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ABSTRACT

Purpose: A review was conducted to synthesise the available research literature on the pathogenesis of rotator cuff tendinopathy.

Relevance: Musculoskeletal disorders of the shoulder are extremely common, with reports of prevalence ranging from one in three people experiencing shoulder pain at some stage of their lives to approximately half the population experiencing at least one episode of shoulder pain annually. Pathology of the soft tissues of the shoulder, including the musculotendinous rotator cuff and subacromial bursa, is a principal cause of pain and suffering.

Conclusions: The pathoaetiology of rotator cuff failure is multifactorial and results from a combination of intrinsic, extrinsic and environmental factors. The specialised morphology of the rotator cuff, together with the effects of stress shielding, may contribute to the development of rotator cuff tendinopathy. Profound changes within the subacromial bursa are strongly related to the pathology and resulting symptoms. A considerable body of research is necessary to more fully understand the aetiology and pathohistology of rotator cuff tendinopathy and its relationship with bursal pathology. Once this knowledge exists more effective management will become available.

Musculoskeletal disorders of the shoulder are extremely common, with reports of prevalence ranging from one in three people experiencing shoulder pain at some stage of their lives[1] to approximately half the population experiencing at least one episode of shoulder pain annually.[2] The incidence of shoulder pain increases substantially with age, and for people over 65 years of age shoulder pain is the most common musculoskeletal problem.[3] As the shoulder is primarily used to place the hand in space, pain in this region adversely affects daily living and work and causes substantial morbidity. Pain is the most common complaint for patients with shoulder problems, and pain leads to a reduction in shoulder strength (pain inhibition) and functional impairment. The musculotendinous rotator cuff and subacromial bursa are considered to be the principal pain-producing structures.

THE SUBACROMIAL BURSA

Bursae are comprised of fibrous, areolar and adipose tissue as well as synovial cells. They function primarily to reduce friction during movement. Approximately seven to eight bursae have been identified around the shoulder.[4] The subacromial bursa (SAB), the largest bursa in the body, separates the coracoacromial arch and deltoid above and the rotator cuff tendons below, and acts to reduce friction during shoulder movement. The SAB is innervated by the suprascapular nerve posteriorly and by the lateral pectoral nerve anteriorly (C5, 6),[5] providing proprioception and nociception (free nerve endings Aδ and C) to the bursa.[6] The SAB also has an unspecified contribution to the kinaesthetic sense and mechanoreception of the shoulder. Ide *et al*[6] identified pressure-sensitive Pacinian corpuscles and Ruffini endings (mechanical and pressure-sensitive) in the SAB adjacent to the coracoacromial ligament. The presence of pressure detectors under the coracoacromial ligament suggests that a reflex system involving the rotator cuff may control displacement of the humeral head.

There appears to be a strongly positive correlation between the experience of shoulder pain and the amount of proinflammatory and pain chemicals as well as cytokines in bursal tissue. Patients with mechanical shoulder pain exacerbated by shoulder elevation have been shown to have high concentrations of inflammatory, pain-mediating and matrix-modifying proteins in the bursa which may have a catabolic effect on collagen.[7–15] For example, Gotoh *et al*[8] demonstrated a positive correlation between the concentration of the neuropeptide substance P in the bursa and pain.

Clinical studies highlight the relevance of the bursa in shoulder pain. Postsurgical outcomes were similar when a bursectomy was performed with or without an acromioplasty,[16] which challenges the importance of removing the acromion to alleviate shoulder pain. Similarly, both posterior and lateral approach injections relieved pain,[17] but only those injections that reached the bursa reduced pain,[18] while injections targeting other structures increased or did not change pain. This may be a reason why ultrasound-guided injections appear to produce better outcomes than non-guided injections.[19 20] However, the science supporting the use of injection therapy is not robust and requires ongoing investigation.

