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Adhesive capsulitis of the shoulder: review of pathophysiology and current clinical treatments

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Abstract

Adhesive shoulder capsulitis, or arthrofibrosis, describes a pathological process in which the body forms excessive scar tissue or adhesions across the glenohumeral joint, leading to pain, stiffness and dysfunction. It is a debilitating condition that can occur spontaneously (primary or idiopathic adhesive capsulitis) or following shoulder surgery or trauma (secondary adhesive capsulitis). Here, we review the pathophysiology of adhesive shoulder capsulitis, highlighting its clinical presentation, natural history, risk factors, pathoanatomy and pathogenesis. Both current non-operative and operative treatments for adhesive capsulitis are described, and evidence-based studies are presented in support for or against each corresponding treatment. Finally, the review also provides an update on the gene expression profile of adhesive capsulitis and how this new understanding can help facilitate development of novel pharmacological therapies.

Keywords

adhesive capsulitis, arthrofibrosis, frozen shoulder, shoulder capsulitis, shoulder pain, shoulder stiffness

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Introduction

Adhesive shoulder capsulitis, or arthrofibrosis, describes a pathological process in which the body forms excessive scar tissue or adhesions across the glenohumeral joint, leading to stiffness, pain and dysfunction.[1,2] Painful stiffness of the shoulder can adversely affect activities of daily living and consequently impair quality of life. Simon-Emmanuel Duplay is widely recognized as the first physician to describe this pathology, which he called 'scapulohumeral periarthritis'. 'Periarthritis' describes a painful shoulder syndrome that is distinct from arthritis with general radiographic preservation of the joint. Earnest Codman later coined the term 'frozen shoulder' in 1934 to emphasize the debilitating loss of shoulder motion in patients afflicted with this condition. He described this condition as 'difficult to define, difficult to treat and difficult to explain from the point of view of pathology'.[3] In a pioneering histological study published in 1945, Julius Neviaser redefined this condition as adhesive capsulitis, underlying the inflammatory and fibrotic changes observed in the capsule or adjacent bursa.[4]

Adhesive capsulitis can be primary or secondary. Primary (or idiopathic) adhesive capsulitis can occur spontaneously without any specific trauma or inciting event. Secondary adhesive capsulitis is often observed after periarticular fracture dislocation of the glenohumeral joint or other severe articular trauma.[5] It can also be a severe complication after open or arthroscopic shoulder surgery, including rotator cuff repair and shoulder arthroplasty.[6] The incidence of adhesive capsulitis in the general population is approximately 3% to 5% but as high as 20% in patients with diabetes. Idiopathic adhesive capsulitis often involves the nondominant extremity, although bilateral involvement has been reported in up to 40% to 50% of cases.[2] Adhesive capsulitis is often regarded as a

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self-limiting disease that resolves between 1 and 3 years. However, various studies have shown that between 20% and 50% of patients may go on to develop long-lasting symptoms.[2,7–9] In this patient population, both non-operative and operative interventions are needed to ensure acceptable functional outcomes.

Review

Diagnosis

Adhesive shoulder capsulitis is a clinical diagnosis made on the basis of medical history and physical exam and is often a diagnosis of exclusion. Other causes of a painful stiff shoulder must be excluded before a diagnosis of adhesive capsulitis is rendered, including septic arthritis, mal-position of orthopedic hardware, fracture malunion, rotator cuff pathology, glenohumeral arthrosis or cervical radiculopathy. Clinically, patients with this condition usually first present with shoulder pain followed by gradual loss of both active and passive range of motion (ROM) due to fibrosis of the glenohumeral joint capsule.[1] Boyle-Walker et al.[10] observed that the majority of patients (90.6%) reported developing shoulder pain before loss of motion. External rotation is often the first motion affected on clinical examination, with steady global loss of ROM with disease progression. Pain is generally worse at the extremes of motion, when the contracted capsule is stretched. Passive ROM is lost with firm painful end-points of motion, suggesting a mechanical rather than a pain-related restriction to motion.[1]

