Rotator Cuff Related Shoulder Pain: An Update of Potential Pathoaetiological Factors

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ABSTRACT

Rotator cuff related shoulder pain (RCRSP) was a term proposed to replace scientifically outdated and potentially flawed diagnoses such as subacromial impingement syndrome, as well as uncertain pathoanatomical diagnoses such as rotator cuff tendinitis/tendinosis, and partial thickness and full thickness rotator cuff tears. RCRSP refers to the muscles, tendons, and surrounding structures, such as bursa, bone, ligament, capsule, nerve, and vascular tissue related to the entirety of the rotator cuff of the shoulder. It also recognises the complexity of evolving pain science. The term RCRSP acknowledges that the basis for presenting symptoms is mostly indeterminable and is used when a collection of clinical symptoms is present. RCRSP is probably the most common musculoskeletal shoulder condition and manifests as shoulder pain and weakness, most commonly during shoulder elevation and external rotation. Another important feature suggestive of RCRSP is a history of increased physiological load preceding the onset of symptoms, or a decreased ability to deal with physiological load due to lifestyle factors such as poor sleep, stress, reduced physical activity, uptake in or increased smoking, and poor nutrition. The aim of this narrative review is to discuss possible intrinsic (internal), extrinsic (external), and combined (intrinsic and extrinsic) mechanisms that may contribute to RCRSP. Our synthesis does not find definitive evidence for an extrinsic or combined extrinsic and intrinsic mechanism(s) that results in or is associated with RCRSP. We acknowledge that the narrative nature of this scholarly paper may have influenced our conclusions.

Lo, C. N., van Griensven, H. & Lewis, J. (2022). Rotator cuff related shoulder pain: An update of potential pathoaetiological factors. *New Zealand Journal of Physiotherapy, 50*(2), 82–93. https://doi.org/10.15619/NZJP/50.2.05

Key Words: Rotator Cuff Related Shoulder Pain, Combined, Extrinsic, Intrinsic, Pathoaetiology

INTRODUCTION

The term RCRSP was proposed to avoid uncertainties associated with scientifically outdated diagnoses such as subacromial impingement syndrome (SIS), and myriad pathoanatomical and potentially flawed clinical diagnoses such as bursitis and rotator cuff tears, and to help the patient make sense of their experience of shoulder pain and weakness (Lewis, 2016). A definitive diagnosis of RCRSP is not possible and it remains at best a clinical hypothesis. As such, following the physical assessment clinicians should inform patients that based on the interview and assessment it is likely that they have RCRSP, what this means, and what the management options are.

Another term that has emerged to replace SIS is subacromial pain syndrome (SPS). The use of this term is problematic as online searches (Google™, Google Scholar™) that may be conducted by patients and other interested people continue to associate this term with the outdated term SIS. SPS refers to an anatomical location that is not readily understood, and by definition excludes the acromion and the coracoacromial ligament (CAL) which may be directly related to symptoms (see below). In addition, the term subacromial has no appreciable lower border and is confusing and imprecise.

Diagnostic reductionists may argue that the term (non-specific) shoulder pain/strain is more appropriate than both RCRSP and SPS, analogous to use of the term 'non-specific low back pain' for symptoms experienced by people with lumbopelvic region pain. While there may be merit in this argument, we contend that it lacks utility both in clinical practice and for research purposes. Most people who seek care for musculoskeletal shoulder conditions present with varying combinations of shoulder pain, weakness, and loss of movement. It is the role of the clinician employing clinical reasoning skills (Jones et al., 2022) and working metaphorically as a clinical detective to make sense of the combination of symptoms. Although it is arguable that it would be clinically expedient to lump all presentations under the umbrella of (non-specific) shoulder pain, we contend this would be a retrograde step. For example, a clinician might categorise the following case presentations as non-specific shoulder pain.

- A 50-year-old woman presenting with Type 1 diabetes together with severe shoulder pain, a normal radiograph, painful shoulder weakness, and concomitant substantial loss of active and passive shoulder external range of movement.

- An 18-year-old gymnast whose current main complaint is shoulder pain, with minimal loss of movement and weakness, following multiple episodes of non-traumatic shoulder dislocations.

However, we suggest that it is clinically achievable and meaningful to subcategorise these different presentations. We hypothesise that the combination and manifestation of symptoms in the first scenario are likely to be related to a frozen shoulder, and in the second are likely related to an unstable shoulder. We contend that these subclassifications may benefit clinical practice by facilitating interventions specific to different conditions or unique stages of a condition, such as the painful and stiff phases of frozen shoulder (Lewis, 2015; Lewis, Boyd, et al., 2022). We also argue that subclassification is essential to support meaningful research investigations.