Several studies have reported no difference between injections of analgesic and combination analgesic and steroid injections,[21 22] whereas others have reported definite benefit with steroid injections.[23] These equivocal findings may relate to different histological findings from different subgroups of patients. No classic inflammatory cells were identified by Sarkar and Uhthoff[24] in a sample of bursal tissue from patients having surgery for rotator cuff disease. However, Santavirta *et al*[25] reported that inflammatory cells were found in bursal tissue in patients who were experiencing constant shoulder pain and night pain, whereas no inflammatory cells were found in those with pain only on movement. This suggests that different injection care pathways for different clinical presentations may be required.

Further work is essential to understand the histological and biochemical nature of bursal

pathology and pain and the relationship between bursal pathology, tendon pathology and shoulder pain.

THE ROTATOR CUFF

The rotator cuff comprises the supraspinatus, subscapularis, infraspinatus and teres minor tendons. They originate from the superior, anterior and posterior aspects of the scapula, respectively, and form a confluent aponeurotic tendon that surrounds the humeral head and contributes to movement, stability and sensory motor control of the glenohumeral joint.[26–29]

Structurally, the rotator cuff insertion onto the humeral tuberosities is broad, continuous, multilayered and interwoven[30] and tightly adherent to the glenohumeral joint capsule near their insertions onto the humeral tuberosities.[31] The supraspinatus and infraspinatus fuse 15 mm proximal to their insertions and the teres minor and infraspinatus are inseparable just proximal to their musculotendinous junctions. The supraspinatus and subscapularis fuse to form a tunnel for the biceps tendon at the proximal end of the bicipital groove. This structure improves the rotator cuff's resistance to failure, as load in any one musculotendinous unit is distributed over a wide area.[30 32]

The contribution of the rotator cuff to glenohumeral movement is unclear, as is the relative contribution of deltoid and supraspinatus to abduction of the glenohumeral joint. Temporary paralysis of the left deltoid and right supraspinatus in 10 young healthy men resulted in a 50% reduction in abduction torque in both shoulders, suggesting an equal contribution from both muscles;[33] however, a suprascapular nerve block would also influence the infraspinatus, which has also been shown to contribute to abduction torque.[28] Cadaver research suggests that deltoid produces more abduction torque than supraspinatus[28] and the moment arm of supraspinatus suggests it is more important than deltoid for initiating abduction, with its abduction moment peaking at 30°.[34]

ROTATOR CUFF TENDON STRUCTURE

The structure of the supraspinatus tendon is unique. The tendon is made up of between six and nine structurally independent parallel fascicles.[30 35] The fascicles are separated by endotendon and appear to contain seams of proteoglycan (possibly hyaluronic acid), which may act as a lubricant to facilitate independent sliding of individual fascicles.[35 36] This has important clinical relevance as the rotator cuff tendons are required to move through a wider range of movement than any other tendon in the body. During movement part of the tendon may be "stretched" and the opposite side may be "compressed". For example, during the movement from adduction with the arm by the side of the body to full abduction the joint-side fibres of the supraspinatus become relatively "elongated" and the bursal-side fibres "shortened". This asynchronous movement may contribute to shear stress within the tendon and predispose to pathology.

Tendons are comprised primarily of water (55% by weight) and collagen. The major collagen in normal tendon is type I, with smaller amounts of other collagens, proteoglycans, blood vessels and cells (fibroblasts/tenocytes). The cells produce the collagen and other extracellular matrix proteins. Total collagen content of the supraspinatus has been reported not to vary significantly with age, gender or location within the tendon.[37]

Proteoglycans are hydrophilic and are made up of a protein core and at least one polysaccharide (glycosaminoglycan) chain. Berenson *et al*[36] reported that the proteoglycan content of the rotator cuff taken from "normal" adult cadavers demonstrated high concentrations of the proteoglycans: aggrecan, decorin and biglygan. In comparison, only decorin was found in the distal tensional aspect of the biceps brachii tendon in the same subjects. The proteoglycan content of the rotator cuff was similar to fibrocartilage levels in tendons subjected to compressive loads, suggesting that adult rotator cuff has adapted to compressive loads and not only to tensional loading.