Imaging studies are not necessary for the diagnosis of adhesive shoulder capsulitis but may be helpful to rule out other causes of a painful and stiff shoulder. Plain films of the shoulder may reveal osteopenia in patients with prolonged adhesive capsulitis secondary to disuse (i.e. disuse osteopenia).[1] Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) may reveal thickening of capsular and pericapsular tissues as well as a contracted glenohumeral joint space.[1] Mengiardi et al.[11] reported that MRA findings of coracohumeral ligament (CHL) ligament thickness ≥ 4 mm (95% specificity, 59% sensitivity) or capsule thickness ≥ 7 mm (86% specificity, 64% sensitivity) may aid in the diagnosis of adhesive capsulitis. Dynamic sonography may reveal thickening of the joint capsule and limited sliding movement of the supraspinatus tendon.[12] These findings correlate with intraoperative direct visualization, documenting thickening of primarily the rotator interval and CHL.[13,14]

Risk factors

Risk factors for adhesive capsulitis include female sex, age over 40 years, preceding trauma, HLA-B27 positivity and prolonged immobilization of the glenohumeral joint. It is estimated that 70% of patients with adhesive shoulder capsulitis are women.[15] Additionally, men do not respond to treatments as well as women.[16] Demographic studies have shown that most patients with adhesive capsulitis (84.4%) fall within the age range of 40 years to 59 years.[10] A recent meta-analysis study by Prodromidis and Charalambous[17] suggested a genetic predisposition to adhesive capsulitis, noting a higher predilection of this condition in white patients, patients with a positive family history, and patients with HLA-B27 positivity.

Adhesive capsulitis is associated with diabetes, thyroid disease, cerebrovascular disease, coronary artery disease, autoimmune disease and Dupuytren's disease.[3,18] Interestingly, both type I and type II diabetic patients are at increased risk of developing adhesive capsulitis, with prevalence of 10.3% and 22.4%, respectively.[19] Diabetic patients with adhesive capsulitis have worse functional outcomes compared to their nondiabetic counterparts.[16] A nationwide population-based study led by Huang et al.[20] showed that, compared to the general population, patients with hyperthyroidism have 1.22 times the risk of developing adhesive capsulitis. Patients with cerebrovascular disease, especially those surgically treated for subarachnoid haemorrhage, are more susceptible to developing adhesive shoulder capsulitis; in one prospective study of this high risk population, 23 of 91 patients (25.3%) developed adhesive capsulitis within 6 months.[21] Smith et al.[22] showed that Dupuytren's disease was found in 52% of patients (30 of 58) with adhesive capsulitis. Although the prevalence of adhesive capsulitis is higher in patients with the associated conditions stated above, further studies are needed to determine why such relationships exist.

Natural history

Neviaser and Neviaser[23] broke down the natural progression of adhesive capsulitis into four stages based on clinical presentation and arthroscopic appearance. In Stage I, patients present with a primary complaint of shoulder pain, especially at night, although they have preserved motion. Arthroscopically, there is evidence of synovitis without adhesions or contractures. In Stage II, patients begin to develop stiffness. Synovitis is again observed on arthroscopy, although there is also some loss of the axillary fold, suggestive of early adhesion formation and capsular contracture. Stage III is characterized by profound global loss of ROM and pain at the extremes of motion. During this stage, also known as the maturation stage, synovitis is resolved but the axillary fold is obliterated as a result of significant adhesions. Finally, in Stage IV or the chronic stage, there is persistent stiffness but minimal pain as synovitis has resolved. With pain controlled,

patients may begin to exhibit slow improvement in shoulder mobility. Advanced adhesions and restriction of the glenohumeral joint space are observed arthroscopically.

Histologically, Stage I is characterized by inflammatory cell infiltration of the synovium, Stage II by synovial proliferation and Stage III by dense collagenous tissue within the capsule,[1] supporting the theory that inflammation leads to reactive fibrosis.

Adhesive capsulitis is often regarded as a self-limiting disease that resolves in approximately 1 years to 3 years. Neviaser's four classical stages of adhesive capsulitis are sometimes reclassified as the 'painful phase', 'stiff phase', and 'thawing phase', implying that this condition resolves spontaneously. However, as previously noted, approximately 20% to 50% of patients may have enduring symptoms,[2] making non-operative and operative interventions necessary.