We suggest, for non-traumatic presentations, the following:

1. That clinical diagnoses are presented, whenever possible, using non-pathoanatomical labels. For example, to replace the terms SIS, and partial and full thickness rotator cuff tendon tears with RCRSP.
2. That clinicians consider using consistent language when presenting clinical findings to patients, e.g., "Based on our discussion and following the physical examination it is *likely* that you have rotator cuff related shoulder pain." The clinician can then discuss the role and function of the rotator cuff muscles, tendons, and related structures. This should be followed with a discussion of appropriate management options (potential harms, benefits, expected time frames, commitments, etc.), guided by shared decision making (Hoffmann et al., 2020; Jones et al., 2022).

People seeking care want to understand why they have shoulder pain (Lewis, 2016; Lewis & Powell, 2022). Understanding the possible cause(s) and/or reasons for their symptoms may help facilitate an understanding of why a specific management may be beneficial (Barber et al., 2022; Mantel, 2003; Maxwell et al., 2021; Plinsinga et al., 2021). Shared decision-making enables the clinician and patient to agree on management that is most appropriate for the patient (Hoffmann et al., 2020; Jones et al., 2022).

In summary, we contend that RCRSP is both a non-threatening and non-pathoanatomical term that may help patients make sense of their symptoms, while (non-specific) shoulder pain may not be. Furthermore, RCRSP refers to something tangible while SPS does not, and is better supported than a diagnosis such as SIS, which is arguably outdated and no longer supported by recent research (Lewis, 2018). Clinicians may hypothesise that RCRSP is present if evidence of increased load relative to load-bearing capacity (physical and/or lifestyle) is identified, and referred pain, shoulder instability, and shoulder stiffness are excluded as best as possible. Clinically, when bilateral muscle performance tests – isometric, repetitions to pain, repetitions to fatigue – are assessed, reduced performance on the side of symptoms is identified, most commonly (but not exclusively) in the directions of shoulder elevation and external rotation. The clinician could then inform the patient, "Based on our discussion and the findings of the clinical assessment it is *likely* that you have RCRSP. The rotator cuff are the muscles and tendons and surrounding structures that contribute to shoulder movement." This may facilitate a discussion about the management options for muscles, tendons, and related structures, within a shared decision-making model of care.

PATHOAETIOLOGY

The pathoaetiology associated with historic clinical antecedents to RCRSP (e.g., SIS, rotator cuff tendinitis) have been discussed in the literature for more than 150 years (Adams, 1852; Codman, 1934). Since the 1970s, mechanisms to explain the symptoms have been debated and have included external or extrinsic theories, internal or intrinsic theories, and combinations of external and internal theories. We present a summarised discourse of these theories in the following section.

Extrinsic or external models leading to pain and disability

Fifty years ago, Neer (1972) introduced the term SIS, proposing that acromial abrasion onto the underlying subacromial bursa and rotator cuff tendons lead to tendon damage and symptoms. In his seminal paper, Neer argued that 95% of RC pathology was caused by the impingement of the overlying acromion. Although Neer's model of pathology was never proven, supporters of the impingement model initially performed open and then arthroscopic surgery to remove the anterior aspect of the inferior of the acromion. Estimates of 19,743 acromioplasties were performed in New York State, US, in 2006 (Vitale et al., 2010) and 21,353 in England, UK, in 2010 (Judge et al., 2014), so it is conceivable that millions of people around the world have had their acromions resected since 1972.

These data are of concern as studies have demonstrated that this surgical procedure has no greater clinical benefit, when comparing bursectomy in isolation versus acromioplasty and bursectomy (Henkus et al., 2009; Kolk et al., 2017), comparing acromioplasty to procedures designated as surgical placebos (Beard et al., 2018; Lähdeoja et al., 2020; Paavola et al., 2018), and comparing rehabilitation with acromioplasty followed by rehabilitation (Lähdeoja et al., 2020; Lewis, 2022). Furthermore, no subgroup of people have been identified that will benefit from an acromioplasty (Ketola et al., 2015). After Neer (1972) proposed his theory and extended his original thoughts a decade later (Neer, 1983), others have endeavoured to further substantiate the extrinsic acromial intrinsic model. These have included acromial shape, scapula dyskinesis, and acromiohumeral distance. These, together with challenges to these theories, are presented in the following sections.

Acromial shape

Based on a study of 140 shoulders in 71 cadavers, Bigliani et al. (1986) suggested that the acromion has three distinct shapes: flat (type I), curved (type II), and hooked (type III). Biomechanically, the hooked shaped acromion was argued to lead to more damage, although this proposition has been challenged (Lewis, 2016, 2018; Lewis et al., 2001; Lewis et al., 2015; Lewis, 2009a, 2009b).

