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Exercise for rotator cuff tendinopathy: Proposed mechanisms of recovery

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Abstract

Rotator cuff (RC) tendinopathy is a common recurrent cause of shoulder pain, and resistance exercise is the first-line recommended intervention. Proposed causal mechanisms of resistance exercise for patients with RC tendinopathy consist of four domains: tendon structure, neuromuscular factors, pain and sensorimotor processing, and psychosocial factors. Tendon structure plays a role in RC tendinopathy, with decreased stiffness, increased thickness, and collagen disorganization. Neuromuscular performance deficits of altered kinematics, muscle activation, and force are present in RC tendinopathy, but advanced methods of assessing muscle performance are needed to fully assess these factors. Psychological factors of depression, anxiety, pain catastrophizing, treatment expectations, and self-efficacy are present and predict patient-reported outcomes. Central nervous system dysfunctions also exist, specifically altered pain and sensorimotor processing. Resisted exercise may normalize these factors, but limited evidence exists to explain the relationship of the four proposed domains to trajectory of recovery and defining persistent deficits limiting outcomes. Clinicians and researchers can use this model to understand how exercise mediates change in patient outcomes, develop subgroups to deliver patient-specific approach for treatment and define metrics to track recovery over time. Supporting evidence is limited, indicating the need for future studies characterizing mechanisms of recovery with exercise for RC tendinopathy.

Keywords

rotator cuff, tendinopathy, resisted exercise, mechanisms

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Introduction

Rotator cuff (RC) tendinopathy is a common cause of musculoskeletal shoulder pain.[1,2] The prevalence in the general population ranges from 2.4% to 14%[3] and it can go up to 45% in manual repetitive workers.[4] What's in the name? In this narrative review, the term "tendinopathy" is persistent tendon pain with associated loss of shoulder function, as defined by the International Scientific Tendinopathy Symposium Consensus.[5] The term 'subacromial impingement' is no longer recommended as a diagnostic label, as current evidence challenges the theory that the main causal mechanism is tendon impingement within the subacromial space.[6–9] Other labels such as 'subacromial pain syndrome' and 'RC-related shoulder pain' are commonly used, allowing for any mechanism of injury to the RC tendon or pain related to structures within the subacromial space.[10,11]

The two mechanical theories for RC tendinopathy are tendon degeneration and compression with repetitive loading. Tendon degeneration with repetitive overload is related to intrinsic factors of tendon biology, morphology, material and mechanical properties, genetics, and vascularity.[12–15] Extrinsic factors of altered kinematics driven by neuromuscular deficits can contribute to tendon degeneration or compressive loading of the tendon. Two areas of compressive loading are possible; in the subacromial space (external impingement) or between the glenoid rim and humeral head which is known as posterior-superior

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impingement (internal impingement).[13,14,16–20] However, impingement as the primary mechanism of RC tendinopathy is called into question, with the biomechanical evidence limiting the possibility of RC tendon compression and the lack of superior outcomes for surgical and non-surgical management focused on reducing tendon impingement over other interventions.[6,9,21–25] The mechanical model of tendon injury provides just that, a biomechanical model devoid of other explanatory factors.[26,27] The muscle-tendon unit is controlled by high-order centers in the nervous system. Central factors related to deficits in sensorimotor and pain processing have been identified in those with RC tendinopathy.[27,28] Moreover, yellow flag psychological factors are related to increased pain and shoulder functional loss.[29–31] A inclusive model can improve mechanistic knowledge of RC tendinopathy, and enable the development of patient-specific treatment to deliver individualized care.

Recovery of RC tendinopathy is limited, with 40%–50% of patients developing recurrent chronic symptoms.[32,33] Physical therapy is the first-line treatment for RC tendinopathy. Specifically, resisted exercise is the first-line recommended intervention in clinical practice guidelines.[34,35] Resistive exercise improves patient outcomes, but non-response rates are unacceptably high.[36,37] This may be explained by the fact that exercise alone addresses only a few of the factors that influence outcomes. A deeper understanding of the spectrum of patient features can be used to inform treatment approaches that address these patient-specific factors in an informed and targeted management strategy.[38] This will enable clinicians to deliver the "right treatment approach for the right patient and the right time."