Pathoanatomy

Contracture of the glenohumeral capsule is the hallmark of adhesive capsulitis. Findings include loss of the synovial layer of the capsule, adhesions of the axillary to itself and to the anatomical neck of the humerus, and overall decreased capsular volume.[1] In particular, a thickened and fibrotic rotator interval, a structure that is critical to glenohumeral joint stability, is associated with adhesive capsulitis.[24] The rotator interval is bordered by the supraspinatus tendon superiorly, subscapularis tendon inferiorly, transhumeral ligament laterally and coracoid process medially. The rotator interval contains the CHL, biceps tendon and the glenohumeral capsule. A contracted CHL is considered the essential finding in adhesive capsulitis. The CHL ligament is placed under tension with maximal external rotation;[25] therefore, it is the main target of operative treatment of adhesive capsulitis. Patients with adhesive capsulitis have stiffer CHL ligament in the affected shoulder compared to the non-affected shoulder as measured by shear-wave elastography.[26] MRA and MRI studies reveal that the CHL is also thickened (4.1 mm versus 2.7 mm) in patients with adhesive capsulitis.[11,27] Likewise, the capsule in the rotator interval is thicker (7.1 mm versus 4.5 mm) and the volume of the axillary recess is smaller (0.53 mL versus 0.88 mL) compared to controls.[11]

Pathogenesis

Adhesive capsulitis has long been considered to be a primarily fibrotic disorder similar to Dupuytren's disease because the histology of affected specimens primarily show fibroblasts mixed with type I and type III collagen.[28] These fibroblasts were observed to transform into smooth muscle phenotype (myofibroblasts), which is assumed to be responsible for capsular contracture. There are altered levels of matrix metalloproteinases (MMPs), which are involved in scar tissue remodelling. For example, MMP-14 is expressed in control patients but not at all in patients with adhesive capsulitis.[29] MMP-14 is an activator of MMP-2, involved in collagen degradation, and this may result in excessive collagen production compared to breakdown. Expression of MMP-1 and MMP-2 is lowered in patients with adhesive capsulitis; at the same time, expression of tissue inhibitor of metalloproteinases (TIMPs) such as TIMP-1 and TIMP-2 is elevated.[30] Those findings support the notion that adhesive capsulitis is the result of an imbalance between extracellular matrix tissue degradation, remodelling and regeneration. Future therapy may directly inhibit fibrogenesis or promote remodelling of fibrotic tissue.

It is now generally accepted that the development of adhesive capsulitis involves an inflammatory as well as fibrotic process. Corroborating this are studies demonstrating elevated inflammatory cytokines including interleukin (IL)-1α, IL-1β, tumour necrosis factor (TNF)-α, cyclooxygenase (COX)-1 and COX-2 in capsular and bursal tissues of patients with adhesive capsulitis compared to controls.[31] Thus, it might be argued that adhesive capsulitis is primarily an inflammatory process that eventually leads to fibrotic changes. Almost all of the samples obtained from the rotator interval of patients with adhesive capsulitis contain inflammatory cells, including T cells, B cells, macrophages and mast cells.[32] Mast cells are known to regulate fibroblast proliferation *in vivo* and may act as an intermediary between the inflammatory and subsequent fibrotic processes.

Recent studies have sought to link molecular pathogenesis with known risk factors and genetic susceptibility for adhesive capsulitis. Cytogenetic analysis study has revealed elevated fibrogenic (MMP-3) as well as inflammatory (IL-6) cytokines in patients with adhesive capsulitis.[33] Ling et al.[34] found that specific single-peptide polymorphisms (SNP) of IL-6 (rs1800796 SNP) and MMP-3 (rs650108 SNP) are associated with severity and susceptibility of shoulder stiffness following rotator cuff repair, demonstrating a genetic predisposition for secondary adhesive capsulitis.

Kim et al.[35] reported that intercellular adhesion molecule-1 (ICAM-1), a transmembrane protein on endothelial cells and leukocytes that facilitate leukocyte endothelial transmigration, is increased in capsular tissue, synovial fluid and serum of patients with adhesive capsulitis. Interestingly, the ICAM-1 level is also elevated in diabetes mellitus. This observation provides a potential molecular link between the two conditions.[35] Raykha et al.[36] reported elevated expression

of IGF-2 and β-catenin in Dupuytren's disease and adhesive capsulitis.

