coordination training [8].

Chronic RTC injuries or those that did not respond to acute therapies may benefit from glucocorticoid-analgesic mixed injections. Evidence is limited in support of glucocorticoid injections, but few studies show some benefit of glucocorticoid injections over placebo and often equally but not more effective than NSAIDs. There have been studies, however, that show that a single subacromial glucocorticoid injection prior to initiation of physical therapy is superior to that of physical therapy alone, as it reduces acute pain and allows for more aggressive range of motion exercises [2, 9]. Another treatment option for patients with chronic RTC tendinopathies is topical nitrates. One double-blinded, placebo-controlled study showed a significant improvement in patients with chronic RTC tendinopathies treated with topical nitrates [10].

Surgical options are considered when conservative treatment has failed or if the RTC injury is an acute complete tear in an athlete or patient whose work requires a significant amount of overhead use. Lack of consistent improvement in the current treatment options has led to multiple new innovative measures in the treatment of RTC tendinopathies including topical NSAIDs, shockwave therapy, and regenerative techniques [11].

Biceps Tendinopathy

Biceps tendinopathies encompass a broad range of pathology most often involving the long head of the biceps tendon. They are generally known to be “overuse” injuries and over time tend to progress to a degenerative, thickened tendon that becomes entrapped in the bicipital groove causing significant discomfort and pain. Biceps tendinopathies typically occur in conjunction with other injuries to the shoulder girdle, particularly the RTC [12].

The biceps brachii muscles are primarily elbow flexors and forearm supinators. Provocative testing is performed to isolate these motions and aid in the diagnosis of biceps tendinopathy. The two commonly performed provocative maneuvers are the Speed’s and Yergason’s test which assess for pain in resisted elbow flexion and forearm supination, respectively [12].

Treatment of biceps tendinopathy usually begins conservatively with ice, rest, and a short 5–7-day course of NSAIDs. Topical NSAIDs are also often used in the early treatment phase, although their efficacy is not yet well established. Management continues with a comprehensive rehabilitation program focused on strengthening the muscles of the shoulder girdle, range of motion exercises, and proper stretching techniques. If ineffective, glucocorticoid injections into the biceps tendon sheath are tried next and should be done with ultrasound guidance for accuracy and to prevent intratendinous injection [12–14].

Surgical management of biceps tendon injuries includes biceps tenotomy and biceps tenodesis. These are generally performed after conservative management has failed in complete tendon rupture and when the patient is an athlete or does work requiring significant upper extremity strength. Although surgery is often performed, there is limited evidence in its efficacy and in overall patient satisfaction [15].

Tendinopathy in the Shoulder: Regenerative Medicine Applications

Lack of consistent improvement using current standard of care treatments in patients with shoulder dysfunction has led to the exploration of alternative means of therapy, particularly through regenerative medicine. Although relatively novel, regenerative therapies such as application of platelet-rich plasma (PRP) or mesenchymal stem cells are rapidly evolving and being experimented in the treatment of a variety of shoulder pathologies.

Rotator Cuff Tendinopathies and Tears

The majority of therapies using PRP or autologous stem cells to treat RTC tendinopathies involve injection into the subacromial space, with few studies published about injecting directly into the tendon.

The subacromial space can be accessed using ultrasound guidance. The patient is seated with the affected arm hanging down and ultrasound transducer placed in the coronal view over the lateral end of the acromion (Fig. 8.1a). Using sterile technique, use a 25-gauge, 1.5-inch needle to enter in plane with the transducer aiming for the anechoic space between the peribursal fat which represents the subacromial bursa (Fig. 8.1b). Once the needle tip is visualized within the subacromial bursa, aspirate and inject [16].

When injecting the tendon directly, identify the target tendon, specifically the site of pathology (tendon tear or area of tendinopathy). A 25-gauge needle is then inserted in-plane with the transducer aiming for the lesion. It is provider preference whether to use lidocaine first. Once the needle tip is visualized within the lesion, aspirate and inject directly into the lesion. If difficult to inject directly into the lesion itself, then the injectate is infiltrated around the lesion [17].

Kesikburun et al. performed a randomized study comparing the efficacy of PRP to saline when injected into the subacromial space in patients with chronic RTC tendinopathy. While both groups showed significant improvement in pain and functional measures at each point throughout the 2-year time course, there were no significant differences found between PRP and saline [18].