Clinical trials comparing different treatment modalities of exercise versus best practice advice or different dosing of resisted exercise find no difference in patient outcomes.[39–41] How can interventions that supposedly work via different mechanisms have similar effects on clinical outcomes? There are likely distinct patient subgroups. There is potential to optimize management and improve outcomes if subgrouping around underlying mechanistic biomarkers are used to inform and adapt patient management In other body regions, researchers have defined patient subgroups,[42] and demonstrated that targeted treatments for subgroup deficits have improved outcomes over a non-specific general approach.[43–46] Studies exploring the development of treatment subgroups for RC tendinopathy are warranted. This mechanistic knowledge will enable the design of a stepped and matched treatment approach. Those with a limited positive response to pain and disability will be 'stepped' to alternative care that is 'matched' to their deficits such as psychologically-informed treatments to address psychological deficits and brain pain-processing dysfunction, and/or alternative exercise approaches to improve neuromuscular and tendon deficits. Matched and stepped approaches have been emphasized in recently recommended frameworks to improve care and outcomes for musculoskeletal conditions.[47–49]

We propose four mechanistic domains of factors for resisted exercise in patients with RC tendinopathy: tendon structure, neuromuscular, pain and sensorimotor processing, and psychosocial. The proposed four domains are based on the current evidence of both deficits in patients with RC tendinopathy and the impact of resisted exercise on these specific factors. In the absence of evidence specifically for RC tendinopathy, literature from other musculoskeletal pain conditions and basic science studies are used to hypothesize potential mechanisms of exercise (Figures 1 and 2).

Tendon structure

Tendon structure is complex; characterized by morphology, mechanical properties, material properties, vascularity, and genetics.[15] Patients with RC tendinopathy often have changes to multiple aspects of tendon structure.[15,50,51] The primary RC tendon involved in RC tendinopathy is the supraspinatus tendon, thus the majority of the literature is focused on this tendon. Tendon factors may modulate the effects of resisted exercise and thus are important mechanistic biomarkers.

Material and mechanical properties

Tendon response to mechanical stress can be quantified by changes in mechanical and material properties. The tendon is made of elastic components that facilitate storage and return of strain energy during movement, impacting movement performance and efficiency.[52,53] Decreased tendon stiffness is a feature of tendinopathy.[54–58]

Stiffness and elasticity properties play vital roles in tendon function. Elasticity or modulus describes the relationship between tendon stress and strain. Elasticity represents tendon properties independent of the cross-sectional area, with greater tendon modulus indicating increased stiffness. Stiffness describes the change in tendon length with force applied. Stiffness is dependent on both the cross-sectional area and modulus, thus an increase in either result in greater tendon stiffness. Two mechanisms potentially account for decreased stiffness, a change in tendon material (i.e., collagen fiber amount and laydown) and morphology (i.e., tendon thickness and cross-sectional area).

Tendon material properties have been assessed in cross-sectional studies in those with RC tendinopathy (see Supplemental Table 1) using sonoelastography.[57,59–65] These studies indicate a relationship between decreased tendon elasticity and greater tendon degeneration, which is consistent with findings in lower extremity tendinopathy. The effects of a long-term exercise intervention on RC tendon material and mechanical properties have been