Fibrocartilage is also found at tendon attachment to bone and is typically 0.5 to 0.7 mm long,[32 38] but is uncharacteristically long (20 mm) in the supraspinatus tendon. Fibrocartilage has been reported in the area of the "critical zone" described by Codman,[39] which is a common location of structural degeneration and tears.

Normal tendon tissue undergoes continual remodelling (degradation and rebuilding). It is thought that this process is mediated by matrix metalloproteinases (MMPs) and their inhibitors (TIMPs). Highly stressed tendons, such as the supraspinatus, demonstrate higher levels of matrix remodelling proteins than those under less stress.[40 41] Gotoh *et al*[42] reported high concentrations of MMP1 in patients with both partial and full-thickness rotator cuff tears and proposed that MMP1 might play a role in the pathogenesis of a rotator cuff tear. This finding was not supported by Tillander *et al*,[43] who did not report increased concentrations of MMP1 in patients with subacromial impingement and supraspinatus tendon rupture. The expression of MMP3, TIMP2 and TIMP3 is decreased in torn rotator cuff tendons[44] and, as MMP3 potentially plays a major role in maintenance and remodelling of normal tendon,[41 45] the decreased expression may contribute to tendon degeneration.

The vascularity of the supraspinatus tendon and the changes associated with ageing have been the focus of research for over three-quarters of a century, but it has still not been determined whether vascular changes occur, vary with ageing or are associated with rotator cuff pathology. Lindblom[46] was the first to demonstrate areas of avascularity near the insertion of the supraspinatus, which corresponded with the area that Codman[39] believed to be the "critical portion" of the tendon approximately 1 cm from its insertion. This area was susceptible to calcification and degeneration.

Since then studies using a variety of techniques have produced a range of findings:

- Moseley and Goldie[47] did not find an area of reduced vascularity, and perfusion was not reduced with age.
- Clark and Harryman[30] also reported that the vascular pattern observed within the rotator cuff tissue did not appear to change with age.
- Rothman and Parke[48] described a hypovascular area in 63% of subjects just proximal to the insertion of the tendon, but were unable to determine whether a correlation with ageing existed.
- Rathbun and Macnab[49] argued that a zone of relative avascularity was present when the blood vessels were filled with the arm in adduction. When the arm was abducted no avascular area was evident.
- Loehr and Uhthoff[50] described a hypovascular area close to the insertion of the supraspinatus tendon and reported that the hypovascular zone was more prominent on the articular side of the tendon and that size varied among the specimens independent of age.
- Swiontowski *et al*[51] showed that the majority of patients with partial thickness tears demonstrated high blood flow rates in the "critical zone".

- Fukada *et al*[52] reported that bursal-side rotator cuff tears were found to be hypervascular in the distal portion of the tear and hypovascular proximally.
- Biberthaler *et al*[53] reported that capillary density and blood flow were significantly reduced by approximately 80% in degenerative rotator cuff disease.
- Matthews *et al*[54] revealed an increase in blood vessels associated with the small tears, and a decrease in blood vessels together with increased degeneration associated with the larger tears. There was no correlation between the size of the tears and age or duration of symptoms.

Areas of avascularity appear to occur around the margins of rotator cuff tears, especially if tears are large. These findings have important implications for management, as the absence of inflammatory cells and the extent of the degeneration in larger tears suggest that they may never heal and current surgical practice for this group of patients may be unwarranted. Further research is required to enhance understanding of the influence of ageing, biomechanical considerations and pathological variations within different regions of the rotator cuff.

ROTATOR CUFF TENDINOPATHY

Tendinopathy is a generic term without aetiological, biochemical or histological implications and is used to describe pathology in, and pain arising from, a tendon. The theories of the pathogenesis of rotator cuff tendinopathy may be divided into extrinsic and intrinsic causes and combinations of both.

