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CLINICAL COMMENTARY

CURRENT CONCEPTS OF ROTATOR CUFF TENDINOPATHY

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ABSTRACT

Purpose/Background: Tendinopathies are a broad topic that can be examined from the lab to their impact upon function. Improved understanding will serve to bring this pathology to the forefront of discussion, whether in the clinic or the classroom. The purpose of this current concepts clinical commentary is to explore intrinsic and extrinsic mechanisms of rotator cuff (RC) tendinopathy in order to improve clinical and research understanding.

Methods: Pubmed, Medline, Cinahl, PEDro, and Cochrane databases were searched, limiting results to those published in the English language, between the years of 2005 and 2012. The key search terms utilized were intrinsic mechanisms, tendinopathy, stem cells, biologics, platelet-rich plasma (PRP), healing, rotator cuff tears, full-thickness tears, tests, impingement, imaging, ultrasound, Magnetic Resonance Imaging (MRI), radiograph, shoulder advances, treatment, diagnoses, tendon disorders, pathogenesis, matrix metalloproteinase, injections, and RC repair. Over 150 abstracts were reviewed and 43 articles were analyzed for quality and relevance using the University of Alberta Evidence Based Medicine Toolkit.

Results/Conclusions: Current evidence suggests that tendinopathies arise from a multivariate etiology.It is increasingly evident that intrinsic mechanisms play a greater role than extrinsic mechanisms in this process. Emphasis should be placed on patient information (i.e. background information and personal description of symptoms) and imaging/ injection techniques in order to aid in diagnosis. Future treatment technologies such as cell therapy and biological engineering offer the hope of improving patient outcomes and quality of life.

Level of Evidence: Level 5 – Clinical Commentary Related to a Review of Literature

Key Words: Rotator cuff, tendinopathy, tendinitis, tendinosis

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INTRODUCTION

Shoulder pain is the third most common musculoskeletal complaint.[1] Some commonly diagnosed shoulder problems include impingement of the rotator cuff tendons or subdeltoid bursa, bicipital tendonitis, frozen shoulder, and glenohumeral (GH), and acromioclavicular (AC) arthritis.[2] With the unknown incidence of partial rotator cuff tears (PRCTs), defined as tears involving less than 50% of the muscle, the clinician needs to fully understand the condition in order to best address the patient's problem.[2] Authors have shown that full thickness tears are usually due to chronic degeneration.[3,4] Furthermore, most rotator cuff pathologies can be treated with reasonable success using conservative therapy despite the lack of high quality evidence.[2]

If a diagnosis of tendinopathy has been made, it is important to take the diagnosis a step further and decipher whether the tendinopathy is from extrinsic causes, intrinsic causes, or a combination of the two. When a patient partially tears their rotator cuff (RC), it is common that they present with reduced shoulder function (i.e. dyskinesis, weakness, pain, and stiffness).[2] They may also have pain at rest, night pain, or a painful arc.[2] Upon evaluation, the clinician may find weak external rotators, a weak supraspinatus, and signs of impingement.[2] Signs of impingement may include painful overhead reaching, an inflamed subdeltoid bursa, or positive special tests meant to provoke symptoms. In patients over the age of 60 with two out of three of the aforementioned symptoms (i.e. weak external rotators, weak supraspinatus, impingement signs previously listed), there is a 98% chance of a RC tear.[5] Patients can also present with pain radiating to the lateral mid-humerus or anterolateral acromion, pain while lying on the shoulder or sleeping with the arm overhead, and pain that occurs when reaching above the head.[6] In addition, Fukuda observed that PRCTs are more painful than full thickness tears.[7]

Factors taken into account when considering surgery include the patient's functional needs, age, health, size of the tear, and amount of fatty infiltration into the muscle.[2,8,9] It is estimated that 75,000 RC surgical repairs are performed in the United States each year.[10] Age plays a factor as it is unusual for young patients to have RC tears requiring surgery.[11] If a young patient presents with acute, post-traumatic weakness without any pre-existing RC problem, then it is generally accepted as an absolute indication for surgery.[2] In terms of tear size, if the RC tendons are greater than 50% torn, then surgery is commonly recommended.[2]

Pre-operative rotator cuff tear size is the main factor in determining long-term outcome of repair in relation to range of motion (ROM), strength, and need for another surgery.[12] Chronic tears are less likely to heal with surgery than acute tears.[13] Surgery on chronic RC injuries has a wide ranging failure rate (30-94%) even with the use of newer techniques (e.g., double-row repairs), which could point to other variables for surgical failure such as aging, tendon to bone failure, and degeneration.[14-21] Poor muscle quality, delamination of tendons, and longer post-operative follow-up, are all related to lower healing rates and inferior results.[22,23] Even if the structural status of the repair is not ideal, the patient's symptoms after surgery can still improve.[14,24] In addition, better outcomes are associated with proper healing of the greater tuberosity and an intact repair,[14,24] and acromioplasty appears to play a role in successful outcomes after surgery for reducing impingement.[25-27]

Physical therapy can also play a role in the success after a RC surgery, but often varies widely between therapists and typically orthopedic surgeons do not choose their therapist.[28] Physical therapists may consider mechanisms involved in the genesis of tendon injury, but the treatment of both tendinopathy and subsequent RC repair is based on the impairments.[29] Research supports strengthening the scapular stabilizers and RC muscles, addressing flexibility of the posterior shoulder structures, pectoralis minor muscle, the thoracic spine (with postural education), and activity modifications designed to reduce pain and disability from RC tendinopathy.[30-32] There is a bias seen with exercise programs to target outlet impingement, which is an extrinsic mechanism.[29] Limited evidence exists to support therapeutic exercise and manual therapy for the treatment of RC tendinopathy.[2]

The purpose of this clinical commentary is to present the findings of a literature review identifying various mechanisms proposed for the development of RC tendinopathy. These mechanisms, or factors associated with RC tendinopathy will then be discussed with emphasis on the supporting evidence.

METHODOLOGY

Pubmed, Medline, Cinahl, PEDro, and Cochrane databases were electronically searched, limiting articles to those published in the English language between the years of 2005 and 2012. Search terms included: intrinsic mechanisms, tendinopathy, stem cells, biologics, platelet-rich plasma (PRP), healing, RC tears, full-thickness tears, tests, impingement, imaging, ultrasound, magnetic resonance imaging (MRI), radiograph, shoulder advances, treatment, diagnoses, tendon disorders, pathogenesis, matrix metalloproteinase, injections, and RC repair. Over 150 abstracts were reviewed and 43 articles were analyzed for quality and relevance using the University of Alberta Evidence Based Medicine Toolkit.

DEFINING TENDINOPATHY

It is important that tendinopathy, tendinitis, and tendinosis are systematically defined, in order to ensure that healthcare providers are effectively communicating regarding the condition to be treated. A tendinopathy is an overuse condition that manifests itself as pain in and around tendons[28] and happens when the body fails to regenerate properly.[33] This painful condition is associated with tendon disorganization and thickening that reduces its physical properties, which causes the tendon to fatigue, further exacerbating the painful condition with ultimate failure.[33] Tendinitis, which is usually painful, is a generic term that has to do with overuse, irritation, strain, degeneration and poor mechanics.[33] Degenerated and disorganized collagen that has increased vascularity and cellularity without obvious inflammatory cells is termed tendinosis.[33,34] Tendinitis and tendinosis represent tendon pathology and are subsets of tendinopathy.[29]

Tendons must be able to handle tensile loads and their ability to do so relies on Type 1 collagen.[35] However, a key feature of tendinopathy can be seen through collagen structure analysis by showing the disruption of tendon microarchitecture, which helps to understand the response to variable amounts of cyclic loading.[35-37] The aging process and repetitive use of tendons are thought to be contributors to RC tendinopathy.[35] The three general areas of tendinopathy that have been described in the literature are bursal sided, articular sided, and mid-substance.[38,39]

RC tendinitis is a term used to described chronic and acute conditions that involve the inflammatory process.[29] Histological research shows that there are a minimal number of inflammatory cells present in RC tendons and subacromial bursa.[40] RC disease has traditionally been thought to be a progressive disorder.[41] Neer believed the process started with tendonitis, then progressed to tendinosis with degeneration and partial thickness tears, and finally resulted in full thickness tears.[41] RC tendinosis is the diagnostic label for tendon pathology that is degenerative with or without inflammation,[29] whereas RC tendinopathy is used to signify a combination of pain and impaired performance associated with injury to the RC tendons.[42,43]