The *scapuloacromial angle* is used to quantify the acromion shape. The angle is formed between the inferior aspect of the acromion and the coracoid process (Moses et al., 2006). Moses et al. (2006) reported that the mean scapuloacromial angle

was 113–114° (*n* = 56). The angle was similar in people with RCRSP with or without RC tear, and in a group of people with glenohumeral instability (Moses et al., 2006). An association between acromial shape and full-thickness rotator cuff tendon tears may exist (Worland et al., 2003) but many of these tears are asymptomatic and may be part of normal ageing (Lewis, 2016; Lewis, 2009a; Maalouly et al., 2020; Worland et al., 2003).

The *critical shoulder angle* is the angle formed between the line connecting the inferior border of the glenoid with the most inferolateral point of the acromion and the line connecting the inferior with the superior border of the glenoid fossa (Moor et al., 2013). Björnsson Hallgren and Adolfsson (2021) did not find a correlation between the critical shoulder angle or the acromion index and the development of RC tears, or osteoarthritis, over a median 20-year period in people with unilateral shoulder pain. Furthermore, there were no radiological differences between the symptomatic shoulder and the contralateral side (Björnsson Hallgren & Adolfsson, 2021). Their findings challenged the reported aetiological association between acromial shape and the development of rotator cuff tears (Björnsson Hallgren & Adolfsson, 2021). No current research evidence has supported a causative relationship between acromial shape and RCRSP (Lewis, 2016; Lewis et al., 2015).

If correct, the acromial impingement theory should predict damage to the upper or superior (bursal) surface of the tendon (i.e., that part of the tendon that contacts the acromion), but this logical association does not appear to exist. In a study involving 43 athletes with partial-thickness RC tears, 39 (91%) had tears on the articular (joint) side, only 4 (9%) on the bursal side, and 100% of those with non-traumatic shoulder pain had articular side tears (Payne et al., 1997). In a study involving 249 cadavers, 13% (*n* = 33) had partial-thickness tears among whom 82% (*n* = 27) were either intra-tendinous or on the inferior surface and 28% (*n* = 6) were on the superior or bursal surface of the tendon (Fukuda, 2003). Sixty-nine partial-thickness tears mostly on the articular side of the tendon were observed in 200 shoulders from 100 cadavers (Ozaki et al., 1988). Another study of 306 cadaveric rotator cuff tendons showed that the prevalence of partial-thickness tears was 32%, and the majority were intra-tendinous or on the joint side of the tendon (Loehr & Uhthoff, 1987). Based on these consistent findings, partial thickness tears are principally intrasubstance or on the joint side of the tendon (see Figure 1). This directly challenges the validity of the acromial model of impingement. Further information is available (Lewis, 2016; Lewis, 2009a).