Intrinsic theories

Intrinsic tendinopathy is defined as tendon pathology that originates within the tendon, usually as a consequence of overuse or overload (including compression). Increases and changes in collagen, proteoglycans, vascularity and cells have been described in tendon pathology. Hashimoto *et al*[55] identified diffuse degenerative changes within rotator cuff tendons that included tendon thinning, fibre disorientation, degeneration, calcification, fatty infiltration and vascular proliferation. With the exception of fat infiltration and neovascularisation, the changes were more pronounced in the middle and deeper tendon layers. In painful and degenerate rotator cuff, increases in type III collagen were found,[37] which could reduce the strength of the tendon tissue. Amyloid deposits within the rotator cuff have been observed, suggesting irreversible structural change.[56]

Evidence suggests that intrinsic degeneration within the rotator cuff is the principal factor in the pathogenesis of rotator cuff tears.[55] Soslowsky *et al*[57] compared the supraspinatus tendon at 4, 8 and 16 weeks in control rats with rats subject to an overuse running programme. The running rats had similar changes to those observed in human tendinopathy at all time stages, namely: increase in the number of tendon cells with a more rounded appearance, a loss of the normal tendon fibre organisation, and a weakening of the tendon tissue. Perry *et al*[58] used a similar model and reported high concentrations of vascular endothelial growth factor, which is involved in the formation and growth of new blood vessels. Inflammatory markers were increased in the experimental animals, suggesting that inflammatory mediators are present in overuse tendon pathology.[58]

The issue of tendon inflammation is contentious and the evidence for the presence of cells classically associated with inflammation is not robust. Fukuda *et al*[52] reported no infiltrations of cells classically associated with inflammation in rotator cuff tendon pathology. Similarly, Sarkar and Uhthoff[24] reported no inflammatory cells in bursal specimens taken during surgery for rotator cuff tendinopathy. Bursal specimens taken from patients with constant shoulder pain were reported as having inflammatory cell infiltration whereas those with pain only on movement did not.[25] These findings are similar to findings from other tendon studies[59–63] and the role of inflammation in tendon pathology is unclear.

The movement of the subunits of the rotator cuff tendons[35] will subject the tendon to internal compressive forces,[64] and fibrocartilage develops in these regions.[64] Fibrocartilage in the supraspinatus tendon close to its insertion occurs predominantly on the articular side of the tendon.[65–67] Changes on the articular side of the tendon are not unique to the supraspinatus and have been reported in the extensor carpi radialis brevis[68] and at the Achilles insertion into the calcaneus.[69] Articular-side fibres are reported to be subject to less strain than the non-articular side and this has been termed stress shielding.[70] In the supraspinatus less relative strain occurs on the articular side compared with the superior aspect of the tendon during glenohumeral abduction.[71]

Fibrocartilage is less capable than tendon of withstanding tensional load. In the supraspinatus, Nakajima *et al*[72] identified tendon fibres of a smaller cross-sectional area on the articular side compared with the superior bursal-side fibres, which had a reduced ability to withstand strain. The two different sections of the tendon were stretched to the point of rupture and the joint-side fibres ruptured with half the force required for the bursal-side fibres. Similarly, Bey *et al*[71] reported significantly higher levels of strain in the joint-side fibres of the tendon at 60° abduction than at 15° and 30° abduction. Reilly *et al*[73] clearly demonstrated differences in strain between the bursal and joint sides of the tendon, suggesting that higher strain occurred in the fibres on the joint side of the tendon. Thus differences in mechanical stress may contribute to tendon failure.

Burkhart *et al*[74] have described the presence of the rotator cable and crescent near the insertion of the rotator cuff onto the humerus. The supraspinatus and infraspinatus tendons insert into the cable, which is located approximately 1.5 cm from the insertion of the fibres into the humerus. The cable lies at 90° to the long axis of the tendon fibres. Between the cable and the humerus are the thinner and structurally weaker insertional fibres of the tendons, known as the rotator crescent. This cable is much thicker (4.7 mm) than the crescent (1.8 mm). The thinner crescent is located within the hypovascular region (critical zone) described by Codman.[39] The muscle and tendon fibres medial to the cable may act through the cable to produce humeral movement, and by doing so the cable may stress-shield the crescent tissues. Due to the function of the cable, the rotator crescent tissues are relatively underloaded and potentially more prone to degeneration and tearing.