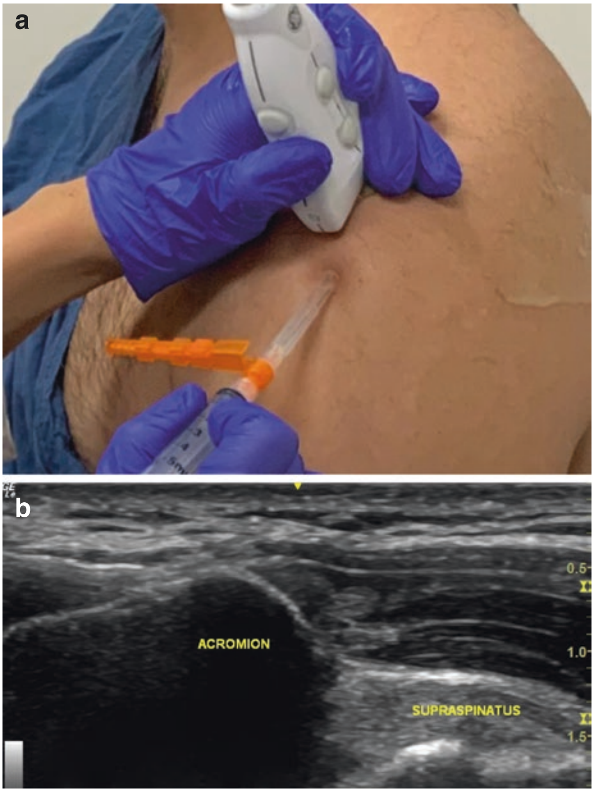

Fig. 8.1 (**a**) Transducer and needle placement for ultrasound guided subacromial injection. (**b**) Ultrasound image of subacromial space with patient seated and affected arm hanging

Rha et al. performed a randomized controlled trial comparing the effects of PRP versus dry needling directly into an RTC tendon that either had tendinosis or a partial tear. Their study showed that while both groups had symptomatic relief and functional improvements at 6 months, the PRP group had significantly more relief and functional improvement than the dry-needling group [17].

Von Wehren et al. performed a randomized study comparing treatment of partial RTC tears using a subacromial PRP injection with that of a subacromial corticosteroid injection. While both groups showed significant improvements in shoulder score outcomes in the 6 months they were monitored, the PRP group showed a significantly greater improvement in all shoulder score outcomes at each measured time point. MRI findings improved in both groups as well, but no significant differences were found between the two groups. Shams et al. replicated this study with similar results [19, 20]. These results are significant as they provide a potentially safer alternative treatment to corticosteroid injections which have been shown to weaken tendons and increase the risk of tendon rupture [21].

Several studies have also been published comparing the use of regenerative techniques in conjunction with arthroscopic rotator cuff repairs. While evidence is scarce and sometimes conflicting, the current research suggests that use of PRP in conjunction with arthroscopic rotator cuff repairs may decrease the retear rate of the tendon [22–25].

There is paucity of literature that evaluates the use of bone marrow-derived stem cells in the treatment of RTC repairs. Gomes et al. complemented conventional RTC repair with the use of mononuclear autologous stem cells in 14 patients and found a significant improvement in overall functional scores and tissue integrity when compared to conventional RTC repair alone [26]. Additional studies by Gullota et al. have evaluated the effects of autologous stem cells transduced with helix-loop-helix transcription factor in rat model repairs of supraspinatus tears. Early studies have revealed enhanced healing in the first 2–4 weeks post-RTC tendon repair [27].

Biceps Tendinopathy

At this time there is limited evidence evaluating the efficacy of platelet-rich plasma or other regenerative techniques for proximal biceps tendinopathies.

The biceps tendon sheath should be injected using a sterile technique with ultrasound guidance. With the axial-in-plane technique, the patient should be seated with the elbow flexed and hand supinated (Fig. 8.2a). The ultrasound transducer will then be placed in the axial plane on the proximal humerus, centering the biceps tendon in the bicipital groove (Fig. 8.2b). The circumflex humeral artery should be identified in this groove using Doppler imaging. Avoiding the artery, a 25-gauge needle is then inserted in-plane with the transducer from lateral to medial aiming for the tendon sheath between the biceps tendon and the transhumeral ligament (Fig. 8.2c). Once the needle tip is visualized in the tendon sheath, aspirate and inject, observing for injectate flowing around the tendon [16].