INTRINSIC MECHANISMS

RC tendinopathy occurs for a multitude of reasons. Intrinsic mechanisms are associated with the tendon itself and can be from aging,[44,45] altered biology,[46-48] microvascular blood supply,[38,41,49] degeneration, tendon overload, overuse, or trauma.[50-52] Intrinsic factors that contribute to RC tendon degradation with tensile/shear overload include alterations in biology, mechanical properties, morphology, and vascularity (See Table 1 for a summary of cellular changes associated with intrinsic mechanisms).[29,46-48,53,54]

As the human body ages, the properties of tendons are negatively impacted by processes such as calcification, fibrovascular proliferation, degeneration, decreased tensile loading, decreased toe-region on the stress strain curve, and decreased elasticity.[55,46]

Vascularization may be another intrinsic factor to consider.Codman described a critical zone where there was deficient blood supply within supraspinatus tendons.[56] But the research of some authors refutes this thought process and describes the lack of this region of hypovascularity, or that the hypovascularity is only limited to the articular side and not the bursal side of the tendon.[49,57] In RC tendinopathy, neovascularization occurs in regions that have sustained smaller tendon tears and degenerative changes.[38,39,46,58-60] Levy et al showed that subjects with acute RC tendinopathy had hypovascularity in the supraspinatus tendon that compared to subjects without RC disease.[58] In chronic tendinopathy, the tears showed hypervascularity near the degenerative changes.[58] Thus, the literature is not clear on whether hypovascularity directly causes tendinopathy per se, but there is conjecture that the presence

Table 1. *Proposed cellular changes associated with intrinsic mechanisms of rotator cuff tendinopathy*

Cellular changes associated with injury, reduced mechanical stimulation, certain medications, etc.: [166-173] Increased matrix metalloproteinases (MMP); Reduced tissue inhibitors of MMP (TIMPs); Tendon cell apoptosis; Insulin-like growth factor (IGF-1); Nitric oxide synthetase (NOS); Chondroid metaplasia of the tendon and matrix changes; Fatty infiltration (following tears); Cytokines; Caspases	NOTE: All of these changes negatively affect the turnover rate of collagen, adversely affecting collagen proliferation, and likely lead to tendon changes such as degeneration and apoptosis.

of blood vessels in the tendon matrix crowds out necessary collagen, which may further weaken the tendon prior to failure.[61]

EXTRINSIC MECHANISMS

Extrinsic mechanisms for RC tendinopathy include anatomic variables that set up conditions for impingement (usually occurring at the anterior aspect of the acromion).[62-64] It is currently thought that between 44-64% of all shoulder pain is from subacromial impingement syndrome (SAIS), the most common shoulder disorder.[65] Seitz et al showed that anatomical variants (acromial shape, subacromial joint spurs, and AC joint spurs) can lead to RC tendinopathy[29] and have proposed that these variables, along with overuse, could predispose an individual to the pathology.[66] Also, the angle and shape of the acromion could be a possible cause of the pathology.[29,67] The acromial shape has been broken down in to three types flat (Type 1), curved (Type 2), and hooked (Type 3).[68] It is still unclear if the shape changes with age or if its shape is determined congenitally or if both may contribute to the occurrence of tendinopathy.[51,69,70] Prior RC damage could cause increased stress to the coracoacromial arch and cause a hooked acromion to develop.[51] Wang et al found that as age progressed so did the shape of the acromion from flat to curved or hooked.[71] Shah et al found that this was possibly due to traction forces on the acromion,[72] which could offer some explanation as to why there is a higher incidence of RC tears with age but still suggests an initiating intrinsic reason.[51] It is believed that acromial shape and the severity of RC pathology are related.[73,74]

The AC joint could be another contributing factor. Over time, this joint degenerates and osteophytes can form on the inferior aspect of the distal clavicle.[69,75] These arthritic signs have been correlated with the presence of RC pathology.[75] Whether bone spurs cause RC tears continues to be debated.[51] The spurs are termed an enthesopathy and are thought to form from a coracoacromial ligament sprain.[51] These spurs may also be a secondary formation after sustaining a bursal-side RC tear.[76,77] Utilizing conservative treatment with a patient with the Type 1-acromion has a better outcome than conservative care in those with other types of acromion.[78,79] The majority of patients with SAIS can be treated nonsurgically, however, many authors have demonstrated the success of a variety of surgical procedures.[6] Further high-quality research is needed on the treatment and diagnosis of SAIS.[6]

Shoulder impingement is the main extrinsic cause of RC tendinopathy. It occurs with mechanical compression of the external portion (bursal side) of the tendon, which leads to inflammation and degeneration.[41] Upon repeated occurrence, the coracoacromial ligament may thicken, decreasing the subacromial space.[6] Overuse activity coupled with coracoacromial arch changes have a significant effect on tendon injury.[6] Significant relationships have been demonstrated between acromion morphology, the patient's self reported shoulder function, and the severity of the RC pathology.[50]

Decreased microvascular blood supply has been discussed as a possible cause of intrinsic pathology but it can also be from an extrinsic cause.[51] For example, when the arm is in full abduction, and the supraspinatus is compressed by the humeral head, the reduction in perfusion may be significant.[51]

A tight posterior capsule may cause changes in GH movement which could set up the patient for the development of impingement.[6] Harryman et al showed that when posterior capsule tightness was surgically induced in cadaveric specimens, there was an increase in anterior superior humeral head translation during passive GH flexion, leading to a narrowing of the subacromial space (SAS).[80] Stretching should be used to address impairments in posterior shoulder tightness.[81] Due to this relationship between posterior shoulder tightness and those with RC tendinopathy,[82] horizontal adduction and internal rotation ROM should be examined.[81,83-85]

Newer models of impingement have been proposed with limited supporting evidence.[51] Internal impingement (also known as posterior superior impingement or superior impingement) accounts for the majority of articular sided tears because the humeral tuberosity compresses the RC on the glenoid fossa.[86] Internal impingement (extrinsic mechanism for tendinopathy) is unique and occurs in overhead throwing athletes.[87-89] This is due to the extreme external rotation, abduction and extension of the arm, which can, in turn, cause the humerus to pinch the RC tendons on the superior glenoid rim.[90,86] The articular side of the tendons, not the bursal side, compresses between the humerus and the upper rim of the glenoid fossa when the arm is in extension, abduction and full external rotation.[6] In this case, the clinician will not usually see a narrowing of the SAS.[29] Most PRCTs are articular sided as opposed to bursal-sided, are degenerative in nature, and occur before the acromion degenerates.[91-93]

Aberrant scapular muscle activity has been identified in patients with SAIS and has been directly linked to abnormal scapular motion.[6,94-96] The serratus anterior and trapezius stabilize the scapula and induce scapular upward rotation, ER (external rotation), and/or posterior tilt, allowing the humeral head the appropriate amount of space for clearance during elevation motions.[94] Individuals can have reduced muscle performance or balance, latency in activation, and EMG (electromyography) activity of these muscles.[94-96]

Individuals who have some sort of impingement are thought to develop compensational movement patterns that relieve the compression and increase the subacromial space (SAS).[97] Published evidence does not currently support scapular dyskinesis as a major finding and does not describe it as a prime extrinsic mechanism for individuals with RC tendinopathy.[29] Scapular dyskinesis in subjects with RC tendinopathy has been theorized to include aberrant scapular and RC neuromuscular activation and muscle performance, thoracic kyphosis, pectoralis minor shortening, and posterior shoulder tightness.[29] A shortened pectoralis minor muscle at rest has been indirectly correlated with RC tendinopathy, functional deficits, and pain.[29,98-100] This is again thought to be attributed to abnormal scapular kinematics.[29] In subjects with RC tendinopathy, it was found that the serratus anterior and lower trapezius muscles demonstrate reduced muscle force and performance.[95,101]