Other molecules that have been shown to be elevated in local tissues obtained from adhesive shoulders include mitogen-activated protein kinases (ERK and JNK), NF-kappa B, CD29 (β-1 integrin) and VEGF.[37] Markers for blood vessels (CD34) and nerves]nerve growth factor receptor p75, growth associated protein 43 (GAP43), protein gene product 9.5 (PGP9.5)] are also elevated. This suggests concluded that both neoangiogenesis and neoinnervation occur in adhesive capsulitis, and the latter process may explain why adhesive capsulitis is unbearably painful.[38] One key growth factor involved in adhesive capsulitis is TGF-β.[39] Watson et al.[40] demonstrated that overexpression of TGF-β1 using an adenovirus vector in the knee joints of rats lead to development of adhesive capsulitis as early as within 5 days.

Non-operative management

The goal of treatment of adhesive capsulitis is to restore the shoulder to a painless and functional joint.[41,42] Because some patients with adhesive capsulitis improve spontaneously, treatment varies greatly from benign neglect to invasive open capsulotomy. There is no universal treatment algorithm, and therefore treatment should be patient-specific.

Physical therapy. For patients with early stages of adhesive shoulder capsulitis, physical therapy is the first line of treatment. In general, physical therapy is simultaneously combined with other treatment modalities, as a Cochrane study concludes that there is little overall evidence to support physical therapy alone in the treatment of adhesive capsulitis.[43] Although early mobilization with physical therapy is recommended, the technique (i.e. gentle therapy versus aggressive therapy beyond the pain limits) and frequency of therapy remain controversial. Diercks and Stevens[44] reported that only 63% of patients undergoing intensive physical therapy demonstrated improvement in shoulder function compared to 90% who did pendulum and gentle exercises, improvement in shoulder function at 2-year follow-up compared to 90% who did pendulum and gentle exercises. On the other hand, Vermeulen et al.[45] showed no difference between gentle (low-grade) and aggressive (high-grade) mobilization techniques. Many clinicians would not recommend physical therapy until the patients are beyond phase I, or the painful phase, of adhesive capsulitis, when supervised or self-directed mobilization becomes more tolerable. In a prospective nonrandomized study, Griggs et al.[16] documented satisfactory outcomes in 90% of patients (64 of 75) with phase-II adhesive shoulder capsulitis undergoing a stretching exercise programme; only 7% of patients (five of 75) required surgical intervention. Home self-exercise has been shown to be equally effective or superior to supervised stretching-exercise.[46,47] Posterior glide mobilization technique is considered to provide improved external rotation compared to an anteriorly directed technique.[48] Physical therapy can be combined with ultrasonic therapy, transcutaneous electrical nerve stimulation, short-wave therapy, low-level laser therapy and hydrotherapy. More aggressive treatment modalities should be employed in refractory cases after 4 months of physical therapy because those patients are likely to fail non-operative treatment.[49]

Pharmacological therapy. Pharmacological therapy, including non-steroidal anti-inflammatory drugs (NSAIDs) and systemic or intra-articular corticosteroids, provides symptomatic management and serves as an adjunct to physical therapy. Both COX-1 and COX-2 expressions are elevated in capsular and bursal tissues of patients with adhesive capsulitis,[31] and these anti-inflammatory agents target synovitis as the source of pain. Pain management is a key feature to allow patients to tolerate physical therapy to improve ROM. There have been few studies evaluating the effectiveness of NSAIDs for the treatment of adhesive capsulitis. NSAIDs are generally recommended for short-term pain relief during the early inflammatory stages of adhesive capsulitis.[3,50] Rhind et al.[51] performed a double-blinded study comparing the effectiveness of naproxen to indomethacin in the treatment of adhesive capsulitis. Patients in both groups demonstrated improved pain relief but no objective improvement in shoulder mobility. Additionally, 70% (14 of 20) of patients taking naproxen and 76% (16 of 21) of patients taking indomethacin reported side effects, most commonly nausea and headache.[51]

Four randomized controlled trials (RCTs) have been published, evaluating the effectiveness of oral corticosteroids in the treatment of adhesive capsulitis.[52–55] Binder et al.[54] compared the treatment group (10 mg of prednisone daily for 4 weeks, followed by 5 mg for 2 weeks) to the nontreatment group. All patients were encouraged to carry out pendulum exercises at home. The only statistically significant difference between the two groups was pain at night, although this was short lived. There was no difference in pain with movement, pain at rest or ROM.[54] Buchbinder et al.[55] utilized a higher dose of prednisone over a shorter duration (30 mg of prednisolone daily for 3 weeks) and showed greater improvement in pain at 3 weeks compared to the placebo group. Improvements in disability, ROM and participant-rated score were also statistically significant; however, these improvements were not sustained beyond 6 weeks. Interestingly, at 12 weeks, the placebo group tended to do better than the treatment

group, which the authors attributed to rebound symptoms after cessation of prednisolone.[55]