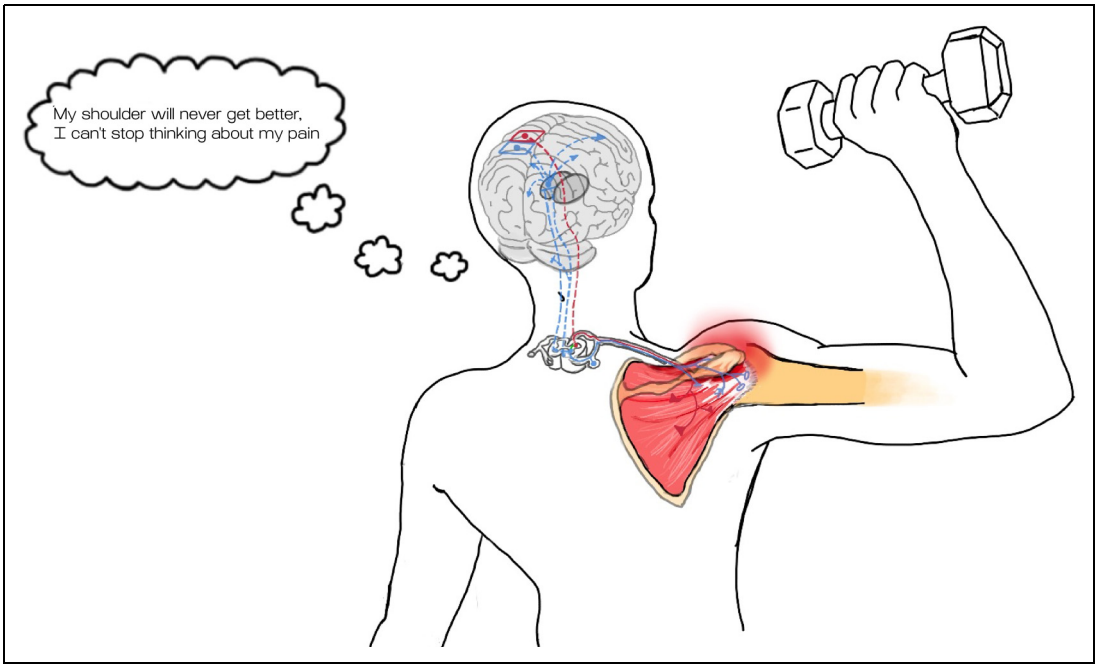


Figure 1. Illustration of the 4 proposed mechanisms of resisted exercise in patients with rotator cuff tendinopathy: tendon structure, neuromuscular factors, psychosocial factors, and pain and sensorimotor processing.

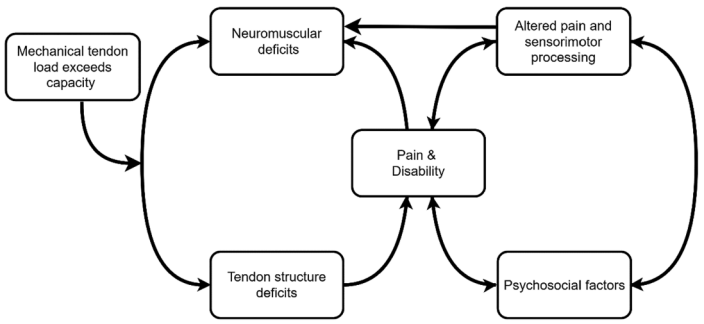
examined in only a single study that looked at the infraspinatus.[64] Despite improvements in outcomes, there were no changes in tendon elasticity with treatment. It is possible that elasticity varies in tendinopathy subgroups. While some may have more deficits in mechanical properties at baseline, some others may not. Furthermore, those who do present deficits may respond differently to exercise depending on whether those deficits are a result of deficits in tendon material (collagen degeneration) or morphology (cross-sectional area). Different exercise approaches may be needed. A systematic review[66] of lower extremity tendinopathy indicates tendon material properties improve with resisted exercise, specifically. exercise can improve tendon mechanical properties (stiffness), material properties (Young's modulus/elastic modulus), and morphological properties (cross-sectional area and tendon thickness). Two exercise studies included in the systematic review found increased Young's modulus but without changes in the tendon cross-sectional morphology.[67,68] This supports the assumption that material properties may change independent or in series with exercise. While changes in material properties may be a short-term mechanism for increased stiffness with exercise, tendon hypertrophy may be the primary mechanism for long-term changes in stiffness.[69,70]

Supraspinatus tendon macromorphology

Tendon thickness as a morphological measure has been of great interest in RC tendinopathy research. Neer proposed impingement of the supraspinatus tendon as the primary mechanism for development of RC tendinopathy in 1972.[93] This mechanism has been the predominant explanation for many years, and thus the investigation of tendon thickness, acromiohumeral distance, and occupation ratio of the tendon in the space. Subacromial impingement is no longer considered the primary mechanism in RC tendinopathy now.[6,9,21–25] Cross-sectional studies have explored supraspinatus tendon thickness in RC tendinopathy[22,23,50,71–76] (see Supplemental Table 2). The majority of the studies report increased tendon thickness with RC tendinopathy.[23,50,72–74]

There is evidence that overuse, or overloading can impact tendon morphology. Pozzi et al.[77] measured tendon thickness of dental hygienist students at the beginning of their educational program and 1 year later. Tendon thickness increased in all students, but significantly greater increase in those who developed tendinopathy-related shoulder pain. There is also evidence to suggest that the tendon thickens after acute bouts of non-therapeutic exercise in healthy populations. Pitching in youth baseball players[78] lead to thickening in the infraspinatus tendon.[79] In patients with RC tendinopathy, a single bout of resisted external rotation and abduction results in increased thickness for 1 and 6 h while healthy controls exhibited no tendon changes.[80] Porter et al.[81] also found increased supraspinatus thickness immediately after one swimming practice and at 6 h after practice in the painful shoulder of swimmers.

Investigations of the effects of resistance exercise on tendon morphology are limited (Supplemental Table 3).