Muscle deficits, soft tissue tightness and abnormal posture directly influence shoulder kinematics.[29] Weakness or dysfunction of the rotator cuff muscles can set up a situation that leads to SAIS due to a narrow SAS.[6,102] Authors have shown that there is superior humeral head translation and decreased abduction torque when there is reduced force of RC muscles, especially infraspinatus.[103,104] RC tendinopathy is seen in individuals with significant decreases in muscle peak isometric, eccentric and concentric torque when compared to those without these deficits.[105,106] Decreased muscle co-activation ratios between subscapularis, infraspinatus, and supraspinatus during the first 30 degrees of arm elevation and an increase at above 90 degrees was seen in patients exhibiting impingement as compared to the control group with no impingement.[29,107]

HEALING

After a tendon injury, the tendon normally heals through scar tissue formation which can take up to 24 months to fully mature.[108] The types and characteristics of collagen in scar tissue are different from that which comprises normal tissue.[33] A greater ratio

of Type 1 and Type 3 collagen is present in scar tissue (20-30%, instead of 1%).[109] Type 3 collagen, although possessing excellent elastic properties, demonstrates inferior strength properties because the diameter of Type 3 fibers is smaller than Type 1 fibers.[33] As the scar matures, it becomes much stronger because of improved interdigitation of collagen fibers and increased fiber diameter.[33] However, the properties are still inferior to native tendon because of the structural organization and poor matrix formation.[110] Therefore scar tissue must thicken to make up for its mechanical insufficiency, resulting in a stiffer tendon.[33]

Subjects who use tobacco products (e.g., cigarettes) are at greater risk for RC disease and poorer surgical outcomes.[111,112] This relationship becomes stronger as the dose and length of exposure increases.[51] Nicotine induces vasconstriction, which decreases oxygen delivery, and carbon monoxide reduces cellular oxygen levels.[113,114] Nicotine also contributes to a decrease in collagen concentrations, mechanical properties, deposition and repair after surgical intervention, while also causing unrelenting inflammation.[115,116] Postoperative outcomes of smokers are poorer than nonsmokers in terms of pain levels, postoperative satisfaction and overall function.[112]

Metabolic diseases can also negatively impact tendon healing and have a higher rate of complications, including infections (10%) and failures (7%).[51,117] Gharaibeh et al stated "In vitro experiments showed that a Cox-2- specific inhibitor (NS-398) slows the proliferation and maturation of differentiated myogenic precursor cells and thus delays the regenerative myogenesis process."[118] This may impair skeletal muscle healing.[118] Similar results have been seen using the Cox-2 selective inhibitor SC-236.[119] Even in highly vascularized skeletal muscle, NSAIDs seem to impair the healing process and may affect the recovery of other soft tissues.[118]

HEALING: QUANTIFYING LEVELS OF MATRIX METALLOPROTEINASE – 13 (MMP-13)

MMPs, aka zinc dependent proteases, are important for tendon repair and are associated with tenocyte cellular changes (see Table 1). Elevated levels of MMP-13, determined through equalized protein extracts in an enzyme-linked immunosorbent assay, could be an indicator of an impending tear because they play a critical role in the degradation process of RC tissue. Appropriate pharmacological management is important, as ibuprofen appears to be associated with upregulation of MMP-13 and other enzymes associated with collagen-degradation.[120] If MMP-13 activity is unchecked, then tears can occur.[121-123] Furthermore, MMP-13 levels show a significant relationship with patients' pain ratings,[121] and it has been observed that MMP-13 contributes to the inflammation found in OA (Osteoarthritis), RA (Rheumatoid arthritis), and periodontal disease and is found at increased levels in full thickness RC tears.[35,123-125]

EVIDENCE IN IMAGING

The function of the upper limb is critical in deciding the treatment approach and determining the patient's prognosis.[126] Clinical evaluation of the shoulder correlates well with magnetic resonance imaging (MRI) findings.[126] MRI and ultrasound have comparably high accuracy for finding RC tears and biceps pathologies,[126-130] clinical tests have moderate accuracy for both conditions.[126]

Patients with RC tendinopathy will not always show significant narrowing in SAS with the arm at rest.[131-133]Clinicians should look at the active range of motion biomechanics and then examine the SAS.[134] Glenohumeral internal and external rotation have opposing effects on subacromial pressure with external rotation decreasing the pressure in this space.[135,136] Some MRI studies show that active arm elevation reduces the acromial humeral distance (AHD) in those with RC tendinopathy but more research is necessary.[134,137] AHD is the shortest distance between the acromion and the humerus and the term can be used interchangeably with acromial humeral interval.Ardic et al found that the basic office clinic exam (not radiography or ultrasound) has 78.3% sensitivity for patients with subacromial impingement syndrome.[126] Advanced imaging plays an essential role when conservative therapy approaches fail after three weeks.[126] Clinical exam impingement tests have 71.2% accuracy, far better than the 40.7% accuracy of Speed's test for an injured biceps tendon.[126] Musculoskeletal ultrasound had 93.2% accuracy in finding RC tears and was 100% accurate in displaying biceps pathology.[126] MRI has been shown to be superior to ultrasonography for the detection of overall pathologies, except when there is

damage to the biceps tendon.[126] Some studies found that ultrasonography and MRI had no significant difference when comparing their sensitivity and specificity ratings.[127,128,130] Ultrasongraphy, however, is poorly correlated with surgery or arthrography for diagnosing RC tears.[126,138-140]

When measuring the coracoacromial arch in relation to the humerus and the AHD both have a similar measurements and can vary from 1.0 to 1.5 cm as seen on radiographs.[6] Some studies place the AHD for healthy shoulders between 0.7 cm and 1.4 cm when viewed with ultrasonography, radiography, and MRI.[6] When the AHD is less than 0.7 cm with the arm resting, a less favorable surgical outcome can be predicted.[141] Mayerhoefer et al. stated that AHD and measurements of the acromial shape do not correlate using radiography or MRI and that the acromial shape does not actually mean that the subacromial space is smaller.[142] This means that just because an acromion has a particular shape that it does not mean that the subacromial space is smaller or the acromial humeral distance is reduced.

The lateral acromial angle (LAA) is the relationship between the scapular glenoid plane and the slope of the inferior surface of the acromion. The LAA and acromial humeral interval (AHI) are reliable techniques when measured objectively on X-ray and MRI and their reliability increases with experienced observers.[143] LAA measurements have shown that a downsloping acromion correlates to an increased incidence of RC tears.[143-145] The significance of the AHI needs more research in examining its connection to impingement syndrome.[143]

INJECTIONS

Various injections can and have been used to aid in the diagnosis or treatment of RC tendinopathy. Andres et al found that corticosteroid injections relieve pain in cases of tendinitis for up to six Proposed cellular changes associated with intrinsic mechanisms of rotator cuff tendinopathy weeks, but there is no evidence for benefit beyond six months.[28,146-148] Arroll et al observed that corticosteroid injections into the SAS for RC tendinitis can be effective for up to nine months.[149] It is thought that higher doses may be more effective than lower doses and that the injections are most likely more effective than NSAIDs.[149] Additionally, accuracy can be improved when using ultrasound guidance to ensure effective injection placement, which could help to improve outcomes.[150,151]

Bursal-sided PRCTs should receive a subacromial injection whereas intra-articular injections provide greater pain relief for articular sided PRCTs or in patients with PRCTs along with other conditions such as capsulitis.[2] An indirect suprascapular nerve block may improve pain levels, allowing greater compliance with a rehabilitation program and improving comfort when sleeping.[2]

PLATELET-RICH PLASMA

Platelet-rich plasma (PRP) is developed from autologous blood injections[152] with the aim of improving tendon healing.[152] Evidence points to specific growth factors within the blood that promote the healing process, but evidence refutes the effects of using whole blood injections.[152,153] When using PRP, the platelets add more growth factors to the injection site for seven to ten days.[152] These growth factors are transforming growth factor b1 (TBFb), platelet-derived growth factor, vascular endothelial growth factor, hepatocyte growth factor, and insulin-like growth factor 1.[152] These factors are biologically active and stimulate angiogenesis, epithelialization, cell differentiation, proliferation, and the formation of extracellular matrix and fibrovascular callus.[154-156]

Previous studies examining tenocyte cultures showed that cell proliferation and total collagen production was enhanced with platelet-rich plasma-clot releasate (PRCR).[157,158] Recent studies provide evidence that PRP treatment in vivo may enhance tendon healing by increasing tenocyte number and production of collagen (types 1 and 3), which makes up a major portion of the tendon.[110,159]

PRP can be used to enhance extracellular matrix organization in the short term.[152] Injections given one week post-op showed increased tendon strength after four weeks when combined with early therapy.[160] There are have been no adverse effects reported after treatment.[152] Some low level evidence exists of improved healing times and increased strength, and in some cases subjects have avoided surgery.[152] It has also been used as a safe adjunct to surgery to improve healing.[152] No studies exist proving that the use of NSAIDS affect the efficacy of PRP but it is currently recommended that NSAIDS

should not be taken 2 days before or 14 days after the injections.[152] At this point, there is only limited clinical support for PRP when used for RC repair and cartilage healing, although it is safe for clinical use.[13]

STEM CELLS AND BIOLOGIC AIDS

Stem cell research is rapidly evolving and the literature is uncovering evidence that could greatly improve the treatment of tendinopathy through cell therapy.[33] The evidence is currently limited in humans and not many clinical trials exist,[33] thus, discussion of this area will be limited.