Osteoarthritis in the Shoulder, Glenoid Labral Tears, and Adhesive Capsulitis

Glenohumeral Osteoarthritis

Osteoarthritis is a multifactorial process characterized by degeneration of joint cartilage. There are morphologic changes in the joint including cartilage degeneration, synovial inflammation, subchondral sclerosis, and osteophyte formation which can be seen on radiological studies [28]. Osteoarthritis (OA) becomes clinically significant when it causes symptoms; in the glenohumeral joint, these usually manifest as shoulder pain and eventually loss of range of motion (ROM). Shoulder pain is usually gradual and progressive; ROM is decreased, usually with a decrease in external rotation first. On physical exam the person may have tenderness to palpation in the anterior, lateral, and/or posterior compartments of the shoulder. The workup

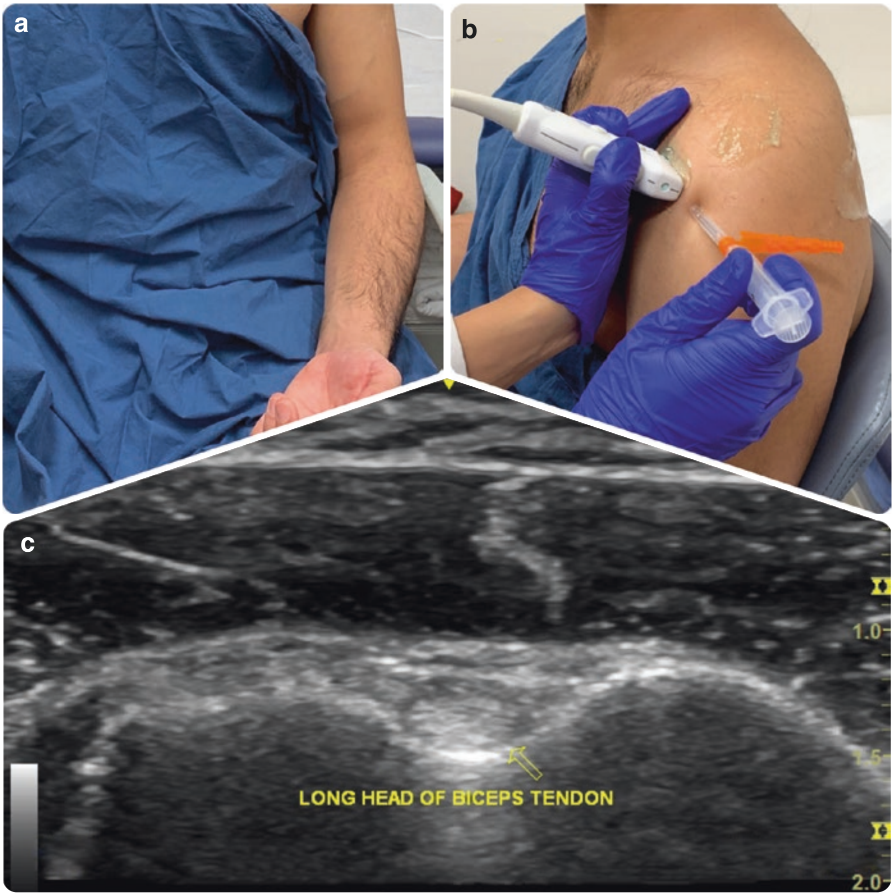

Fig. 8.2 (**a**) Patient positioning for ultrasound guided biceps tendon injection. (**b**) Transducer and needle placement for ultrasound guided injection. (**c**) Ultrasound image of biceps tendon with patient seated with elbow flexed and hand supinated

for suspected GH OA includes shoulder X-rays, including anterior posterior (AP), axillary, and scapular in Y views. Common X-ray findings include joint space narrowing, subchondral sclerosis, and osteophyte formation [28].