MECHANISMS	Effects of exercise	Level of evidence
Tendon structure		
Tendon stiffness	↑	V
Tendon thickness	↓	IV
Collagen organization	↑	IV
Neovascularization	↓	V
Water content	↓	V
Tenocyte	↑	V
Neuromuscular		
RC muscle onset time	↓	V
Glenohumeral translation	↓	IV
Mechanical efficiency	↑	V
Muscle coordination	↑	IV
Rate of force development	↑	IV
Psychosocial		
Self-efficacy	↑	V
Anxiety	↓	V
Pain Catastrophizing	↓	V
Kinesiophobia	↓	V
Pain and sensory processing		
Pain perception & processing	↓	IV
Proprioception	↑	IV
Motor drive	↑	V

Figure 2. Theoretical model of mechanisms of rotator cuff tendinopathy. The table contains the summary of the evidence for the mechanisms of exercise; evidence rate by Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence.

Pre-post exercise studies have shown a small or no effect on morphological tendon thickness, from two small case-series[82,83] and a cohort study with 23 participants.[64] However, the effects may be patient-specific, with a decrease (healing) in tendon thickness defining a positive patient outcome. There may be patient subgroups, differing in the degree of tendon structural change.[42] Clustering of participants was performed in one study that demonstrated a patient-specific response where only those who had a positive response to exercise had a meaningful change in tendon thickness.[83] There is mixed evidence for the patella and Achilles tendons, but several studies have found decreased tendon thickness in those with improved clinical outcomes after exercise interventions.[84–88] This highlights the heterogeneity of those with tendinopathy, and the need for a patient-specific resistance exercise approach.[36,40,89] More studies are needed to define the use of tendon thickness as a biomarker of improvement or use for exercise dosing in patients with RC tendinopathy.

Tendon micromorphology

Material properties are directly related to the geometric arrangement of collagen fibers. Repetitive tendon strain can cause collagen micro-tears and inflammation, contributing to degeneration.[15,90] During the initial phase of the injury response type III collagen is produced. However, the type III collagen is laid down in an irregular disorganized alignment, resulting in diminished mechanical strength.[91,92] In later stages of tendon repair, type III collagen is replaced by stronger and better aligned type I collagen. Critically, the process of tendon repair can be inhibited by continued tendon overloading.[93]

In healthy tendons, water content of the tendon is about 55% of the total weight, and its exchange can cause rapid macromorphology changes.[94,95] A cadaveric study[96] found 10% more water content in the tendinopathy samples versus healthy tendons. Evidence for other tendons (Achilles) is contradictory, with MRI-based studies looking at a single bout of exercise that found an acute decrease in water content[97] and studies that found increased water levels.[86] To our knowledge, no prospective studies have looked at the effects of longer exercise interventions on water content. Based on the available evidence regarding the mechanical properties of other tendons[98] we could hypothesize that exercise interventions induce an exudation of water from the supraspinatus tendon that may lead to decreased cross-sectional area and increased stiffness. This could be facilitating the transition from the inflammatory and proliferative phases, where the increased water content optimizes the initial recovery, to the remodeling phase, where mechanotransduction may play a more important role in the collagen synthesis.

The fundamental component of the dry weight of tendons is type I collagen (75%).[94,95] Collagen fiber disorganization in tendinopathy impacts tendon architecture and

mechanical properties.[99,100] More recently, tendon collagen organization has been quantified using a two-dimensional spatial frequency analysis on ultrasound tendon images to define the peak spatial frequency radius. One study explored peak spatial frequency radius of supraspinatus tendon and found no difference between individuals with RC tendinopathy and healthy controls.[101] Conversely, a pilot study assessing the effects of exercise[102] found that peak spatial frequency radius values were lower at baseline in patients with RC tendinopathy when compared to healthy controls, indicating more collagen disorganization. After a resisted exercise intervention peak spatial frequency radius values increased, matching those from the controls. Micromorphology with two-dimensional spatial frequency analysis has been explored in lower extremity tendinopathy. In those with patellar tendinopathy after 12 weeks of heavy slow resistance training, tendon fibril density increased and mean fibril area significantly decreased.[103] This could explain why, even though the number of collagen fibers is increased with exercise, we may see a decrease in tendon thickness together with decreased water content, proteoglycans, and glycosaminoglycans, along with collagen fibril reorganization. Similarly, another study looking at the patellar tendon found increased collagen concentration after an exercise intervention.[84] Pending research in the RC exploring collagen changes after an exercise intervention, we could speculate based on findings for other tendons. Exercise would induce an increased collagen concentration and reorganization that would mediate the improvement in clinical outcomes. Due to the slow repair rate of the collagen fibers,[104,105] it is likely that acute changes are due to other factors such as water exchange and blood flow changes, and long-term changes include collagen fiber repair and reorganization.