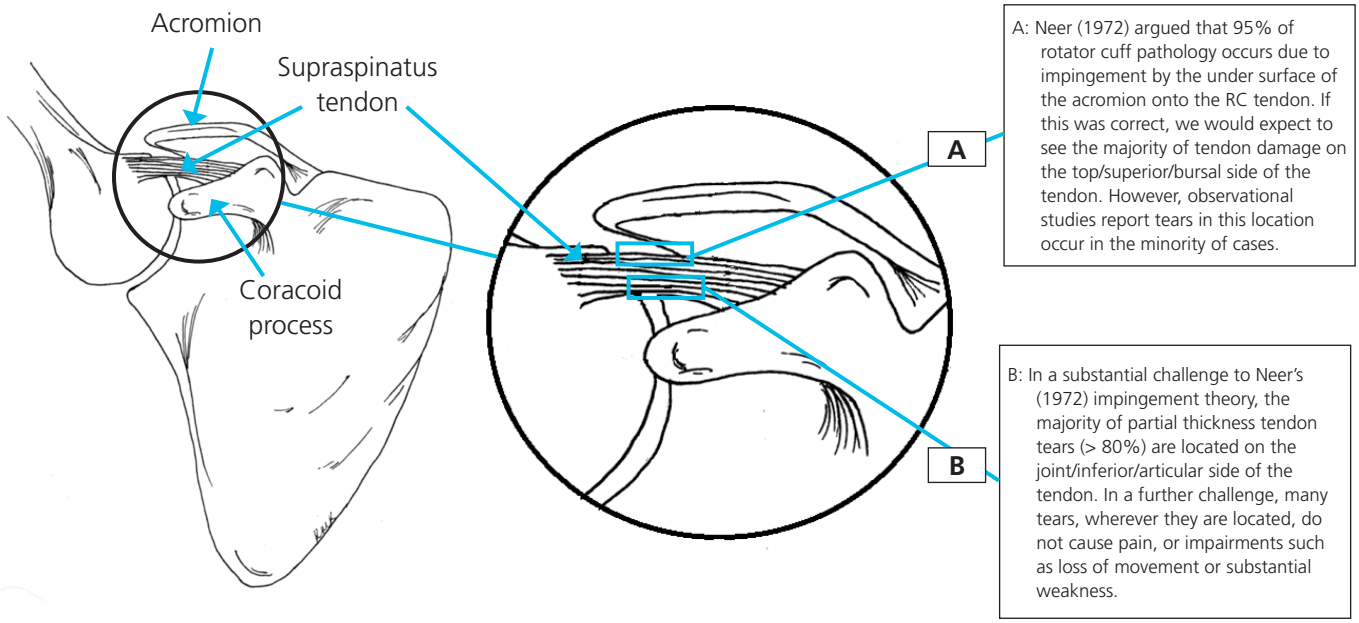
Scapular dyskinesis

Scapular dyskinesis refers to the deviation of the scapular position during shoulder movement (Kibler et al., 2012; Kibler & McMullen, 2003) and has been suggested as an extrinsic aetiological factor in the development of RCRSP (Hébert et al., 2002; Ludewig & Cook, 2000; McClure et al., 2006). Changes in the coordination of the scapular and humeral movements during shoulder elevation may affect the size of the subacromial space (Silva et al., 2010).

Although the reliability and validity of current scapular dyskinesis assessment is at best equivocal (D'Hondt et al., 2020; McClure et al., 2009; Plummer et al., 2017), it has been suggested as an extrinsic factor in the pathogenesis of RCRSP (Mackenzie et al., 2015; Seitz et al., 2011). Increased scapular upward rotation in the coronal plane during arm elevation in people with shoulder impingement syndrome has been reported (Finley et al., 2005;

Figure 1

Locations of Rotator Cuff Tendons Tears



McClure et al., 2006), but, in contrast, others have reported a decrease in scapular upward rotation (Ludewig & Cook, 2000; Su et al., 2004). In the transverse plane, studies have reported equivocal findings: increased scapular anterior tipping (Borstad & Ludewig, 2002), decreased posterior tipping (Lin et al., 2011; Lukasiewicz et al., 1999), and increased posterior tilting (McClure et al., 2006). Medial rotation of the scapula has been reported (Borstad & Ludewig, 2002; Hébert et al., 2002; Ludewig & Cook, 2000; Warner et al., 1992), but the results have not been duplicated in other kinematic studies (Finley et al., 2005; Lukasiewicz et al., 1999). This may, in part, be due to the many methodologies used to assess scapular position and movement.

Although scapular dyskinesis has been associated with RCRSP and is considered part of its pathogenesis, the patterns of dyskinesia vary remarkably between studies (Borstad & Ludewig, 2002; Finley et al., 2005; Hébert et al., 2002; Lin et al., 2011; Ludewig & Cook, 2000; Lukasiewicz et al., 1999; McClure et al., 2006; Su et al., 2004; Warner et al., 1992). Clearly, more research is warranted, and a causative relationship between scapular dyskinesis and RCRSP has not be established.

Reduction in the subacromial space distance

The subacromial space is the area between the inferolateral edge of the acromion and the apex of the greater tuberosity of humerus. It can be quantified by measuring the *acromiohumeral distance* (AHD) (Cholewinski et al., 2008; Desmeules et al., 2004; McCreesh et al., 2014; McCreesh et al., 2016; McCreesh et al., 2015). The mean AHD has been reported to be 9–11 mm (Flatow et al., 1994; Petersson & Redlund-Johnell, 1984). A reduction in AHD normally occurs during arm elevation (Flatow et al., 1994). Swelling of the rotator tendons may not directly cause a reduction in the AHD reduction but may increase the subacromial occupation ratio, which means the tendon occupies relatively more space within the AHD (McCreesh et al., 2017). Although the AHD may be decreased significantly in people with RCRSP (Leong et al., 2016; Maenhout et al., 2012), this observation does not appear to be consistent, as the AHD in people with RCRSP at rest or during shoulder abduction does not appear to be significantly different when compared to the AHD in people without symptoms (Desmeules et al., 2004; Kalra et al., 2010; McCreesh et al., 2017; Michener et al., 2015; Navarro-Ledesma et al., 2017; Savoie et al., 2015; Timmons et al., 2013).