The body of available evidence suggests that the pathoaetiology of rotator cuff tendinopathy is multifactorial. Overuse, where the physiological limit of the tendon unit is surpassed, results in pain, weakness and structural failure. In addition, the pathoaetiology conceivably occurs primarily as a result of intrinsic failure in the articular-side fibres of the tendon, possibly due to a combination of stress shielding and internal compression in this region. The decreased function in the rotator cuff may lead to superior translation of the humeral head and irritation of bursal tissue, increasing the strain on the coracoacromial ligament and the acromion. As such, extrinsic impingement from the coracoacromial ligament and acromion may be a secondary phenomenon.

Extrinsic theories

Neer[75 76] argued that 95% of all rotator cuff pathology was caused by irritation from the anteroinferior aspect of the acromion onto the superior aspect of the rotator cuff. Neer argued that if conservative treatments, such as anti-inflammatory medications and injections and physiotherapy, did not alleviate the symptoms then removal of the anteroinferior aspect of the acromion (acromioplasty) was necessary. Although acromioplasty has become one of the most common surgical procedures performed on the shoulder,[77] recent evidence questions the involvement of the acromion in the development of rotator cuff tendinopathy.[78 79] Gill *et al*[79] reported that no significant association existed between acromial morphology and rotator cuff pathology in older patients, and Worland *et al*[78] demonstrated acromial osteophytes and spurs in people without symptoms.

Success rates of 80–90% following subacromial decompression for impingement have been reported.[80–83] When acromioplasty was compared with conservative care (physiotherapy exercises and pain relief), surgery appeared to be no more beneficial clinically at 6, 12 or 48 months.[84–86] Improvement reported in the surgical studies may be due either to the procedure or to the extensive period of relative rest and reduction in activity following the procedure. There is also the distinct possibility that the operation itself is a placebo or that the benefit is related more to the removal of the bursa than the acromion.[13 16 87–89]

The questionable benefit of performing an acromioplasty as part of arthroscopic repair of the rotator cuff also exists.[90] Hyvonen *et al*[91] reported that acromioplasty does not prevent the progression of impingement syndrome to a rotator cuff tear. After open acromioplasty, 14 shoulders that were symptom-free following the surgical procedure had all become painful and demonstrated signs of rotator cuff degeneration after 5 years. Of these, six had complete tears and four had partial thickness tears of the rotator cuff. This suggests that removal of the anteroinferior aspect of the acromion[75 76] has questionable long-term benefit.

Neer[75 76] argued that, in addition to the acromion, the coracoacromial ligament may contribute to external impingement. Sarkar *et al*[92] disputed this and proposed that changes seen in the ligament (fatty deposits and a high level of matrix metabolic activity) were induced by chronic strain in the ligament from volume changes in the tendons. Edelson and Taitz[93] reported that traction spurs were seen at the insertion of the coracoacromial ligament in 18% of 200 acromion specimens with no changes on the corresponding coracoid process. The spurs may have been isolated to the acromion because the coracoid process has a greater area of insertion to distribute the tensile forces.

Free nerve endings and neovascularity have been identified in the coracoacromial ligament of subjects with clinically diagnosed subacromial impingement syndrome when compared with subjects undergoing anterior shoulder stabilisation procedures.[94] These changes may have occurred as a result of chronic strain and suggest that the ligament itself may be a source of symptoms. As resection of the coracoacromial ligament may have a deleterious effect on glenohumeral biomechanics, leading to superior subluxation of the humeral head,[95–97] alternative means of assessing the contribution of the ligament to pain and identifying new treatments are required. Acromioplasty and the subsequent anterosuperior translation of the humeral head following the procedure[98 99] may contribute to increased strain in the coracoacromial ligament.