Neovascularization within the tendon proper is a common finding in tendinopathy literature.[106] However, the evidence for the RC tendons is scarce. Two studies found increased neovascularization in patients compared to controls[107,108] and one that found no differences.[109] In contrast, there are studies that have proposed vascular insufficiency as one of the causes of RC tendinopathy.[110,111] This hypothesis has been supported by studies that found decreased blood flow in RC tendinopathy without associated tears.[112,113] One potential explanation for this discrepancy is that initial decreased vascularity may lead to failure of tissue integrity, followed by neovascularization in the inflammatory and proliferative phases.[114] Finally, emerging methods to quantify neovascularization show correlation with pain and function,[115] which may help explain the importance of this mechanism in the future. There are no studies examining changes in neovascularization with exercise in those with RC tendinopathy. In Achilles tendinopathy literature, research has shown that, after an exercise intervention, there is improved physical activity level, decreased pain and a concomitant reduction in neovascularization.[88] Based on this, we speculate that a similar pattern could be expected for the RC, where exercise would induce a reduction in neovascularization that partially explains the improvement in clinical outcomes.

Neuromuscular factors

Mechanistic models of RC tendinopathy propose that repetitive motion overloads the tendon, leading to degeneration, which is associated with neuromuscular deficits.[13,91,116] Force production, muscle activation, and control are common neuromuscular deficits in those with RC tedinopathy.[117–121] Concurrently, shoulder kinematics may be altered. Resistance exercise is aimed at improving muscle capacity (muscle activation and force) and muscle control (timing and rate of force development) to impart load to the tendon to stimulate healing and restore coordinated shoulder motion.

Kinematics

Shoulder movement is coordinated across the scapulothoracic, scapulohumeral, sternoclavicular, and acromioclavicular joints. Scapulothoracic kinematics are altered in individuals with RC tendinopathy assessed during constrained arm elevation tasks,[122–124] most commonly as decreased upward rotation and posterior tilt[122–124] However, the findings from systematic reviews report different conclusions, and state insufficient evidence and methodological inconsistencies across studies. The literature exploring glenohumeral kinematics differences is more limited, in part due to the difficulty in tracking humeral head translation in vivo with external markers. Skin-motion artifact[125,126] and the small magnitude of translations of the humeral head[127,128] challenge the validity of these measurements. Lawrence et al.[129] analyzed glenohumeral kinematics using a combination of electromagnetic motion capture system and transcortical bone pins drilled into the scapula and humerus. They found increased humeral head anterior and inferior translation in patients with RC tendinopathy as compared to healthy controls.

One of the challenges of proposing altered kinematics as a mechanism of RC tendinopathy is that the change in kinematics is not well correlated with the resolution of symptoms. Most exercise intervention studies find that participants improve in clinical outcomes (i.e., pain and function) without changes in kinematics[130–138] (See Supplemental Table 4). Hotta et al.[139] performed a causal mediation analysis and determined that changes in scapular motion did not mediate the improvements in pain or disability with resisted exercise with RC tendinopathy.

In summary, there is mixed evidence regarding kinematic baseline deficits in patients with RC tendinopathy. Resisted exercise improves pain and function regardless

of the changes or lack thereof in shoulder kinematics. However, the methods used to analyze kinematics are not without limitations, indicating advanced techniques may be warranted to determine the contribution of kinematics in explaining the presence of RC tendinopathy and effects of exercise.

Muscle activation

Several studies report differences in muscle activation magnitude between individuals with and without RC tendinopathy.[140–154] Increased activation of the upper trapezius and decreased activation of the lower trapezius and serratus anterior are the most common findings, despite inconsistency in shoulder tasks and results across studies.[121,155] Several cross-sectional studies have investigated the muscle activation timing.[156–161] The vast majority of studies explore scapular muscles and find differences in recruitment timing between healthy and injured individuals. However, there is no consistent pattern regarding the difference in activation timing of the muscles. An explanation for this is that every study uses a different task, ranging from rapid small movements[156] to constrained elevations,[158] reaching tasks,[157] or sudden downward falling movement.[160] Every study finds different activation patterns, although altered timing of the trapezius muscles seems to be the most consistent. Specifically, the delay of the lower trapezius is a common finding across studies. These muscle activation magnitudes and timing findings could partially explain the kinematic alterations found with RC tendinopathy.[122–124] The increased activation of the upper trapezius with a delayed activation of the lower trapezius could be a causative factor of altered scapular superior translation and decreased upward rotation and posterior tilt. We speculate that this scapular pattern could alter the foundation for the rotator cuff muscle activation, and thus loading to the tendon. Theoretically, this pattern could also decrease the subacromial space and thus increase the compressive load on the tendon, however, this hypothesis has been challenged.[21,22,71,73,74] There is limited research on muscle activation timing of the RC and deltoid muscles, as all the studies that have explored these muscles have only looked at EMG amplitude and found no consistent pattern.[118,145–147,153,154,157]

