Trauma-related rotator cuff tears. From the outside to the inside.

Aagaard, Knut Espen

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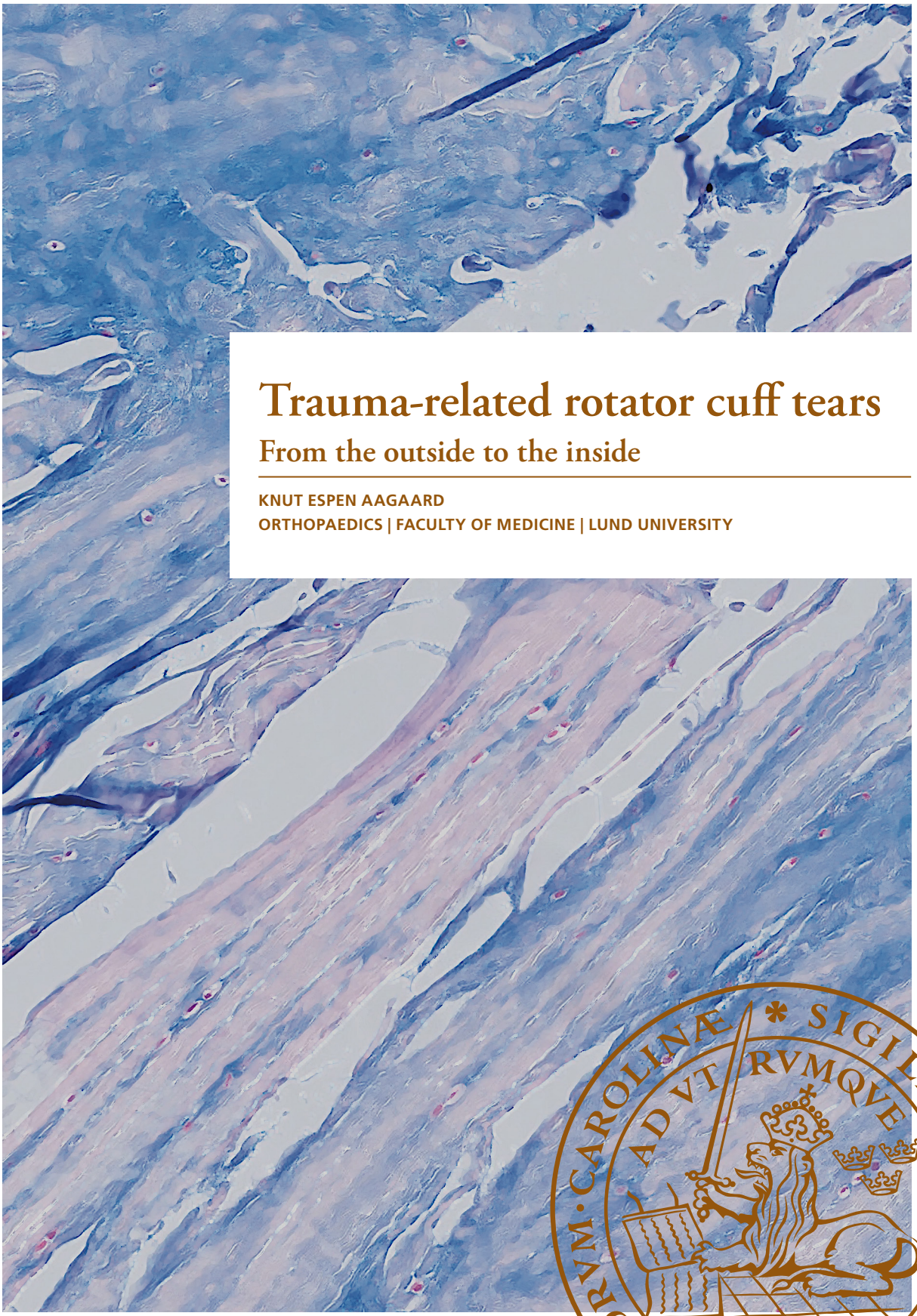

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From the outside to the inside

KNUT ESPEN AAGAARD
ORTHOPAEDICS | FACULTY OF MEDICINE | LUND UNIVERSITY

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Title and subtitle

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Rotator cuff tear is common in the general population. This thesis focuses on acute, trauma-related rotator cuff tears which are often discussed and treated separately from nontraumatic, degenerative tears. In the four papers included, we investigate the incidence, tissue quality, outcome after early surgical treatment, and risk factors for healing failure.

In *Paper I*, the epidemiology of acute, trauma-related injuries to the shoulder girdle was investigated. Individuals aged between 18-75 years with acute shoulder trauma combined with sudden onset of pain and loss of function were screened - 331 patients were clinically examined over a period of 24 months. In 60 patients, clinically indicated full-thickness rotator cuff tears (FTRCT) were confirmed by magnetic resonance imaging (MRI). Our results suggest that the annual incidence of FTRCT is 16 (95% CI 11-23) per 100,000 inhabitants and that 60% of patients had at least two tendon ruptures. FTRCT was more common among males and a combined tear of the subscapularis and supraspinatus tendon was most common.