Corticosteroid intra-articular injection. Intra-articular corticosteroid injection has been observed to offer faster and superior improvement in symptoms compared to oral steroid treatment.[56,57] Intra-articular steroid injection decreases fibromatosis and myofibroblasts in adhesive shoulders.[58] Bulgen et al.[59] reported that intra-articular methylprednisolone injection provided more rapid improvement in pain and ROM compared to physiotherapy, ice therapy and no treatment. However, there was no difference between the groups at 6 months.[59] Van der Windt et al.[60] observed that 77% of patients (40 of 52) treated with one to three intra-articular injections of 40 mg of triamcinolone acetonide had improved pain and shoulder disability scores compared to only 46% (26 of 56) in patients treated with physiotherapy (two times weekly for 6 weeks). This difference was sustained at 1-year follow-up. Adverse effects were more commonly reported in women, including facial flushing and irregular menstrual bleeding.[60] More recently, Ryans et al.[61] published a RCT study demonstrating that intra-articular injection of 20 mg of triamcinolone led to improved self-assessment of global disability at 6 weeks, whereas physical therapy improved passive external rotation at 6 weeks. Interestingly, the group that received both triamcinolone injection and standardized physical therapy did not have combined benefits of both treatment modalities (or interaction effect). At 16 weeks, all groups had similar improvements in all outcome measures.[61]

Sodium hyaluronate intra-articular injection. Sodium hyaluronate is an unbranched polysaccharide considered to be chondro-protective[62] and has been shown to provide equivalent outcomes to intra-articular corticosteroid injection.[18] Pharmacologically, hyaluronate has 'metabolic effects on articular cartilage, synovial tissue and synovial fluid'.[62] Additionally, using dynamic MRI enhanced with Gd-DTPA, Tamai et al.[63] demonstrated that hyaluronate injection leads to a lower coefficient of enhancement (a measurement of synovitis) in the synovium of patients with adhesive capsulitis. A systematic review by Harris et al.,[18] which included four level I and three level IV studies, concluded that sodium hyaluronate injection leads to improved ROM, constant scores and pain at short-term follow-up. Additionally, hyaluronate is found to be safe with no reported complications.[18] Rovetta and Monteforte[64] reported that a combined injection of 20 mg of sodium hyaluronate plus 20 mg of triamcinolone acetonide with physiotherapy yielded better improvements in shoulder pain and joint motion compared to triamcinolone injection with physiotherapy.

Suprascapular nerve block. Suprascapular nerve block (SSNB) can be performed in the hospital or office setting to provide temporary pain relief to facilitate mobilization. The suprascapular nerve provides sensory fibres to approximately 70% of the glenohumeral joint.[65] A double-blinded RCT by Dahan et al.[66] concluded that patients receiving three successive bupivacaine SSNBs experienced improved short-term pain but not shoulder function compared to patients receiving placebo injections at 1-month follow-up. In another RCT study, SSNB (9.5 mL 0.5% bupivacaine, 20 mg of triamcinolone) offered greater pain control and improved ROM at 3-month follow-up compared to intra-articular corticosteroid injection (20 mg of triamcinolone).[67] More recently, Ozkan et al.[65] reported that SSNB is a feasible therapeutic option for patients with adhesive capsulitis refractory to intra-articular steroid injections.[65] Using electromyography to guide the SSNB is superior to SSNB by palpating anatomical landmarks.[68]

Hydrodilation

Hydrodilation, otherwise known as distention arthrography or brisement, describes a process in which capsular distention is achieved by injection of air or fluid under fluoroscopy and local anesthetic to stretch the contracted capsule and thereby increasing the intracapsular volume.[69,70] In a level II RCT by Quraishi et al.,71 an improved Constant score and visual analogue scale (VAS) pain score was observed in the hydrodilation group compared to the manipulation under anesthesia (MUA) plus intra-articular triamcinolone group. There was no difference in ROM between the two groups.[71] Hydrodilation with normal saline and corticosteroid (40 mg of methylprednisolone acetate) provides improved pain, range of active motion, shoulder-specific disability measure and patient preference measure compared to placebo (arthrogram) at 3 weeks.[72] In a Cochrane review by Buchbinder et al.[73] that included five clinical trials, it was concluded that hydrodilation with steroid and saline may improve pain at 3 weeks and disability at up to 12 weeks; however, there may be no difference in pain and disability compared to steroid injection alone.