There are a limited studies investigating changes in muscle activation with exercise interventions in combination with changes in clinical outcomes.[132,162–165] (Supplemental Table 5) These studies have looked at both muscle activation magnitude and timing during different arm elevation tasks. All the studies found changes in EMG timing of scapular muscles concurrently with positive patient-reported outcomes. Ortega-Cebrián et al.[162] also reported decreased onset time for the deltoid and periscapular muscles after an exercise intervention. However, they also looked at RC muscles and found no changes in onset. There is no consistent pattern in muscle activation changes associated with recovery, but the variability in study methodology may partially explain these findings. We speculate that muscle activation patterns are altered in the presence of pathology but manifest differently for each individual due to the noxious stimuli and sensorimotor processing. Muscle activation patterns and thus changes with intervention may be patient-specific.

It is unclear whether baseline muscle activation differences are the cause or the consequence of RC tendinopathy. Assuming they precede injury, we could speculate that exercise to correct the muscle activation deficits will optimize tensile load transfer across the tendon and/or decrease the compressive tendon load (subacromial or posterior-superior). In this case, exercise would need to target muscle specific activation goals based on commonly reported deficits, or patient-specific identified deficits. If we consider muscle activation deficits a consequence of RC tendinopathy, we propose two hypotheses: 1- exercise will build tendon tolerance to load by improving its' morphological and mechanical properties and this will normalize muscle activation, and 2- increased shoulder use with exercise will lead to decreased kinesiophobia and sensorimotor processing deficits that will lead to normalized motor drive and muscle activation patterns. For hypothesis 1, exercise should be designed and progressed by the tendon structural response to optimize tendon tissue recovery. For hypothesis 2, intervention programs should deliver exercises that are perceived as helpful and non-threatening to facilitate improved shoulder use alongside concurrent treatment to reduce psychological factors present.

There are other EMG analysis techniques such as muscle coordination patterns[166,167] and frequency analysis to assess intermuscular coherence[168,169] that have not been used to identify deficits and explore changes with exercise. These analyses may further explain the neuromuscular deficits and changes that occur with exercise and potentially provide a more consistent pattern across participants.

In summary, muscle activation magnitude and timing deficits are present in those patients with RC tendinopathy. Changes in clinical outcomes with exercise are associated with changes in muscle activation, but the pattern of these changes varies across studies due to the methodological inconsistencies across studies and to potential individual differences in baseline deficits. Other EMG analyses such as coordination patterns and coherence may be warranted to explore mechanistic underpinnings of exercise on tendinopathy.

Force

Despite strength being commonly associated with shoulder joint function, the literature regarding deficits in maximal force production in the presence of RC tendinopathy is

inconsistent.[117,118,170–173] There is no clear evidence that force deficits are consistently present in RC tendinopathy.

Several exercise clinical trials have used strength (via peak force or peak torque) as the primary outcome variable to measure progress in the exercise program.[174–187] Even those exercise trials that did not include measures of peak force, propose this variable as the mechanism leading to improvement in pain and function.[135,188–194] This hypothetical relationship between force and clinical outcomes is challenged. There are inconsistencies across the literature, with several studies noting improved pain and functional outcomes without changes in peak force.[39,40,177,179,182,187]

This phenomenon is not new to musculoskeletal injuries. Research in other body regions has shown that there may be other force variables that are more relevant and explanatory of changes in pain and function. One of them is rate of force development (RFD).[195] Research in knee anterior cruciate ligament injuries has described arthrogenic muscle inhibition as decreased function of the musculature surrounding the injured joint. This is a multifactorial process that involves peripheral and central mechanisms that lead to decreased RFD but not necessarily to peak force production.[196] A similar process could be hypothesized for RC tendinopathy. The noxious stimuli together with the tendon tissue damage (and associated proprioceptive receptors[197]) could lead to a similar phenomenon. In a small pilot study, improvement in patient reported outcomes was related to increased RFD during resisted isometric external rotation.[198] In other words, those who had improved outcomes with exercise concurrently had the most increase in RFD. The capacity of generating rapid and controlled motions may be much more relevant than a maximal force exertion. There are inconsistent findings for peak force in the RC, and promising results for metrics such as RFD in other body regions, along with the preliminary results[198] for RC tendinopathy. Other variables should be considered that combine several neuromuscular skills such as rapid muscle activation, coordination, and rapid force exertion. Future work should also investigate these variables as targets for exercise interventions.