Current treatment for glenohumeral OA includes activity modification, analgesic medication including acetaminophen and nonsteroidal anti-inflammatories (NSAIDs), physical therapy, and injections, usually of a steroid solution or viscosupplementation [29]. There is limited evidence-based literature on the efficacy of intra-articular glenohumeral steroid and viscosupplementation for GH OA. Merolla et al. found improvements in the visual analog pain scale for both intra-articular steroid injection of methylprednisolone (for 1 month posttreatment) and intra-articular Hylan G-F 20 (for 3 months posttreatment) although the results were not as favorable in severe OA or in patients with concomitant large rotator cuff tears [30].

There have also been case series of intra-articular GH botulinum toxin injections for the pain modulation effect; however, more research works need to be done in this area to assess efficacy [31].

Surgical treatments for GH OA include surgical debridement and shoulder arthroplasty (hemiarthroplasty versus total shoulder arthroplasty). Most of the evidence is level IV, and in some studies, patients undergoing total shoulder arthroplasty show better shoulder function compared to hemiarthroplasty [32, 33].

Acromioclavicular Osteoarthritis

Acromioclavicular (AC) osteoarthritis (OA) often presents as pain in the deltoid region. On physical exam there may be tenderness over the AC joint and pain with horizontal adduction movements of the shoulder. Diagnostic imaging for AC OA includes shoulder X-rays, specifically the Zanca view. Arthritic changes include joint space narrowing, subchondral sclerosis, and other findings discussed previously. Conservative treatment usually begins with activity modification and oral analgesics such as acetaminophen and NSAIDs. Steroid injections in the AC joint, either palpation guided or ultrasound guided are also common practice [34]. Efficacy of intra-articular AC joint steroid injections in the literature is controversial, but most studies show short-term (<2 mo) relief [34].

Glenoid Labral Tears

Glenoid labral tears are an important cause of shoulder pain. Symptoms may be nonspecific, but usually patients will complain of shoulder pain which worsens with abduction and external rotation (ABER). Special physical exam tests include pain with ABER as well as with a positive O'Brien test. The O'Brien test is performed with the patient flexing their arm at the shoulder with their thumb facing down, with the shoulder slightly adducted and elevating against resistance; pain in that position which improves when changing the arm to the supinated position is considered positive [35]. Traditionally, a MR arthrogram with contrast injected intra-articularly is obtained to confirm a suspected labral tear in the shoulder. Now, some physicians are also evaluating for posterior superior labral tears with arthrosonography [36]. Treatment for symptomatic glenoid labral tears includes activity modification, physical therapy, NSAIDs, and glenohumeral steroid injections. Studies show that for glenoid labral tears this conservative treatment may improve function and pain [37].

Adhesive Capsulitis

Adhesive capsulitis presents as shoulder pain accompanied with progressive loss of range of motion, initially of external rotation. It is due to shoulder capsular thickening and contracture. It may be divided into four stages: (1) pre-freezing: limited ROM and start of symptoms; (2) freezing: severely limited ROM and pain; (3) frozen: severely limited ROM, pain subsides; and (4) thawing: improving ROM and minimal pain [38]. It can take 1 year or more for the four stages to advance. Conservative treatment includes activity modification, physical therapy, NSAIDs, and glenohumeral steroid injections, including glenohumeral capsular distention. This involves injecting the GH joint with a high volume of injectate, usually a combination of a steroid, anesthetic, and saline.

Osteoarthritis in the Shoulder, Glenoid Labral Tears, and Adhesive Capsulitis: *Regenerative Medicine Applications*

Many regenerative treatments, including platelet-rich plasma, bone marrow aspirate, adipose-derived stem cells, and viscosupplementation, are being used to treat different shoulder pathologies. We will discuss injection techniques as well as available evidence for these treatments in different causes of shoulder pain.

Glenohumeral Osteoarthritis (GH OA)

The glenohumeral joint may be injected using ultrasound or fluoroscopic guidance. When using ultrasound guidance, a posterior approach is utilized. The author finds that the best position is to have the patient side-lying with the affected shoulder up and the patient facing the physician (Fig. 8.3a). The posterior glenohumeral joint is identified by placing the transducer axially, below the spine of the scapula (Fig. 8.3b, c). Once the joint is identified it can be reached using a lateral to medial, in-plane approach (Fig. 8.3b). Using sterile technique, the area of entry is anesthetized with a 25-gauge, 1.5-inch needle with about 2 mL of 1% lidocaine. A 22-gauge, 3.5-inch needle is then used to enter the joint space, and after negative aspiration, the injectate is administered [39].