Navarro-Ledesma et al. (2017) investigated 97 patients with RCRSP and found no significant correlation between AHD, shoulder pain, and disability index. Individuals with and without shoulder pain all had a significant decrease in AHD after exercise. However, only the symptomatic group showed a significant increase in rotator cuff tendon thickness (McCreesh et al., 2017). Although AHD is a two-dimensional measurement, a recent study (n = 52) demonstrated that AHD is significantly correlated (R = 0.61, p = 0.01) with the subacromial volume measured by magnetic resonance imaging (Kocadal et al., 2022). The results of this study align with that of McCreesh et al. (2017), and suggest that an increase in the rotator cuff tendon volume is a possible cause of the decrease in subacromial volume (Kocadal et al., 2022). Therefore, although a reduction of space between the acromion and humerus may not cause RCRSP, RCRSP may be associated with rotator cuff tendon swelling. This summary does not find definitive support for changes in AHD being associated with the symptoms associated with RCRSP.

Acromioclavicular osteophytes and the CAL

Osseous changes in the acromioclavicular joint and the CAL may be factors in RCRSP (Lewis et al., 2001; Mackenzie et al., 2015). Osteophytes in the acromioclavicular joint were reported to occur in 28.9% of individuals aged 15–100 years (n = 692 shoulders), and a strong correlation with increasing age (r = 0.65, $p < 0.001$) has been reported (Mahakkanukrauh & Surin, 2003). These results are consistent with those of clinical studies demonstrating that acromial bone spurs are significantly related to rotator cuff tears (Hamid et al., 2012; Ogawa et al., 2005; Oh et al., 2010; Sasiponganan et al., 2019). However, an acromial bone spur and rotator cuff tear may not have a cause-and-effect relationship but be normal age-related changes. Acromioplasty (removal of bone spurs) is not superior to an exercise programme without surgery or a placebo acromioplasty (Cheng et al., 2018; Lähdeoja et al., 2020; Lewis, 2016, 2018; Lewis, 2009a; Sun et al., 2018).

Degenerative changes in the CAL may be associated with symptoms for people with RCRSP. This ligament is typically under tension with the arm in a neutral position, and the tension increases (up to 38 N) during arm elevation (Chambler et al., 2003; Park et al., 2015; Yamamoto et al., 2010). A significantly greater displacement was observed in people with RCRSP (Wang et al., 2019; Wu et al., 2012; Wu et al., 2010). CAL samples from people with RCRSP taken at the time of subacromial decompression revealed free nerve endings and neovascularity (Tamai et al., 2000). These two findings suggest possible inflammation within the CAL that may be related to symptoms. Research is needed to better understand the relevance and relationship between the CAL and RCRSP.

In summary, although acromial spurs have been suggested as the major external cause of pathology in RCRSP, the available evidence does not support this hypothesis. The CAL may be associated with pain in people with RCRSP, but further research is needed. If a relationship does exist, it may not be external pressure from the CAL onto the tendon that leads to symptoms but from the underlying structures (such as tendon swelling) onto the CAL and changes within the CAL that are associated with symptoms in RCRSP. Currently, any relationship (associative or causative) is speculative and requires further research to support or refute the involvement of the CAL with RCRSP.

Intrinsic or internal models

The source of the symptoms

The evidence for an extrinsic or external pathoaetiological process leading to RCRSP is at best equivocal. Because of this, others have proposed an internal or intrinsic model as the basis for symptoms. The mechanisms causing pain are uncertain (Lewis, 2018, 2022; Lewis et al., 2015; Lewis, 2009a), although tendon (Littlewood, 2012) and bursal tissues (Gotoh et al., 1998; Henkus et al., 2009) are commonly considered. There is no definitive evidence that the basis for the pain is due to bursal or tendon-based nociception and as such symptomatic diagnoses such as rotator cuff tendinitis (tendon

inflammation), tendinosis (tendon degeneration), and even tendinopathy (source of the pain is the tendon but of unknown aetiology) cannot be made with certainty. Vascular, myofascial, neuropathic, and central pain mechanisms may also be involved (Dean & Griffin, 2022; Van Griensven et al., 2020; Vardeh et al., 2016; Worsfold et al., 2022). Collin et al. (2014) and Costouros et al. (2007) respectively reported that 12.2% (6/49) and 5.6% (14/216) of people with shoulder symptoms had neuropathy, as detected by electrodiagnostic studies. Neuropathic pain in RCRSP may be due to comorbidities such as brachial plexus injury or supraspinal nerve neuropathy in some cases (Collin et al., 2014; Lewis, McCreesh, et al., 2022; Shi et al., 2014). For those living with persistent RCRSP, Ngomo et al. (2015) and Berth et al. (2009) reported a significant decrease in the motor signal of the affected shoulder, in the brain. These changes were unrelated to the pain intensity ($r < 0.03$, $p = 0.43$), but rather to pain chronicity ($r = 0.45$, $p = 0.005$) (Ngomo et al., 2015).