Shoulder neuromuscular dysfunction is commonly found in patients with RC tendinopathy, which could be solely a peripheral deficit and/or a result of central (brain) factors. It is unclear if the neuromuscular deficits are a cause or an effect of the RC tendon pathology. The neuromuscular deficits could precede injury, caused by the nature of the repetitive task performed (e.g., fatigue and overload that leads to tissue damage). On the other hand, they could also be a consequence of sensorimotor and pain processing deficits along with presence of psychological factors.

Psychosocial factors

The presence of psychological factors can impact the perception of bodily pain.[199] Psychological factors are associated with poor clinical outcomes in patients with musculoskeletal shoulder pain,[31,200] and specifically those with RC tendinopathy.[201] These psychological factors include depression, anxiety, sleep disturbance, distress, pain catastrophizing, kinesiophobia, self-efficacy, expectations of recovery, and resilience.[30,31,200–206] Most recently, higher levels of emotional distress and kinesiophobia were associated with greater disability over one year in patients with shoulder pain.[207] These psychological factors may develop concurrently with pain, or precede the development of symptoms. A longitudinal study reported the development of shoulder pain concurrently with elevated levels of anxiety.[77] It is unclear if these psychological factors are traits or states concurrent with the experience of shoulder pain.

Psychosocial factors can partially explain the clinical outcomes of resisted exercise programs.[31,200,203,207] A 2019 systematic review[200] identified that baseline measures of treatment expectations and self-efficacy were predictive of patient-reported outcomes with rehabilitation for shoulder pain. Prospective studies[31,207] identified expectations of recovery, self-efficacy, kinesiophobia, and pain catastrophizing at baseline to be predictive of patient-reported outcomes with rehabilitation for musculoskeletal shoulder pain. These studies are limited in that measures of psychological factors occurred only at baseline, and without considering the contributions of the central nervous system. Psychological factors may be states associated with the current symptoms in the course of rehabilitation, and thus should be measured over the course of care.[208] In other musculoskeletal conditions, brain functional connectivity alterations are related to psychosocial factors and clinical outcomes. Functional connectivity is a temporal correlation of brain activity in regionally distinct areas. In females with patellofemoral pain, brain functional connectivity alterations are related to disability and kinesiophobia.[209] In adults with low back pain, altered brain functional connectivity was found to mediate the development of depression and chronic symptoms.[210]

Over time, the presence of psychological factors may increase or decrease. This is important, as the presence of psychological factors may indicate patient-specific additional care to address these factors. For example, pain reprocessing therapy successfully reduced kinesiophobia and mediated reductions in pain in those with chronic low back pain.[211] We speculate that exercise may have an effect on psychological health and/or be a mediator by which resisted exercise produces beneficial outcomes. Future studies should measure psychological factors throughout rehabilitation, to determine if and when treatment programs need to be modified to optimize outcomes of care.

Pain and sensorimotor processing

Emerging evidence suggests central nervous system dysfunction exists in RC tendinopathy. Decreased corticospinal

excitability[212] and increased pain sensitivity[213] are related to worse clinical outcomes. Investigations are limited that characterize whole-brain activity in those with RC tendinopathy and the effects of exercise on measures of central nervous system activity following exercise. The available evidence does suggest successful outcomes are related to fewer baseline psychological factors,[207] along with improved pain and sensorimotor processing.[214,215]

Pain processing

Central nervous system dysfunction can manifest in altered pain processing. Pain processing deficits can be indicators of central sensitization, which is defined by the International Association for the Study of Pain as 'increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input'.[216] Common findings that infer central sensitization are reports of widespread pain and increased pain sensitivity at remote body sites with quantitative sensory testing in those with RC tendinopathy.[214,217,218] Quantitative sensory testing includes measures of pain threshold and descending pain modulation with pressure, heat, and cold at the site of pain and at remote locations (e.g., contralateral shoulder and leg), which indicates widespread pain sensitivity. Decreased pain threshold on both the involved and uninvolved shoulder has been consistently found in those with RC tendinopathy, which is suggestive of central sensitization.[217,219–221] Recently, increased activity in the anterior insula, a region that encodes the unpleasant experience of pain and a biomarker for chronic pain,[222,223] has been found in patients with RC tendinopathy.[206] The anterior insula is a primary node of the salience network,[224] which is commonly dysregulated and increasingly connected to other neural networks in chronic musculoskeletal pain.[225] These findings suggest sensitization is common in RC tendinopathy and may be related to underlying dysregulation in neural circuitry.