Other nonoperative therapies. Whole-body cryotherapy (WBC) involves the exposure of the unclothed body in a chamber that circulates very cold air maintained between –110 °C to –140 °C for 2 minutes to 3 minutes. WBC is assumed to provide anti-inflammatory and analgesic effects to the body. Ma et al.[74] compared physical therapy alone versus physical therapy with WBC, noting that the group receiving physical therapy with WBC demonstrated higher improvement in VAS,

active ROM (flexion, abduction, internal rotation and external rotation) and self-assessed functional score using the American Shoulder and Elbow Surgeons Standardized Shoulder Assessment Form. Joo et al.[75] reported their prospective controlled trial evaluating the effects of intra-articular administration of botulinum toxin type A (BoNT-A) compared to intra-articular triamcinolone in patients with adhesive capsulitis. Both groups had significant improvements from baseline in pain and ROM, although there was no difference between the two study groups. BoNT-A is more expensive but allows the patient to avoid steroid-induced side effects.[75]

Operative management

Surgical options for treatment of adhesive shoulder capsulitis are generally reserved for patients with persistent symptoms refractory to conservative management. These options include MUA and arthroscopic or open capsulotomy.

Manipulation under anesthesia. MUA relies on aggressive mobilization of the shoulder joint in a controlled setting beyond the normal pain thresholds to tear apart the adhesions and stretch the contracted capsule. Often regarded as a safe procedure, there have been reported incidences of hemarthrosis, capsular tear, labral detachment, SLAP (superior labral anterior and posterior) lesion, and humeral or glenoid fracture following MUA.[3,76,77] Additionally, the effectiveness of MUA remains a topic of debate. Melzer et al.[78] observed that patients receiving pharmacotherapy and physiotherapy did better than patients undergoing MUA with regards to subjective personal rating and ROM. On the other hand, Placzek et al.[79] argued that MUA is a feasible treatment option for adhesive capsulitis, documenting improved passive ROM and VAS pain score following translational manipulation of the glenohumeral joint under brachial plexus block. MUA alone bears equivalent improvements in mobility and pain compared to MUA with intra-articular steroid injection [1 mL of betamethasone (6 mg/mL) and 4 mL of lidocaine (10 mg/mL)].[80] In one RCT, MUA with home exercises provided comparable outcomes to home exercises alone.[81] MUA has been shown to be less effective in diabetic patients with adhesive shoulder capsulitis.[82]

Arthroscopic capsulotomy. Arthroscopic capsular release is an effective and safe method for treatment of adhesive shoulder capsulitis.[83–85] Arthroscopic capsulotomy has two key advantages. First, diagnostic arthroscopy confirms the diagnosis and rules out other potential causes of a painful stiff shoulder. Second, compared to MUA and hydrodilation, it allows for direct visualization of the tightened CHL, thickened rotator interval and contracted capsule to ensure adequate release. The standard arthroscopic capsulotomy is anteroinferior capsular release. The utility of posterior capsular release (or extended capsular release) remains controversial.[86–88].

Smith et al.[89] found that 50% and 80% of patients had good pain relief within 1 and 6 weeks of arthroscopic capsular release, respectively. On average, it takes 16 days to achieve good pain relief, from a VAS score of 6.6 down to 1. Of the 136 patients in that study, only one patient had surgical site infection treated with oral antibiotics.[89] In their series, Le Lievre and Murrell[90] observed that all 43 patients had improvement in pain frequency and severity, shoulder function and ROM at a long-term follow-up of 7 years. Patients who tend to do more poorly with arthroscopic capsular release are female, > 50 years old and have type 2 diabetes mellitus.[91] Diabetic patients with adhesive capsulitis do show improved shoulder function as measured by the modified Constant scores after arthroscopic capsular release, although their results are not as good compared to their nondiabetic counterparts.[92,93] At 1 year, the recurrence can be up to 11% following arthroscopic capsular release.[83]