Tissue overload

The primary hypothesis underpinning the intrinsic model is that an increased and uncharacteristic load, defined as when the physiological capacity of the muscle and tendon unit is exceeded, is the basis for symptoms (Lewis et al., 2015; Lewis, 2009a; McCreesh & Lewis, 2013). Proponents of the term RCRSP acknowledge that overload may be multidimensional (Lewis, 2016, 2022; Lewis, McCreesh, et al., 2022; Lewis et al., 2015) including biomechanical (Lewis & Whiteley, 2022), psychosocial (Chester et al., 2018; Chester et al., 2022), genetic (da Rocha Motta et al., 2014), age-related (Leong et al., 2019), and endocrine (e.g., diabetes) (Leong et al., 2019) factors, and may involve myriad lifestyle factors such as smoking, sleep disturbance, adiposity, inadequate nutrition (Burne et al., 2022), and systemic low-grade inflammation and metabolic syndrome (Burne et al., 2019; Burne et al., 2022).

The relationship between observable structural changes in the rotator cuff tendons such as tendinosis or tears via ultrasound, magnetic resonance imaging, and direct observation (arthroscopy) and symptoms in RCRSP remain at best equivocal (Lewis, 2016, 2022; Lewis et al., 2015; Lewis, 2009a; Lewis, 2011). This has led to the speculation that intrinsic biochemical changes within the tendon and surrounding structures may be related (associated or causative) to the symptoms people experience with RCRSP. This will be discussed in the following section.

Based on the observation of 268 and 180 people with RCRSP, respectively, Tsai et al. (2007) and Chillemi et al. (2016) reported a significant association between pain and subacromial bursa abnormalities, including hypertrophy, inflammation, oedema, and necrosis in patients with RCRSP. Tsai et al. (2007) reported a significant difference in the mean subacromial bursa thickness between painful (1.74 ± 0.41 mm) and asymptomatic (0.75 ± 0.23 mm) shoulders in patients with unilateral RCRSP. Chillemi et al. (2016) categorised patients with RCRSP into three groups according to their pain severity. The pain severity was significantly associated with hypertrophy/hyperplasia (Cramer's index $V = 0.80$, $p < 0.01$), presence of inflammatory cells ($V = 0.58$, $p < 0.001$), bursal oedema ($V = 0.40$, $p < 0.01$), and necrosis of the subacromial bursa ($V = 0.29$, $p = 0.03$). This suggests a relationship between inflammation in the subacromial bursa and RCRSP may exist. Nevertheless, the effectiveness of subacromial bursa-specific treatment is uncertain. Localised subacromial injection may provide short-term (< 3 months) pain relief for RCRSP (Mohamadi et al., 2017), but it remains unclear whether its effect is on the bursa, rotator cuff tendons, the CAL, other biological tissues, or contextual.

Sustained extracellular matrix (ECM) damage due to inflammation is a possible reason for pain and dysfunction in RCRSP. Upregulation of inflammatory cytokines and increased oxidative stress are potential factors associated with RCRSP and may hinder tissue repair (Blaine et al., 2011; Blaine et al., 2005; Ko et al., 2008; Lakemeier, Reichelt, et al., 2010; Lakemeier, Schwuchow, et al., 2010; Millar et al., 2016; Millar et al., 2009; Sakai et al., 2001; Savitskaya et al., 2011; Shindle et al., 2011; Voloshin et al., 2005; Wang et al., 2001; Yanagisawa et al., 2001).

Tendon cells, known as tenocytes, respond to mechano-transduction by communicating with neighbouring cells through cytokines and other immune mediators, such as tumour necrosis factor α (TNFα), transforming growth factor (TGF) β, and prostaglandin E2 (PGE2). *In vitro*, TNFα downregulates collagen expression and increases the production of adhesion molecules and pro-inflammatory cytokines such as interleukin (IL)-6, IL-8, and metalloproteinases (MMPs) gene expression in human tenocyte cultures (Al-Sadi et al., 2012; John et al., 2010). Mechanical shearing of the ECM triggers the release of TGFβ, which reduces the proliferation of tenocytes and collagen production. *In vivo* mechanical stress-induced tenocyte cell death releases high levels of TGFβ and IL-1β, which serve in a paracrine manner to trigger an anabolic response in adjacent tenocytes (Lavagnino et al., 2015). IL-33, an alarmin, is released following tendon tissue damage and activates the immune system. This regulates type I collagen production (Millar et al., 2015). Alarmin protein S100A9 is an endogenous molecule released from activated immune cells in response to persistent inflammatory diseases (Crowe et al., 2019). The levels of IL-33, alarmin proteins S100A9, and hypoxia-inducible factors (HIF)-1α had corresponding changes in painful and post-treatment pain-free human supraspinatus tendon (Millar et al., 2015; Mosca et al., 2017).