Alterations in pain processing have demonstrated a relationship to clinical outcomes. Those with higher severity of widespread pain have reported greater magnitude of pain and had a worse prognosis after surgical subacromial decompression.[226] Many studies have demonstrated a positive effect of exercise in chronic pain conditions,[227] but only one study has evaluated the effect of exercise on pain processing in RC tendinopathy.[213] The study evaluated the effects of exercise and manual therapy over 2 weeks. At baseline, those with shoulder pain had lower local and remote pressure and heat pain thresholds compared to controls, and these differences were normalized after intervention. This suggests exercise and manual therapy may reverse central alterations in pain processing in those with shoulder pain.[213] There are no studies evaluating the direct effects of exercise alone on central pain-processing measures or peripheral measures of central sensitization in those with RC tendinopathy.

Sensorimotor processing

Sensorimotor processing deficits have been recently proposed as relevant factors in RC tendinopathy, highlighting the central nervous system involvement.[27,28] Sensorimotor deficits are observed in those with RC tendinopathy peripherally through proprioception and centrally through corticospinal excitability. Peripherally, individuals with RC tendinopathy demonstrate deficits in proprioception.[228] Joint position sense is measured by the difference in actively or passively repositioning the joint compared to a previously assigned position. Kinesthesia is measured by the distance that the limb travels before detecting movement. Sensation of force is measured by matching a force to which the subject was previously exposed. Proprioception deficits are not consistently identified in individuals with shoulder pain compared to controls.[228,229] Exercise improves proprioception deficits in those who demonstrate baseline differences (Supplemental Table 6).[186,215,230] Importantly, there is likely a subgroup of individuals with RC tendinopathy who do not have deficits and thus do not exhibit improvement.[215] Proprioception deficits have not been shown to predict response to intervention, as those with and without deficits demonstrated similar improvements in function.[215]

Existence of altered sensorimotor processing could be explained centrally by decreased activity within the motor cortex in patients with RC tendinopathy.[206] Alterations in cortical activity may contribute to peripheral motor deficits commonly observed in RC tendinopathy. Transcranial magnetic stimulation demonstrated cortex changes in those with RC tendinopathy,[212] with a higher active motor threshold in the involved shoulder indicating decreased cortical excitability. Chung et al.[231] evaluated characteristics of the motor cortex corresponding to the lower trapezius, upper trapezius, and serratus anterior participants with shoulder pain. Those with shoulder pain had increased active motor thresholds for the lower trapezius and serratus anterior, longer cortical silent period of the lower trapezius, and posteriorly shifted center of gravity in the upper trapezius and serratus anterior compared to controls. While these findings may help explain the deficits in motor drive from the cortex, there are no studies evaluating change in cortical excitability after exercise in RC tendinopathy. Cortical reorganization and improved cortical excitability have been demonstrated following exercise in other musculoskeletal conditions.[219,232] We speculate that exercise may improve sensorimotor excitability resulting in improved muscular activation in RC tendinopathy.

Conclusion

We propose a mechanistic model for resistance exercise in patients with RC tendinopathy. The model contains four mechanistic domains by which exercise is theorized to

improve clinical outcomes: tendon structure, neuromuscular factors, psychosocial factors, and pain and sensorimotor processing. This framework provides clinicians a mechanistic model of four unique constructs to consider how exercise may improve pain and disability. Resisted exercise may normalize these factors, but limited evidence exists to explain the relationship of the four proposed domains to the trajectory of recovery and defining persistent deficits limiting outcomes. The presence of each mechanistic construct may vary across patients and time. Identifying baseline deficits and the change in the deficits over the course of the exercise intervention may help to refine and deliver patient-specific exercise that can optimize patient outcomes or use a stepped and matched approach to refer to alternative care. Patients that are non-responsive to resistance exercise would be stepped to alternative care, and care that is matched to residual deficits that are associated with limited outcomes. This model provides a framework for researchers to use in future mechanistic exercise studies. We speculate this will enable the development of homogeneous treatment subgroups for those with RC tendinopathy. Future studies should test the ability of the proposed mechanisms to define patient subgroups of RC tendinopathy, to enable the delivery patient-specific exercise approach and consider if treatment for psychological and central processing deficits may be appropriate. This model can also be used to define metrics of the trajectory of recovery with exercise. Finally, this mechanistic framework may be applicable to other tendinopathies. Our hypotheses should be evaluated critically and appropriately challenged in future studies as the majority of evidence supporting the proposed mechanisms are based on case series and mechanistic reasoning (Levels IV and V). This highlights the need for research characterizing the mechanisms of recovery with exercise in patients with RC tendinopathy.

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Supplemental material

Supplemental material for this article is available online.

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