Surgical repair failure rates range from 20 to 70%, which can be attributed to a host of factors.[22,161,162] Biologically engineered scaffolds, exogenous growth factors, and stem cells may show potential when used to encourage RC repair and tendon healing.[163-165] The best way to improve tendon healing is probably through a mixture of different growth factors, but the precise combination is unknown.[165] The optimal proportion of catabolic and anabolic factors will create conditions for a superior repair and encourage the redevelopment of glenohumeral cartilage and tendon to bone insertion.[13,165] Greater research is still needed encompassing animal and human trials.

CONCLUSION

The common belief is that tendinopathy is generated from multivariate etiology. It is increasingly evident that intrinsic mechanisms play a greater role than extrinsic mechanisms in this process. Emphasis should be given on the evidence from patient information and imaging/injection techniques in order to aid in diagnosis of RC tendinopathy. It is the belief of the authors of this commentary that increased effort and research should be placed into future treatment technologies such as cell therapy and biological engineering in order to attempt to improve patient outcomes and quality of life.

REFERENCES

1. Urwin M, Symmons D, Allison T, et al. Estimating the burden of musculoskeletal disorders in the community: the comparative prevalence of symptoms at different anatomical sites, and the relation to social deprivation. *Annals of the rheumatic diseases.* Nov 1998;57(11):649-655.
2. Shin KM. Partial-thickness rotator cuff tears. *The Korean journal of pain.* Jun 2011;24(2):69-73.
3. Codman EA. Complete rupture of the supraspinatus tendon. Operative treatment with report of two successful cases. 1911. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* Apr 2011;20(3):347-349.
4. Jozsa L, Kannus P. Histopathological findings in spontaneous tendon ruptures. *Scand J Med Sci Sports.* Apr 1997;7(2):113-118.
5. Murrell GA, Walton JR. Diagnosis of rotator cuff tears. *Lancet.* Mar 10 2001;357(9258):769-770.
6. Umer M, Qadir I, Azam M. Subacromial impingement syndrome. *Orthopedic reviews.* May 9 2012;4(2):e18.
7. Fukuda H. Partial-thickness rotator cuff tears: a modern view on Codman's classic. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* Mar-Apr 2000;9(2):163-168.
8. Goutallier D, Postel JM, Gleyze P, Leguilloux P, Van Driessche S. Influence of cuff muscle fatty degeneration on anatomic and functional outcomes after simple suture of full-thickness tears. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* Nov-Dec 2003;12(6):550-554.
9. Liem D, Lichtenberg S, Magosch P, Habermeyer P. Magnetic resonance imaging of arthroscopic supraspinatus tendon repair. *The Journal of bone and joint surgery. American volume.* Aug 2007;89(8):1770-1776.
10. Vitale MA, Vitale MG, Zivin JG, Braman JP, Bigliani LU, Flatow EL. Rotator cuff repair: an analysis of utility scores and cost-effectiveness. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* Mar-Apr 2007;16(2):181-187.
11. Accousti KJ, Flatow EL. Technical pearls on how to maximize healing of the rotator cuff. *Instructional course lectures.* 2007;56:3-12.
12. Cofield RH, Parvizi J, Hoffmeyer PJ, Lanzer WL, Ilstrup DM, Rowland CM. Surgical repair of chronic rotator cuff tears. A prospective long-term study. *The Journal of bone and joint surgery. American volume.* Jan 2001;83-A(1):71-77.
13. Killian ML, Cavinatto L, Galatz LM, Thomopoulos S. Recent advances in shoulder research. *Arthritis research & therapy.* Jun 15 2012;14(3):214.
14. 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. *The Journal of bone and joint surgery. American volume.* Feb 2004;86-A(2):219-224.
15. Harryman DT, 2nd, Mack LA, Wang KY, Jackins SE, Richardson ML, Matsen FA, 3rd. Repairs of the rotator cuff. Correlation of functional results with

integrity of the cuff. *The Journal of bone and joint surgery. American volume.* Aug 1991;73(7):982-989.

16. Koh KH, Kang KC, Lim TK, Shon MS, Yoo JC. Prospective randomized clinical trial of single- versus double-row suture anchor repair in 2- to 4-cm rotator cuff tears: clinical and magnetic resonance imaging results. *Arthroscopy : the journal of arthroscopic & related surgery : official publication of the Arthroscopy Association of North America and the International Arthroscopy Association.* Apr 2011;27(4):453-462.
17. Chaudhury S, Carr AJ. Lessons we can learn from gene expression patterns in rotator cuff tears and tendinopathies. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* Feb 2012;21(2):191-199.
18. Charousset C, Bellaiche L, Kalra K, Petrover D. Arthroscopic repair of full-thickness rotator cuff tears: is there tendon healing in patients aged 65 years or older? *Arthroscopy : the journal of arthroscopic & related surgery : official publication of the Arthroscopy Association of North America and the International Arthroscopy Association.* Mar 2010;26(3):302-309.
19. Dodson CC, Kitay A, Verma NN, et al. The long-term outcome of recurrent defects after rotator cuff repair. *Am J Sports Med.* Jan 2010;38(1):35-39.
20. Duquin TR, Buyea C, Bisson LJ. Which method of rotator cuff repair leads to the highest rate of structural healing? A systematic review. *Am J Sports Med.* Apr 2010;38(4):835-841.
21. Jost B, Zumstein M, Pfirrmann CW, Gerber C. Long-term outcome after structural failure of rotator cuff repairs. *The Journal of bone and joint surgery. American volume.* Mar 2006;88(3):472-479.
22. Boileau P, Brassart N, Watkinson DJ, Carles M, Hatzidakis AM, Krishnan SG. Arthroscopic repair of full-thickness tears of the supraspinatus: does the tendon really heal? *The Journal of bone and joint surgery. American volume.* Jun 2005;87(6):1229-1240.
23. Tashjian RZ, Hollins AM, Kim HM, et al. Factors affecting healing rates after arthroscopic double-row rotator cuff repair. *Am J Sports Med.* Dec 2010;38(12):2435-2442.
24. Thomazeau H, Boukobza E, Morcet N, Chaperon J, Langlais F. Prediction of rotator cuff repair results by magnetic resonance imaging. *Clinical orthopaedics and related research.* Nov 1997(344):275-283.
25. Bigliani LU, Cordasco FA, McIlveen SJ, Musso ES. Operative treatment of failed repairs of the rotator cuff. *The Journal of bone and joint surgery. American volume.* Dec 1992;74(10):1505-1515.
26. DeOrio JK, Cofield RH. Results of a second attempt at surgical repair of a failed initial rotator-cuff repair. *The Journal of bone and joint surgery. American volume.* Apr 1984;66(4):563-567.
27. Flugstad D, Matsen F, Larry I, Jackins S. Failed acromioplasty: Etiology and prevention. *Orthop Trans.* 1986;10:229.
28. Andres BM, Murrell GA. Treatment of tendinopathy: what works, what does not, and what is on the horizon. *Clinical orthopaedics and related research.* Jul 2008;466(7):1539-1554.
29. Seitz AL, McClure PW, Finucane S, Boardman ND, 3rd, Michener LA. Mechanisms of rotator cuff tendinopathy: intrinsic, extrinsic, or both? *Clin Biomech (Bristol, Avon).* Jan 2011;26(1):1-12.
30. Brox J, Staff P, Ljunggren A, Brevik J. Arthroscopic surgery compared with supervised exercises in patients with rotator cuff disease (stage II impingement syndrome). *BMJ.* 1993;307, 899-903.
31. Haahr JP, Ostergaard S, Dalsgaard J, et al. Exercises versus arthroscopic decompression in patients with subacromial impingement: a randomised, controlled study in 90 cases with a one year follow up. *Annals of the rheumatic diseases.* May 2005;64(5):760-764.
32. Lombardi JI, Magri AG, Fleury AM, Da Silva AC, Natour J, 59. Progressive resistance training in patients with shoulder impingement syndrome: a randomized controlled trial. *Arthritis Rheum.* 2008;59, 615-622.
33. Obaid H, Connell D. Cell therapy in tendon disorders: what is the current evidence? *Am J Sports Med.* Oct 2010;38(10):2123-2132.
34. Khan KM, Cook JL, Bonar F, Harcourt P, Astrom M. Histopathology of common tendinopathies. Update and implications for clinical management. *Sports Med.* Jun 1999;27(6):393-408.
35. Neviaser A, Andarawis-Puri N, Flatow E. Basic mechanisms of tendon fatigue damage. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* Feb 2012;21(2):158-163.
36. Arya S, Kulig K. Tendinopathy alters mechanical and material properties of the Achilles tendon. *J Appl Physiol.* Mar 2010;108(3):670-675.
37. Longo UG, Franceschi F, Ruzzini L, et al. Histopathology of the supraspinatus tendon in rotator cuff tears. *Am J Sports Med.* Mar 2008;36(3):533-538.
38. Fukuda H, Hamada K, Yamanaka K. Pathology and pathogenesis of bursal-side rotator cuff tears viewed from en bloc histologic sections. *Clinical orthopaedics and related research.* May 1990(254):75-80.
39. Hashimoto T, Nobuhara K, Hamada T. Pathologic evidence of degeneration as a primary cause of rotator cuff tear. *Clinical orthopaedics and related research.* Oct 2003(415):111-120.