Results of RCRSP immune biomarker studies have shown an increase in inflammatory markers cyclooxygenase (COX)-1 and -2, TNFα, IL-1β, IL-6, HIFs, vascular endothelial growth factor (VEGF), and degenerative enzymes matrix MMP-1, -9, -13 in patients with RCRSP (Benson et al., 2010; Blaine et al., 2011; Castagna et al., 2013; Chaudhury et al., 2016; Dakin et al., 2015; Gotoh et al., 1999; Jacob et al., 2012; Lakemeier, Schwuchow, et al., 2010; Lo et al., 2004; Millar et al., 2016; Millar et al., 2015; Osawa et al., 2005; Riley et al., 2002; Sakai et al., 2001; Shindle et al., 2011; Voloshin et al., 2005; Yanagisawa et al., 2001).

IL-1β is involved in the inflammatory process in tendinopathies (Mobasheri & Shakibaei, 2013; Tang et al., 2018), and is an inflammatory mediator produced by leukocytes in the connective tissue. IL-1β triggers the release of various pro-inflammatory substances, including COX-1 and -2, PGE2,

and IL-6 (Tang et al., 2018; Tsuzaki et al., 2003). In tendon inflammation, IL-6 regulates the immune function for tendon healing by enhancing collagen synthesis (Andersen et al., 2011). Enzymes MMP-1, -3 and -13 are promoted by IL-1β (Sun et al., 2008), resulting in degenerative changes in tendons following inflammation. *In vivo* and *in vitro* studies have shown that the expression of IL-6 and COX-2 may be facilitated by mechanical strain (Legerlotz et al., 2012; Yang et al., 2005). IL-6 and COX-2 exhibit both pro- and anti-inflammatory effects depending on excessive or gradual loading (Langberg et al., 2003; Mobasheri & Shakibaei, 2013; Spiesz et al., 2015; Thorpe et al., 2015; Yang et al., 2005) and may account for the effectiveness of loading exercise as a treatment for pain and dysfunction in RCRSP.

Activated phagocytes, through the release of MMPs and the deposition of new collagen matrix, facilitate tissue repair via the release of cytokines, including IL-33 and S100A9 proteins as described above. The recruitment of monocytes and neutrophils is a highly coordinated process involving chemokines known as monocyte chemoattractant protein-1 (MCP-1) (Deshmane et al., 2009). Elevated levels of IL-1β, IL-6, IL-33, TNFα, and MMPs are commonly found in other rheumatic conditions, including osteoarthritis, rheumatoid arthritis, and spondyloarthritis (Hirohata & Kikuchi, 2012; Lo et al., 2004; Nishimoto, 2006; Zhao et al., 2013). Increasing evidence indicates that microtrauma to tendons might contribute to the progression of persistent inflammatory arthritis and increase mechanical sensitivity (Gracey et al., 2020; Steinmann et al., 2020). This may be of interest to clinicians in exploring the similarities of arthropathies with RCRSP. A summary of the biochemical studies' results and relevant new hypotheses regarding RCRSP is shown in Table 1.

Unsurprisingly, diabetes, smoking, infection, and persistent inflammation may adversely affect the repair process and prolong inflammation and pain in RCPSP (Burne et al., 2022). Several mechanically sensitive substances, including tenocytes, IL-6, and COX-2, may be involved in the pathophysiology of

Table 1

Summary of the Results of Biochemical Studies in RCRSP and Associated New Formulated Hypotheses

Mechanisms	Tendon physiology	Results of biochemical studies in RCRSP	New hypotheses according to these findings
Inflammatory	Tenocytes Comprise > 90% of cells in healthy tendons Detect mechanotransduction Maintain tendon homeostasis Excessive mechanical stress detected by tenocytes → ↑ TNFα → ↓ collagen expression + ↑ pro-inflammatory cytokine ILs and MMPs IL-1β → ↑ pro-inflammatory substances COX-1 and -2 → ↑ degenerative enzymes MMPs IL-6 → tendon healing by enhancing collagen synthesis	↑ COX-1 and -2 ↑ TNFα ↑ IL-1β, IL-6, ↑ HIFs, ↑ VEGF	↑ inflammatory cytokines (TNFα, IL-1β, VEFG, COX-1, -2) → ↑ oxidative stress on RC tissue (↑HIFs) ↓ tissue repair responses IL-6 and COX-2 exhibit both pro- and anti-inflammatory effects depending on mechanical loading on tissue: Excessive loading may lead to RC tissue inflammation Suitable loading (RC strength training) → regulate inflammation → reduce pain and improve function Need further research on the effect of exercise and changes in IL-6 and COX-2 levels in patients with RCRSP
Degenerative	MMPs are enzymes for tissue degradation MMPs are promoted by cytokines → IL-1β following the inflammation	↑ MMP-1, -9, -13	Enzymes MMPs promote structural degeneration in RC tendon → Tendon stiffness, decrease tensile strength → Traumatic RC tear ↑ IL-1β, IL-6, IL-33, TNFα, and MMPs are also common in other arthritic conditions including osteoarthritis, rheumatoid arthritis, and spondyloarthritis Similarities: Chronic inflammatory signs, stiffness, decreased structural strength (i.e., arthritis → joint deformities; RCRSP → RC tear)