Using fluoroscopic guidance for the glenohumeral joint can be performed both from an anterior and from a posterior approach. Here we will describe a posterior approach. The patient lies prone with their arm lying on their side. Using sterile technique the area overlying the superior lateral humeral head is marked with a

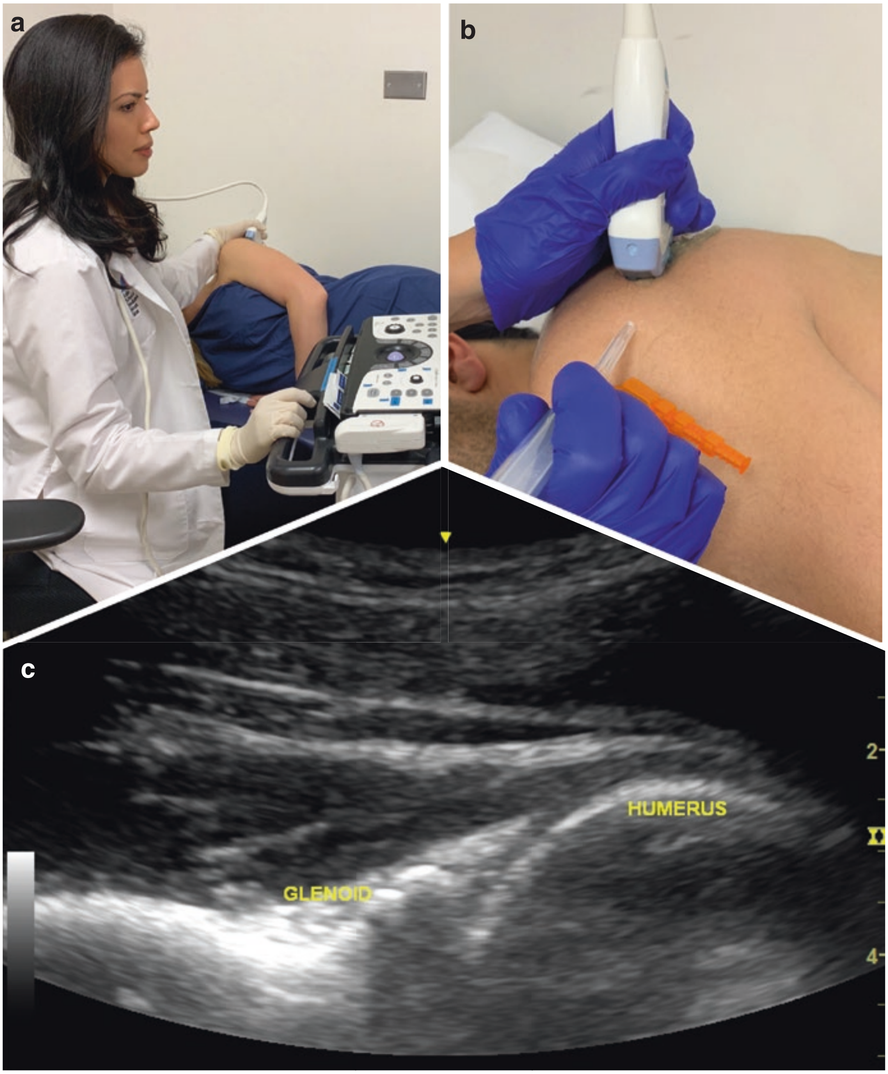

Fig. 8.3 (**a**) Patient position for ultrasound guided glenohumeral injection. (**b**) Ultrasound transducer and needle alignment for glenohumeral injection. (**c**) Ultrasound image of glenohumeral joint with patient sidelying

skin marker. When the desired area is confirmed, the skin is anesthetized using a 25-gauge, 1.5-inch needle with about 2 mL of 1% lidocaine. A 22-gauge, 3.5-inch needle is then used to enter the joint space; when a bony endpoint is felt, 2 mL of contrast dye is injected to confirm joint placement and nonvascular flow. After this is confirmed and negative aspiration, the injectate is administered [40].