40. Sarkar K, Uhthoff HK. Ultrastructure of the subacromial bursa in painful shoulder syndromes. *Virchows Archiv. A, Pathological anatomy and histopathology.* 1983;400(2):107-117.
41. Biberthaler P, Wiedemann E, Nerlich A, et al. Microcirculation associated with degenerative rotator cuff lesions. In vivo assessment with orthogonal polarization spectral imaging during arthroscopy of the shoulder. *The Journal of bone and joint surgery. American volume.* Mar 2003;85-A(3):475-480.
42. Alfredson H. Chronic midportion Achilles tendinopathy: an update on research and treatment. *Clinics in sports medicine.* Oct 2003;22(4):727-741.
43. Alfredson H. The chronic painful Achilles and patellar tendon: research on basic biology and treatment. *Scand J Med Sci Sports.* Aug 2005;15(4):252-259.
44. Milgrom C, Schaffler M, Gilbert S, van Holsbeeck M. Rotator-cuff changes in asymptomatic adults. The effect of age, hand dominance and gender. *The Journal of bone and joint surgery. British volume.* Mar 1995;77(2):296-298.
45. Tempelhof S, Rupp S, Seil R. Age-related prevalence of rotator cuff tears in asymptomatic shoulders. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* Jul-Aug 1999;8(4):296-299.
46. Kumagai J, Sarkar K, Uhthoff HK. The collagen types in the attachment zone of rotator cuff tendons in the elderly: an immunohistochemical study. *The Journal of rheumatology.* Nov 1994;21(11):2096-2100.
47. Riley GP, Harrall RL, Constant CR, Chard MD, Cawston TE, Hazleman BL. Glycosaminoglycans of human rotator cuff tendons: changes with age and in chronic rotator cuff tendinitis. *Annals of the rheumatic diseases.* Jun 1994;53(6):367-376.
48. Riley GP, Harrall RL, Constant CR, Chard MD, Cawston TE, Hazleman BL. Tendon degeneration and chronic shoulder pain: changes in the collagen composition of the human rotator cuff tendons in rotator cuff tendinitis. *Annals of the rheumatic diseases.* Jun 1994;53(6):359-366.
49. Rudzki JR, Adler RS, Warren RF, et al. Contrast-enhanced ultrasound characterization of the vascularity of the rotator cuff tendon: age- and activity-related changes in the intact asymptomatic rotator cuff. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* Jan-Feb 2008;17(1 Suppl):96S-100S.
50. Michener LA, McClure PW, Karduna AR. Anatomical and biomechanical mechanisms of subacromial impingement syndrome. *Clin Biomech (Bristol, Avon).* Jun 2003;18(5):369-379.
51. Maffulli N, Longo UG, Berton A, Loppini M, Denaro V. Biological factors in the pathogenesis of rotator cuff tears. *Sports medicine and arthroscopy review.* Sep 2011;19(3):194-201.
52. Almekinders LC, Weinhold PS, Maffulli N. Compression etiology in tendinopathy. *Clinics in sports medicine.* Oct 2003;22(4):703-710.
53. Bey MJ, Song HK, Wehrli FW, Soslowsky LJ. Intratendinous strain fields of the intact supraspinatus tendon: the effect of glenohumeral joint position and tendon region. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society.* Jul 2002;20(4):869-874.
54. Malliaras P, Purdam C, Maffulli N, Cook J. Temporal sequence of greyscale ultrasound changes and their relationship with neovascularity and pain in the patellar tendon. *British journal of sports medicine.* Oct 2010;44(13):944-947.
55. Woo SL, An KN, Frank CB, Livesay GA, Ma CB, Zeminski J, et al. Anatomy, biology, and biomechanics of tendon and ligament. *American Academy of Orthopaedic Surgeons.* 2000.
56. Codman EA. *The shoulder; rupture of the supraspinatus tendon and other lesions in or about the subacromial bursa*. Boston, Mass.: T. Todd company; 1934.
57. Lohr JF, Uhthoff HK. The microvascular pattern of the supraspinatus tendon. *Clinical orthopaedics and related research.* May 1990(254):35-38.
58. Levy O, Relwani J, Zaman T, Even T, Venkateswaran B, Copeland S. Measurement of blood flow in the rotator cuff using laser Doppler flowmetry. *The Journal of bone and joint surgery. British volume.* Jul 2008;90(7):893-898.
59. Goodmurphy CW, Osborn J, Akesson EJ, Johnson S, Stanescu V, Regan WD. An immunocytochemical analysis of torn rotator cuff tendon taken at the time of repair. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* Jul-Aug 2003;12(4):368-374.
60. Rathbun JB, Macnab I. The microvascular pattern of the rotator cuff. *The Journal of bone and joint surgery. British volume.* Aug 1970;52(3):540-553.
61. Abate M, Gravare Silbernagel K, Siljeholm C, et al. Pathogenesis of tendinopathies: inflammation or degeneration? *Arthritis research & therapy.* 2009;11(3):235.
62. Neer CS, 2nd. Anterior acromioplasty for the chronic impingement syndrome in the shoulder: a preliminary report. *The Journal of bone and joint surgery. American volume.* Jan 1972;54(1):41-50.
63. Brossmann J, Preidler KW, Pedowitz RA, White LM, Trudell D, Resnick D. Shoulder impingement

syndrome: influence of shoulder position on rotator cuff impingement--an anatomic study. *AJR. American journal of roentgenology.* Dec 1996;167(6):1511-1515.