Note. COX = cyclooxygenase; HIFs = hypoxia-inducible factors; IL = interleukin; MMP = matrix metalloproteinase; rotator cuff = rotator cuff; RCRPS = rotator cuff related pain syndrome; TNF = tumour necrosis factor; VEGF = vascular endothelial growth factor.

RCRSP (Costa-Almeida et al., 2019; Langberg et al., 2003; Mobasheri & Shakibaei, 2013; Pingel et al., 2014; Spiesz et al., 2015; Thorpe et al., 2015; Yang et al., 2005). The hypothesis of mechanically induced inflammation in RCRSP may be supported by specific acute RC tendon swelling (Kocadal et al., 2022; McCreesh et al., 2017).

Future research is needed to investigate if the cascade of biomarkers is related to symptoms in RCRSP and if interventions such as exercise and lifestyle management influence the presence of systemic and local biochemistry and impact on pain and related symptoms.

Combined extrinsic and intrinsic models

Seitz et al. (2011) summarised mechanisms that may contribute to RC tendinopathy and SIS, and suggested a combination of extrinsic and intrinsic factors. They suggested that extrinsic factors, such as acromial contiguity and tendon abrasion, and intrinsic factors, such as tendon degeneration, may co-exist, resulting in symptoms.

Seitz et al. (2011) suggested that internal impingement may be the mechanism leading to rotator cuff tendinopathy. Internal impingement was suggested to occur during shoulder abduction and external rotation when the joint (inferior) surface of the supraspinatus tendon becomes impinged between the greater tuberosity and the posterosuperior glenoid fossa. The certainty that this is a direct cause of symptoms remains equivocal and requires further research (Drakos et al., 2009; Lewis et al., 2001; Mackenzie et al., 2015).

The rat shoulder has been used to study the role of extrinsic, intrinsic, and combined rotator cuff pathology. Soslowsky et al. (2002) 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. No tendinopathy was observed in the extrinsic only group. The rats subjected to overload demonstrated an increase in tendon cross-sectional area and reduced maximal strain at all time points. The greatest change was found in the combined intrinsic/extrinsic group, suggesting that compression potentiated overload even though compression alone did not produce pathology.

The application of this finding may be that extrinsic factors, such as an acromial spur may not be sufficient to cause tendon pathology but overload in the presence of extrinsic factors may be the most provocative. However, these findings are problematic and there is no evidence for a relationship between the outcomes measured by Soslowsky et al. (2002) and pain. Furthermore, due to profound anatomical and biomechanical differences between the rat and human shoulder, direct translation would be arguably inappropriate (Lewis, 2009a). In summary, the evidence for a combined extrinsic and intrinsic model for RCRSP is at best uncertain.

CONCLUSION

In this scholarly review we have presented hypothesised mechanisms that may result in pain associated with RCRSP. We have discussed internal or intrinsic models, external or extrinsic models, and combined internal and external models. In addition to physiological overload, lifestyle factors such as stress, smoking, poor sleep, and high BMI may be associated with the pathogenesis and symptoms of RCRSP. Although a summary of findings may favour an internal mechanism, this is by no means certain. Substantial research is needed. One interesting finding is that biochemical imbalances may be an important consideration in the development of pathology and symptoms, and this too must be the focus of future investigations.

KEY POINTS

1. Rotator cuff related shoulder pain (RCRSP) is suggested as a clinical term to replace subacromial/shoulder impingement syndrome.
2. Current research evidence does not support an external (extrinsic) or combined extrinsic and internal mechanism for the pathogenesis of RCRSP.
3. A synthesis of the research supports intrinsic physiological factors in the pathogenesis of RCRSP, of which imbalances of biochemistry may play a role.

DISCLOSURES

No funding was received for this project. No competing interests are at stake and there is no conflict of interest with other people or organisations that could inappropriately influence or bias the content of the paper.

PERMISSIONS

Jeremy Lewis has granted permission for the use of Figure 1.

ACKNOWLEDGEMENTS

We thank Dr Pui Lam Bernard Leung (Singapore Institute of Technology) for his expertise in immunology and his help in writing the manuscript.

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