Mechanical abrasion from the under surface of the acromion or coracoacromial ligament should result in abrasion to the superior (bursal-side) surface of the rotator cuff; however, this is not found during surgery. Two studies have shown that the majority of partial-thickness tears were intrasubstance or joint-side tendon tears and not on the upper bursal side of the tendon adjacent to the acromion.[65 66]

The bias toward joint-side rotator cuff pathology has led a number of investigators to conclude that acromially initiated rotator cuff pathology does not occur,[100–104] arguing that extrinsic impingement (and not intrinsic failure) causes pathology on the articular side of the tendon. This model of impingement is known as internal impingement or superior and posterosuperior impingement, reflecting the belief that the rotator cuff is mechanically damaged by compression between different parts of the superior aspect of the glenoid fossa and the greater tuberosity of the humerus.[104] Although the concept of internal impingement has gained clinical acceptance, substantial ongoing biomechanical, laboratory, imaging and clinical research is required.

Superior translation of the humeral head on the glenoid fossa is observed in patients with subacromial impingement syndrome and rotator cuff pathology,[105 106] and may be due to a combination of degeneration and tearing of the superior structures (supraspinatus) and failure of the inferior components (infraspinatus, subscapularis and teres minor) of the rotator cuff. Thompson *et al*[107] reported that deficiency of the inferior components of the rotator cuff led to superior translation of the humeral head at the initiation of glenohumeral abduction. Wuelker *et al*[108] concluded that the inferior components of the rotator cuff counteract the tendency of the deltoid and the supraspinatus to superiorly translate the humerus and thus reduce subacromial pressure. Subacromial pressure varies with arm position, and maximal subacromial pressure (66.9 mmHg) was reported at 90° abduction, with slightly less pressure recorded at 90° flexion (61.1 mmHg). Subacromial pressure was more than three times greater in shoulder internal rotation (35.6 mmHg) than in external rotation (13.7 mmHg), which was less than the pressure with the arm by the side (17.5 mmHg).[109] These findings question the appropriateness of the simultaneous prescription of both internal and external rotation exercise for patients with a diagnosis of rotator cuff tendinopathy or impingement.

Combining extrinsic and intrinsic theories

The rat shoulder has been used to study the role of extrinsic and intrinsic rotator cuff pathology,[57 58] as well as combinations of both.[57 110] Soslowsky *et al*,[111] utilising earlier data, investigated the effect of extrinsic compression (Achilles tendon allografts wrapped around the left acromion), intrinsic overload using downhill eccentric running or a combination of the two in rats at 4 weeks, 8 weeks and 16 weeks.

Extrinsic compression alone did not produce a tendinopathy. However, rats subject to overuse (running) demonstrated an increase in cross-sectional area and reduced maximal strain at all time points. The greatest change was found in the combined overuse/extrinsic compressions group, suggesting that compression potentiated overload even though compression alone did not produce pathology. The application of this finding may be that an acromial spur is insufficient to cause pathology unless there is a concomitant history of tendon overload. Direct translation of results from animal studies to the human shoulder is difficult because of the difference in human and animal shoulder architecture and biomechanical properties.

What is already known on this topic

Rotator cuff tendinopathy is common and associated with substantial morbidity. Conflicting theories pertaining to the pathogenesis of rotator cuff tendinopathy and bursal pathology exist.

What this study adds

A review is presented attempting to synthesise existing knowledge and highlight areas of deficiency in our understanding of the pathoaetiology of rotator cuff tendinopathy.

CONCLUSION

The pathoaetiology of rotator cuff failure is multifactorial and results from a combination of intrinsic, extrinsic and environmental factors. The specialised morphology of the rotator cuff, together with the effects of stress shielding, may contribute to the development of rotator cuff tendinopathy. Acute and chronic tendon overload may also result in increased volume in the confined subacromial space, which may have a potentially catabolic effect on intratendinous and bursal homeostasis and may trigger the cascade of cytokines, neuropeptides and other chemicals that have been identified within the tendon and bursal tissue. Both tendon overloading and underloading will influence the balance of MMPs and TIMPs and have a detrimental effect on normal tendon remodelling. The tissues medial to the rotator cable may act through the cable to produce movement and the more lateral tissues of the rotator crescent may be stress-shielded, and this may be more pronounced in the articular-side fibres. A considerable body of research is necessary to more fully understand the aetiology and pathohistology of rotator cuff tendinopathy and its relationship with bursal pathology. Once this knowledge exists, more effective management will become available.

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