64. Yamamoto N, Muraki T, Sperling JW, et al. Impingement mechanisms of the Neer and Hawkins signs. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* Nov-Dec 2009;18(6):942-947.
65. van der Windt DA, Koes BW, de Jong BA, Bouter LM. Shoulder disorders in general practice: incidence, patient characteristics, and management. *Annals of the rheumatic diseases.* Dec 1995;54(12):959-964.
66. Soslowsky LJ, Thomopoulos S, Esmail A, et al. Rotator cuff tendinosis in an animal model: role of extrinsic and overuse factors. *Annals of biomedical engineering.* Sep 2002;30(8):1057-1063.
67. Vaz S, Soyer J, Pries P, Clarac JP. Subacromial impingement: influence of coracoacromial arch geometry on shoulder function. *Joint, bone, spine : revue du rhumatisme.* 2000;67(4):305-309.
68. Bigliani LU, Morrison DS, April EW. The morphology of the acromion and its relationship to rotator cuff tears. *Orthop Trans.* 1986;10, 228.
69. Nicholson GP, Goodman DA, Flatow EL, Bigliani LU. The acromion: morphologic condition and age-related changes. A study of 420 scapulas. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* Jan-Feb 1996;5(1): 1-11.
70. Bonsell S, Pearsall AWt, Heitman RJ, Helms CA, Major NM, Speer KP. The relationship of age, gender, and degenerative changes observed on radiographs of the shoulder in asymptomatic individuals. *The Journal of bone and joint surgery. British volume.* Nov 2000;82(8):1135-1139.
71. Wang JC, Shapiro MS. Changes in acromial morphology with age. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* Jan-Feb 1997;6(1):55-59.
72. Shah NN, Bayliss NC, Malcolm A. Shape of the acromion: congenital or acquired--a macroscopic, radiographic, and microscopic study of acromion. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* Jul-Aug 2001;10(4):309-316.
73. Bigliani LU, Ticker JB, Flatow EL, Soslowsky LJ, Mow VC. The relationship of acromial architecture to rotator cuff disease. *Clinics in sports medicine.* Oct 1991;10(4):823-838.
74. Ogawa K, Yoshida A, Inokuchi W, Naniwa T. Acromial spur: relationship to aging and morphologic changes in the rotator cuff. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* Nov-Dec 2005;14(6):591-598.
75. Cuomo F, Kummer FJ, Zuckerman JD, Lyon T, Blair B, Olsen T. The influence of acromioclavicular joint morphology on rotator cuff tears. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* Nov-Dec 1998;7(6):555-559.
76. Ozaki J, Fujimoto S, Nakagawa Y, Masuhara K, Tamai S. Tears of the rotator cuff of the shoulder associated with pathological changes in the acromion. A study in cadavera. *The Journal of bone and joint surgery. American volume.* Sep 1988;70(8):1224-1230.
77. Chambler AF, Pitsillides AA, Emery RJ. Acromial spur formation in patients with rotator cuff tears. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* Jul-Aug 2003;12(4):314-321.
78. Morrison DS, Frogameni AD, Woodworth P. Non-operative treatment of subacromial impingement syndrome. *The Journal of bone and joint surgery. American volume.* May 1997;79(5):732-737.
79. Wang JC, Horner G, Brown ED, Shapiro MS. The relationship between acromial morphology and conservative treatment of patients with impingement syndrome. *Orthopedics.* 2000;23, 557–559.
80. Harryman DT, 2nd, Sidles JA, Clark JM, McQuade KJ, Gibb TD, Matsen FA, 3rd. Translation of the humeral head on the glenoid with passive glenohumeral motion. *The Journal of bone and joint surgery. American volume.* Oct 1990;72(9):1334-1343.
81. Myers JB, Oyama S, Wassinger CA, et al. Reliability, precision, accuracy, and validity of posterior shoulder tightness assessment in overhead athletes. *Am J Sports Med.* Nov 2007;35(11):1922-1930.
82. Borich MR, Bright JM, Lorello DJ, Cieminski CJ, Buisman T, Ludewig PM. Scapular angular positioning at end range internal rotation in cases of glenohumeral internal rotation deficit. *The Journal of orthopaedic and sports physical therapy.* Dec 2006;36(12):926-934.
83. Laudner KG, Stanek JM, Meister K. Assessing posterior shoulder contracture: the reliability and validity of measuring glenohumeral joint horizontal adduction. *Journal of athletic training.* Oct-Dec 2006;41(4):375-380.
84. Tyler TF, Roy T, Nicholas SJ, Gleim GW. Reliability and validity of a new method of measuring posterior shoulder tightness. *The Journal of orthopaedic and sports physical therapy.* May 1999;29(5):262-269; discussion 270-264.
85. Warner JJ, Micheli LJ, Arslanian LE, Kennedy J, Kennedy R. Patterns of flexibility, laxity, and

strength in normal shoulders and shoulders with instability and impingement. *Am J Sports Med.* Jul-Aug 1990;18(4):366-375.

86. Edelson G, Teitz C. Internal impingement in the shoulder. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* Jul-Aug 2000;9(4):308-315.
87. Burkhart SS, Morgan CD, Kibler WB. The disabled throwing shoulder: spectrum of pathology Part III: The SICK scapula, scapular dyskinesis, the kinetic chain, and rehabilitation. *Arthroscopy : the journal of arthroscopic & related surgery : official publication of the Arthroscopy Association of North America and the International Arthroscopy Association.* Jul-Aug 2003;19(6):641-661.
88. Jobe CM. Posterior superior glenoid impingement: expanded spectrum. *Arthroscopy : the journal of arthroscopic & related surgery : official publication of the Arthroscopy Association of North America and the International Arthroscopy Association.* Oct 1995;11(5):530-536.
89. Kibler WB. The role of the scapula in athletic shoulder function. *Am J Sports Med.* 1998;26, 325-337.
90. Davidson PA, Elattrache NS, Jobe CM, Jobe FW. Rotator cuff and posterior-superior glenoid labrum injury associated with increased glenohumeral motion: a new site of impingement. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* Sep-Oct 1995;4(5):384-390.
91. Loehr J, Uhthoff H. The pathogenesis of degenerative rotator cuff tears. *Orthopedic Trans.* 1987;11:237.
92. Ogata S, Uhthoff HK. Acromial enthesopathy and rotator cuff tear. A radiologic and histologic postmortem investigation of the coracoacromial arch. *Clinical orthopaedics and related research.* May 1990(254):39-48.
93. Sano H, Ishii H, Trudel G, Uhthoff HK. Histologic evidence of degeneration at the insertion of 3 rotator cuff tendons: a comparative study with human cadaveric shoulders. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* Nov-Dec 1999;8(6):574-579.
94. Diederichsen LP, Norregaard J, Dyhre-Poulsen P, et al. The activity pattern of shoulder muscles in subjects with and without subacromial impingement. *Journal of electromyography and kinesiology : official journal of the International Society of Electrophysiological Kinesiology.* Oct 2009;19(5): 789-799.
95. Cools AM, Witvrouw EE, Declercq GA, Vanderstraeten GG, Cambier DC. Evaluation of isokinetic force production and associated muscle activity in the scapular rotators during a protraction-retraction movement in overhead athletes with impingement symptoms. *British journal of sports medicine.* Feb 2004;38(1):64-68.
96. Moraes GF, Faria CD, Teixeira-Salmela LF. Scapular muscle recruitment patterns and isokinetic strength ratios of the shoulder rotator muscles in individuals with and without impingement syndrome. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* Jan-Feb 2008;17(1 Suppl): 48S-53S.
97. McClure PW, Michener LA, Karduna AR. Shoulder function and 3-dimensional scapular kinematics in people with and without shoulder impingement syndrome. *Physical therapy.* Aug 2006;86(8):1075-1090.
98. Brox JI, Staff PH, Ljunggren AE, Brevik JI. Arthroscopic surgery compared with supervised exercises in patients with rotator cuff disease (stage II impingement syndrome). *BMJ.* Oct 9 1993;307(6909):899-903.
99. Kuhn JE. Exercise in the treatment of rotator cuff impingement: a systematic review and a synthesized evidence-based rehabilitation protocol. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* Jan-Feb 2009;18(1):138-160.
100. Lombardi I, Jr., Magri AG, Fleury AM, Da Silva AC, Natour J. Progressive resistance training in patients with shoulder impingement syndrome: a randomized controlled trial. *Arthritis Rheum.* May 15 2008;59(5):615-622.
101. Cools AM, Witvrouw EE, Declercq GA, Danneels LA, Cambier DC. Scapular muscle recruitment patterns: trapezius muscle latency with and without impingement symptoms. *Am J Sports Med.* Jul-Aug 2003;31(4):542-549.
102. Reddy AS, Mohr KJ, Pink MM, Jobe FW. Electromyographic analysis of the deltoid and rotator cuff muscles in persons with subacromial impingement. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* Nov-Dec 2000;9(6):519-523.
103. Hurschler C, Wulker N, Mendila M. The effect of negative intraarticular pressure and rotator cuff force on glenohumeral translation during simulated active elevation. *Clin Biomech.* 2000;15, 306-314.
104. Mura N, O'Driscoll SW, Zobitz ME, Heers G, Jenkyn TR, Chou SM, et al. The effect of infraspinatus disruption on glenohumeral torque and superior migration of the humeral head: a biomechanical study. *J. Shoulder Elbow Surg.* 2003;12, 179-184.
105. Leroux JL, Codine P, Thomas E, Pocholle M, Mailhe D, Blotman F. Isokinetic evaluation of rotational strength in normal shoulders and shoulders with

impingement syndrome. *Clinical orthopaedics and related research.* Jul 1994(304):108-115.