Postoperative adhesive capsulitis is a dreaded complication following arthroscopic or open shoulder surgery, including capsulotomy procedures. There is a fine balance between immobilization to allow the surgical construct, fracture or surrounding soft tissue to heal at the same time as promoting early mobilization to prevent arthrofibrosis. Some surgeons would argue that the best treatment for adhesive capsulitis is prevention by providing adequate postoperative pain management to allow patients to comfortably engage in physical therapy. Yamaguchi et al.[94] placed intra-articular bupivacaine pain catheter following their arthroscopic capsular release. It was concluded that postoperative intra-articular analgesia provided statistically significant postoperative pain relief and near-complete restoration of shoulder ROM, with an average follow-up of 22.4 months.[94] Likewise, postoperative analgesia can also be achieved via cervical epidural infusion[95] or interscalene block following arthroscopic release.[96,97]

Open capsulotomy. Open capsulotomy is rarely performed for recalcitrant adhesive shoulder capsulitis because arthroscopic capsular release results in smaller surgical wounds and shorter postoperative recovery. The open procedure remains an option when arthroscopic capsular release has failed in improving pain and ROM for adhesive capsulitis. Release of the CHL and rotator interval have been found to restore motion and improve pain.[13] In their series of 25 patients who failed MUA, Omari and Bunker[14] performed open

capsular release and noted improvement in both pain and function at mean follow-up of 19.52 months.

Future therapies. As we continue to gain better insight into the pathophysiology of adhesive capsulitis, there is equal interest in developing novel non-operative therapeutic interventions for treating this debilitating condition.

One recurring theme in medicine is to apply a successful treatment of one disease to another disease that shares similar pathophysiology. Collagenase is an enzyme isolated from the bacterium *Clostridium histylyticum* and breaks down the peptide bonds in collagen. Collagenase has been approved by the Food and Drug Administration (FDA) for the treatment of two fibrotic tissue disorders, Dupuytren's disease and Peyronie's disease, with good functional outcomes. As previously illustrated, adhesive capsulitis is very similar to Dupuytren's disease, both histologically and molecularly. Although collagenase has been FDA-approved for use in Dupuytren's since 2010, only recently have there been studies investigating the efficacy of off-label use of collagenase injection in patients with adhesive shoulder capsulitis. This is known as enzymatic capsulotomy. In a phase 2 placebo-controlled double-blind RCT, Badalamente and Wang[98] reported that extra-articular collagenase injection into the anterior shoulder capsule (midway between the bicipital groove and coracoid at maximal external rotation) results in improved functional score, shoulder motion and pain compared to injection of placebo (0.9% saline/2 mM $CaCl_2$). Patients also benefited from subsequent injections. Improvements were sustained at a follow-up of 1.8 years. Side effects include tenderness and ecchymosis at the injection sites, which resolved between 7 and 14 days.[98] MRI obtained 3 months after collagenase injection demonstrated no clinically significant injuries to the rotator cuff or surrounding structures.[99]

Although the use of anti-TNF agents in autoimmune and inflammatory disorders is well-documented, its application in the treatment of adhesive capsulitis has not been well-studied. In one randomized pilot study, Schydlowsky et al.[100] demonstrated no efficacy of subcutaneous injection of adalimumab in the treatment of adhesive shoulder capsulitis.

Although neither collagenase nor adalimumab therapy has been proven for the treatment of adhesive capsulitis, the next generation of non-operative therapies should continue to specifically target key steps in the pathophysiology of this disease, either the inflammatory or the fibrotic processes. One animal model developed by Kanno et al.[101] showed that immobilization of the shoulder in rats via internal fixation leads to loss of ROM on *ex vivo* testing, and Liu et al.[102] showed that plaster immobilization of the shoulder in rats results in capsular adhesions and accumulation of collagen within the capsule. More recently, the internal fixation model of adhesive capsulitis in rats have been shown to result in sustained *in vivo* kinematic changes.[103] This animal model, which allows for long-term functional measurements, should pave the way for the testing of new pharmacological therapies.

Conclusions

Adhesive capsulitis of the shoulder remains an unresolved clinical problem. No present treatment protocols are universally effective, and there is a strong need for further research and development of more effective treatment strategies. Morbidity from this condition has significant individual and societal cost, and disability is always long-lasting, if not permanent. There are few validated animal models, and investigational progress has been slow. The recent development of a new validated animal study should lead the way to development of novel therapies. New treatments for adhesive capsulitis, if developed, could also serve to address other aetiologies of arthrofibrosis.

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