Research on platelet-rich plasma for GH OA is limited to case reports. In a case report by Freitag, a 62-year-old woman with GH OA underwent three ultrasound-guided glenohumeral PRP injections, each 1 week apart [41]. Her pain improved substantially on the numerical pain rating scale and stayed between 0 and 1 out of 10 at 42 weeks post-procedure; she also improved functionally. More research is needed in regenerative medicine applications for GH OA. This case report used photoactivated PRP, but the author did not note if it was leukocyte rich or leukocyte poor. Extrapolating from research on knee osteoarthritis, leukocyte-poor PRP seems to be better for joint osteoarthritis than leukocyte-rich PRP, but more research is needed. There is also limited evidence to recommend a series of three injections versus one.

Glenohumeral injections of platelet-rich plasma for adhesive capsulitis have shown benefits in some studies. Kothari et al. randomized 162 patients with adhesive capsulitis to a single GH PRP injection, a corticosteroid injection, or ultrasonic therapy (7 sessions). They found statistically significant improvements in active and passive shoulder ROM and visual analog pain scores in the PRP group compared to the other two groups [42].

The benefits of viscosupplementation for glenohumeral osteoarthritis have been investigated. Kwon et al. compared a series of three sodium hyaluronate injections to saline injections in a randomized controlled trial on subjects with glenohumeral OA. In a subset analysis, they found improvements in pain in the hyaluronate group who did not have concomitant shoulder pathologies; however their initial analysis did not show any statistically significant differences in pain between both groups [43]. Other studies have not found statistically significant differences in viscosupplementation versus placebo (saline injections) for GH OA. More studies are needed.

Glenoid Labral Tears

Literature on outcomes of platelet-rich plasma and other regenerative treatments for glenoid labral tears is scarce. The labrum can be targeted by injecting the glenohumeral joint itself as described above.

Acromioclavicular Osteoarthritis

At this time there is limited evidence evaluating the efficacy of viscosupplementation, platelet-rich plasma, or other regenerative techniques for acromioclavicular osteoarthritis (AC OA).

The AC joint may be accessed for injection using ultrasound guidance. Here we will describe an axial, out of plane approach. Start with the patient in a sitting position with their arm resting at their side. Place the transducer over the acromioclavicular joint in the coronal plane (Fig. 8.4a, b). Using the center marker on the

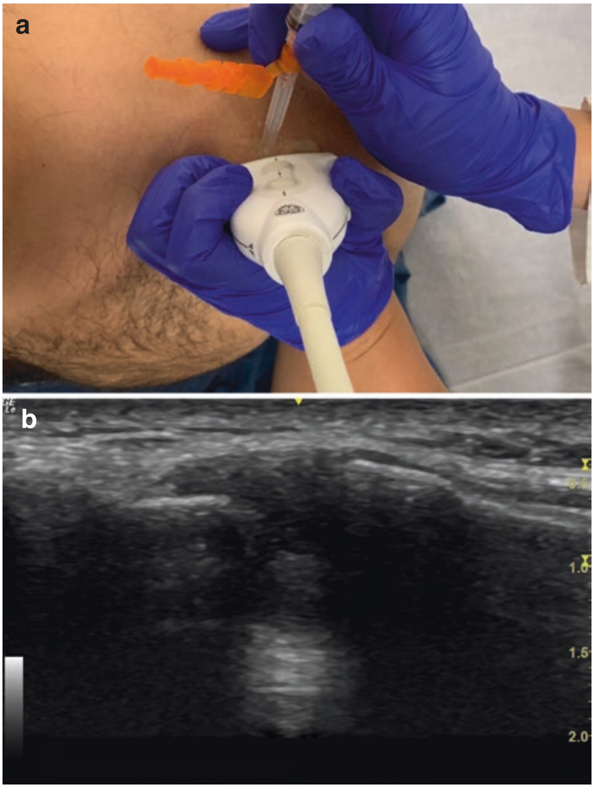

Fig. 8.4 (**a**) Ultrasound transducer placement in the coronal plane for acromioclavicular joint injection. (**b**) Ultrasound image of the acromioclavicular joint with patient in sitting position and arm resting at the side

transducer and corresponding marker on the screen, place the target entry point of the AC joint at this point. Using sterile technique with a transducer cover and sterile gel, use a 25-gauge, 1.5-inch needle to enter; then using a step-down approach, enter the joint. Once your needle tip is visualized within the joint, aspirate and inject [44].

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