106. Tyler TF, Nahow RC, Nicholas SJ, McHugh MP. Quantifying shoulder rotation weakness in patients with shoulder impingement. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* Nov-Dec 2005;14(6):570-574.
107. Myers JB, Hwang JH, Pasquale MR, Blackburn JT, Lephart SM. Rotator cuff coactivation ratios in participants with subacromial impingement syndrome. *Journal of science and medicine in sport / Sports Medicine Australia.* Nov 2009;12(6):603-608.
108. Goodship A, Birch H, AM W. The pathobiology and repair of tendon and ligament injury. Vet Clin North Am Equine Pract. 10:323-349. 1994.
109. Williams IF, Heaton A, McCullagh KG. Cell morphology and collagen types in equine tendon scar. *Research in veterinary science.* May 1980;28(3):302-310.
110. Wang JH. Mechanobiology of tendon. *Journal of biomechanics.* 2006;39(9):1563-1582.
111. Baumgarten KM, Gerlach D, Galatz LM, et al. Cigarette smoking increases the risk for rotator cuff tears. *Clinical orthopaedics and related research.* Jun 2010;468(6):1534-1541.
112. Mallon WJ, Misamore G, Snead DS, Denton P. The impact of preoperative smoking habits on the results of rotator cuff repair. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* Mar-Apr 2004;13(2):129-132.
113. Mosley L, Fineseth F. Cigarette smoking: impairment of digital blood flow and wound healing in the hand. *9:97-101.* 1977.
114. Leow YH, Maibach HI. Cigarette smoking, cutaneous vasculature, and tissue oxygen. *Clinics in dermatology.* Sep-Oct 1998;16(5):579-584.
115. Galatz LM, Silva MJ, Rothermich SY, Zaegel MA, Havlioglu N, Thomopoulos S. Nicotine delays tendon-to-bone healing in a rat shoulder model. *The Journal of bone and joint surgery. American volume.* Sep 2006;88(9):2027-2034.
116. Jorgensen LN, Kallehave F, Christensen E, Siana JE, Gottrup F. Less collagen production in smokers. *Surgery.* Apr 1998;123(4):450-455.
117. Chen AL, Shapiro JA, Ahn AK, Zuckerman JD, Cuomo F. Rotator cuff repair in patients with type I diabetes mellitus. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* Sep-Oct 2003;12(5):416-421.
118. Gharaibeh B, Chun-Lansinger Y, Hagen T, et al. Biological approaches to improve skeletal muscle healing after injury and disease. *Birth defects research. Part C, Embryo today : reviews.* Mar 2012;96(1):82-94.
119. Bondesen B, Mills S, Kegley K, Pavlath G. The COX-2 pathway is essential during early stages of skeletal muscle regeneration. *Am J Physiol Cell Physiol.* 2004;287:C475–C483.
120. Tsai WC, Hsu CC, Chang HN, Lin YC, Lin MS, Pang JH. Ibuprofen upregulates expressions of matrix metalloproteinase-1, -8, -9, and -13 without affecting expressions of types I and III collagen in tendon cells. *J Orthop Res.* Apr 2010;28(4):487-491.
121. Jacob J, Eisemon E, Sheibani-Rad S, Patel A, Jacob T, Choueka J. Matrix metalloproteinase levels as a marker for rotator cuff tears. *Orthopedics.* Apr 2012;35(4):e474-478.
122. Bedi A, Kovacevic D, Hettrich C, et al. The effect of matrix metalloproteinase inhibition on tendon-to-bone healing in a rotator cuff repair model. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* Apr 2010;19(3):384-391.
123. Lo IK, Marchuk LL, Hollinshead R, Hart DA, Frank CB. Matrix metalloproteinase and tissue inhibitor of matrix metalloproteinase mRNA levels are specifically altered in torn rotator cuff tendons. *Am J Sports Med.* Jul-Aug 2004;32(5):1223-1229.
124. Vincenti MP, Brinckerhoff CE. Transcriptional regulation of collagenase (MMP-1, MMP-13) genes in arthritis: integration of complex signaling pathways for the recruitment of gene-specific transcription factors. *Arthritis research.* 2002;4(3):157-164.
125. Hernandez M, Valenzuela MA, Lopez-Otin C, et al. Matrix metalloproteinase-13 is highly expressed in destructive periodontal disease activity. *Journal of periodontology.* Nov 2006;77(11):1863-1870.
126. Ardic F, Kahraman Y, Kacar M, Kahraman MC, Findikoglu G, Yorgancioglu ZR. Shoulder impingement syndrome: relationships between clinical, functional, and radiologic findings. *American journal of physical medicine & rehabilitation / Association of Academic Physiatrists.* Jan 2006;85(1):53-60.
127. Swen WA, Jacobs JW, Algra PR, et al. Sonography and magnetic resonance imaging equivalent for the assessment of full-thickness rotator cuff tears. *Arthritis Rheum.* Oct 1999;42(10):2231-2238.
128. Kluger R, Mayrhofer R, Kroner A, et al. Sonographic versus magnetic resonance arthrographic evaluation of full-thickness rotator cuff tears in millimeters. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* Mar-Apr 2003;12(2):110-116.
129. Strobel K, Zanetti M, Nagy L, Hodler J. Suspected rotator cuff lesions: tissue harmonic imaging versus conventional US of the shoulder. *Radiology.* Jan 2004;230(1):243-249.

130. Teefey SA, Rubin DA, Middleton WD, Hildebolt CF, Leibold RA, Yamaguchi K. Detection and quantification of rotator cuff tears. Comparison of ultrasonographic, magnetic resonance imaging, and arthroscopic findings in seventy-one consecutive cases. *The Journal of bone and joint surgery. American volume.* Apr 2004;86-A(4):708-716.

131. Azzoni R, Cabitza P. Sonographic versus radiographic measurement of the subacromial space width. *La Chirurgia degli organi di movimento.* Apr-Jun 2004;89(2):143-150.

132. Azzoni R, Cabitza P, Parrini M. Sonographic evaluation of subacromial space. *Ultrasonics.* Apr 2004;42(1-9):683-687.

133. Desmeules F, Minville L, Riederer B, Cote CH, Fremont P. Acromio-humeral distance variation measured by ultrasonography and its association with the outcome of rehabilitation for shoulder impingement syndrome. *Clinical journal of sport medicine : official journal of the Canadian Academy of Sport Medicine.* Jul 2004;14(4):197-205.

134. Graichen H, Bonel H, Stammberger T, et al. Three-dimensional analysis of the width of the subacromial space in healthy subjects and patients with impingement syndrome. *AJR. American journal of roentgenology.* Apr 1999;172(4):1081-1086.

135. Lewis JS. Rotator cuff tendinopathy: a model for the continuum of pathology and related management. *British journal of sports medicine.* Oct 2010;44(13):918-923.

136. Werner CM, Blumenthal S, Curt A, Gerber C. Subacromial pressures in vivo and effects of selective experimental suprascapular nerve block. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* May-Jun 2006;15(3):319-323.

137. Hebert LJ, Moffet H, Dufour M, Moisan C. Acromiohumeral distance in a seated position in persons with impingement syndrome. *Journal of magnetic resonance imaging : JMRI.* Jul 2003;18(1):72-79.

138. Nelson MC, Leather GP, Nirschl RP, Pettrone FA, Freedman MT. Evaluation of the painful shoulder. A prospective comparison of magnetic resonance imaging, computerized tomographic arthrography, ultrasonography, and operative findings. *The Journal of bone and joint surgery. American volume.* Jun 1991;73(5):707-716.

139. Martin-Hervas C, Romero J, Navas-Acien A, Reboiras JJ, Munuera L. Ultrasonographic and magnetic resonance images of rotator cuff lesions compared with arthroscopy or open surgery findings. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* Sep-Oct 2001;10(5):410-415.

140. Burk DL, Jr., Karasick D, Kurtz AB, et al. Rotator cuff tears: prospective comparison of MR imaging with arthrography, sonography, and surgery. *AJR. American journal of roentgenology.* Jul 1989;153(1):87-92.

141. Weiner DS, Macnab I. Superior migration of the humeral head. A radiological aid in the diagnosis of tears of the rotator cuff. *The Journal of bone and joint surgery. British volume.* Aug 1970;52(3):524-527.

142. Mayerhoefer ME, Breitenseher MJ, Wurnig C, Roposch A. Shoulder impingement: relationship of clinical symptoms and imaging criteria. *Clinical journal of sport medicine : official journal of the Canadian Academy of Sport Medicine.* Mar 2009;19(2):83-89.

143. Viskontas DG, MacDermid JC, Drosdowech DS, Garvin GJ, Romano WM, Faber KJ. Reliability and comparison of acromion assessment techniques on X-ray and magnetic resonance imaging (reliability of acromion assessment techniques). *Canadian Association of Radiologists journal = Journal l'Association canadienne des radiologistes.* Oct 2005;56(4):238-244.

144. Banas MP, Miller RJ, Totterman S. Relationship between the lateral acromion angle and rotator cuff disease. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* Nov-Dec 1995;4(6):454-461.

145. MacGillivray JD, Fealy S, Potter HG, O'Brien SJ. Multiplanar analysis of acromion morphology. *Am J Sports Med.* Nov-Dec 1998;26(6):836-840.

146. Day BH, Govindasamy N, Patnaik R. Corticosteroid injections in the treatment of tennis elbow. *The Practitioner.* Mar 1978;220(1317):459-462.

147. Hay EM, Paterson SM, Lewis M, Hosie G, Croft P. Pragmatic randomised controlled trial of local corticosteroid injection and naproxen for treatment of lateral epicondylitis of elbow in primary care. *BMJ.* Oct 9 1999;319(7215):964-968.

148. Smidt N, Assendelft WJ, van der Windt DA, Hay EM, Buchbinder R, Bouter LM. Corticosteroid injections for lateral epicondylitis: a systematic review. *Pain.* Mar 2002;96(1-2):23-40.

149. Arroll B, Goodyear-Smith F. Corticosteroid injections for painful shoulder: a meta-analysis. *The British journal of general practice : the journal of the Royal College of General Practitioners.* Mar 2005;55(512):224-228.

150. Naredo E, Cabero F, Beneyto P, et al. A randomized comparative study of short term response to blind injection versus sonographic-guided injection of local corticosteroids in patients with painful shoulder. *The Journal of rheumatology.* Feb 2004;31(2):308-314.

151. Chen MJ, Lew HL, Hsu TC, et al. Ultrasound-guided shoulder injections in the treatment of subacromial bursitis. *American journal of physical medicine & rehabilitation / Association of Academic Physiatrists.* Jan 2006;85(1):31-35.

152. Mei-Dan O, Carmont MR. The role of platelet-rich plasma in rotator cuff repair. *Sports medicine and arthroscopy review.* Sep 2011;19(3):244-250.

153. de Vos RJ, van Veldhoven PL, Moen MH, Weir A, Tol JL, Maffulli N. Autologous growth factor injections in chronic tendinopathy: a systematic review. *British medical bulletin.* 2010;95:63-77.

154. Schnabel LV, Mohammed HO, Miller BJ, et al. Platelet rich plasma (PRP) enhances anabolic gene expression patterns in flexor digitorum superficialis tendons. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society.* Feb 2007;25(2):230-240.

155. Sanchez M, Anitua E, Azofra J, Andia I, Padilla S, Mujika I. Comparison of surgically repaired Achilles tendon tears using platelet-rich fibrin matrices. *Am J Sports Med.* Feb 2007;35(2):245-251.

156. De Mos M, Van der Windt A, Jahr H, et al. Can platelet rich plasma enhance tendon repair? A cell culture study. *Am J Sports Med.* 2008;36:1171–1178.

157. Anitua E, Andia I, Sanchez M, et al. Autologous preparations rich in growth factors promote proliferation and induce VEGF and HGF production by human tendon cells in culture. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society.* Mar 2005;23(2):281-286.

158. de Mos M, van der Windt A, Jahr H, et al. Can platelet-rich plasma enhance tendon repair? A cell culture study. *Am J Sports Med.* 2008;36(6):1171-1178.

159. Zhang J, Wang JH. Platelet-rich plasma releasate promotes differentiation of tendon stem cells into active tenocytes. *Am J Sports Med.* Dec 2010;38(12):2477-2486.

160. Fufa D, Shealy B, Jacobson M, Kevy S, Murray MM. Activation of platelet-rich plasma using soluble type I collagen. *Journal of oral and maxillofacial surgery : official journal of the American Association of Oral and Maxillofacial Surgeons.* Apr 2008;66(4):684-690.

161. Bishop J, Klepps S, Lo IK, Bird J, Gladstone JN, Flatow EL. Cuff integrity after arthroscopic versus open rotator cuff repair: a prospective study. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* May-Jun 2006;15(3):290-299.

162. Bjornsson HC, Norlin R, Johansson K, Adolfsson LE. The influence of age, delay of repair, and tendon involvement in acute rotator cuff tears: structural and clinical outcomes after repair of 42 shoulders. *Acta orthopaedica.* Apr 2011;82(2):187-192.

163. Thomopoulos S, Das R, Birman V, et al. Fibrocartilage tissue engineering: the role of the stress environment on cell morphology and matrix expression. *Tissue engineering. Part A.* Apr 2011; 17(7-8):1039-1053.

164. Garofalo R, Cesari E, Vinci E, Castagna A. Role of metalloproteinases in rotator cuff tear. *Sports medicine and arthroscopy review.* Sep 2011;19(3):207-212.

165. Gulotta LV, Rodeo SA. Growth factors for rotator cuff repair. *Clinics in sports medicine.* Jan 2009;28(1):13-23.

166. Archambault JM, Jelinsky SA, Lake SP, Hill AA, Glaser DL, Soslowsky LJ. Rat supraspinatus tendon expresses cartilage markers with overuse. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society.* May 2007;25(5):617-624.

167. Jones GC, Corps AN, Pennington CJ, et al. Expression profiling of metalloproteinases and tissue inhibitors of metalloproteinases in normal and degenerate human achilles tendon. *Arthritis Rheum.* Mar 2006;54(3):832-842.

168. Lian O, Scott A, Engebretsen L, Bahr R, Duronio V, Khan K. Excessive apoptosis in patellar tendinopathy in athletes. *Am J Sports Med.* Apr 2007;35(4):605-611.

169. Longo UG, Franceschi F, Ruzzini L, et al. Light microscopic histology of supraspinatus tendon ruptures. *Knee surgery, sports traumatology, arthroscopy : official journal of the ESSKA.* Nov 2007;15(11):1390-1394.

170. Scott A, Cook JL, Hart DA, Walker DC, Duronio V, Khan KM. Tenocyte responses to mechanical loading in vivo: a role for local insulin-like growth factor 1 signaling in early tendinosis in rats. *Arthritis Rheum.* Mar 2007;56(3):871-881.

171. Scott A, Khan KM, Duronio V. IGF-I activates PKB and prevents anoxic apoptosis in Achilles tendon cells. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society.* Sep 2005;23(5):1219-1225.

172. Szomor ZL, Appleyard RC, Murrell GA. Overexpression of nitric oxide synthases in tendon overuse. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society.* Jan 2006;24(1):80-86.

173. Yuan J, Murrell GA, Wei AQ, Wang MX. Apoptosis in rotator cuff tendonopathy. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society.* Nov 2002;20(6):1372-1379.