In *Paper II*, we studied clinical and structural outcomes after early rotator cuff repair. All individuals with FTRCT in the well-defined cohort described above (*Paper I*) were offered early surgery. Included patients underwent arthroscopic cuff repair within six weeks of trauma. Repair integrity was determined using MRI as well as measures of shoulder function one year after surgery, whereas PROMs were acquired two years after surgery. We found that 37% of the patients had healing failure of one or more repaired tendons. Individuals with healing failure had significantly lower shoulder function than those with intact repair, whereas no respective difference was seen in PROMs.

In *Paper III*, supraspinatus biopsies obtained during surgery (*Paper II*) were examined to determine the degree of histopathological tendon degeneration as well as inflammation, apoptosis, proliferation, and traces of bleeding from the tendon rupture. Results were compared with a control group of similar tissue samples from individuals with chronic, nontraumatic tears. Between-group analyses showed no significant differences in the degree of degeneration or inflammation. A higher proportion of apoptotic cells and a higher degree of proliferation were found in tissue from trauma-related injuries compared to chronic, nontraumatic tissue samples. Our results suggest that there is no clear difference in the degree of degeneration between ruptured supraspinatus tendons harvested from shoulders affected by trauma compared to those not affected by trauma.

Paper IV examined factors that may explain healing failure after early surgical repair of trauma-related rotator cuff tears. After a careful correlation analysis, by drawing a directed acyclic graph, ten risk factors including the degree of histopathological tissue degeneration, were tested for relationship between intact repair and healing failure as determined by MRI (*Paper II*). The result showed that older age, increased fatty infiltration of the supraspinatus, and disruption of the rotator cable attachments were factors associated with healing failure after early arthroscopic repair. However, histopathological degenerative changes were not associated with healing failure.

In conclusion, acute, trauma-related rotator cuff tears are common in the general population, especially among males. These injuries are overall larger than nontraumatic tears where 60% involve more than one tendon rupture. Since early surgical repair, within six weeks of trauma, did not solve the healing problem, our results suggest that other prognostic factors than time to surgery, including tear type and location, age, and fatty infiltration of the cuff muscle are of greater importance. Even though patients with trauma-related tears have been asymptomatic before the injury, degenerative changes within the tendon tissue do not differ from chronic tears. Healing failure remains a significant problem and surgery needs to be questioned as it may not be superior to conservative treatment in subgroups of individuals with several risk factors for healing failure.

Key words Shoulder Trauma-related rotator cuff tear Histopathology Tendon degeneration Apoptosis Tendon healing Risk factors Bonar score Arthroscopic rotator cuff repair

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Knut Espen Aagaard

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UNIVERSITY

Main supervisor: Richard Frobell, PhD, Associate Professor
Co-supervisor: Karl Lunsjö, PhD, Associate Professor
Co-supervisor: Hanna Björnsson Hallgren, PhD, Associate Professor

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“The desert is so huge, and the horizon so distant,
that they make a person feel small,
and as if he should remain silent.”

- Paulo Coelho

Till Malin, Agnes och Harald

Table of Contents

Abstract

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Svensk sammanfattning

De fyra delarbetena i denna avhandling undersöker och beskriver förekomst, vävnadskvalitet och behandlingsresultat efter traumarelaterad senruptur i axelledens senmanschett (så kallad rotatorkuff). Rotatorkuffen utgörs av fyra senor som alla har sina muskelursprung på skulderbladet. Senorna löper ut mot axelleden och omsluter ledhuvudets bakre, övre och främre del. Alla senor, och deras tillhörande muskler, är viktiga i olika faser av armrörelsen och arbetar tillsammans som en enhet för att dynamiskt stabilisera axelleden. Vävnadens kvalité blir generellt sämre med stigande ålder och det är inte ovanligt att det blir större eller mindre substansförluster (dvs. rupturer) i en eller flera av senorna, oftast drabbas den så kallade supraspinatussenan. Rotatorkuffruptur är vanligt förekommande i den arbetsföra delen av befolkningen samt bland aktiva pensionärer och ofta associerat med smärta och nedsatt funktion i skuldran. Förekomsten ökar med stigande ålder och symptombilden varierar stort, från inga symtom alls till svår nattlig värk och funktionshinder, oavsett skadans storlek. Hos vissa individer diagnosticeras skadan efter ett fall, drag eller ryck i armen och dessa senskador kallas då traumarelaterade rotatorkuffrupturer. För den enskilda individen kan skadan få stora konsekvenser, från att ha levt ett liv med fullt fungerande axlar till att man plötsligt inte kan få upp sin arm. Detta abrupta funktionsbortfall är en av orsakerna till att tidig kirurgisk reparation traditionellt har rekommenderats. En annan orsak är att muskelvävnaden till den skadade senan riskerar att ersättas med fettvävnad, en process som tros vara irreversibel. Teorin är att denna process startar i nära anslutning till skadan och den begränsade forskningen som finns på området pekar på att tidig senreparation kan förhindra fettomvandling av muskeln och därmed minska funktionsbortfallet. Detta står i kontrast till muskulär träning som är förstahandsbehandlingen för de individer som inte upplevt någon akut symptomdebut i samband med fall eller annan skada. Här antar man att skadan funnits en längre tid och att läkningsförutsättningarna är sämre pga. degenererad (”åldersförändrat”) sena. Det övergripande syftet med denna avhandlingen är att undersöka om tidig operation medför god läkning av de reparerade senorna och om det finns några faktorer som kännetecknar god läkning.

I *delarbete I* undersöks förekomsten, både incidens och prevalens, av trauma-relaterade skador i rotatorkuffen. Genom att skapa ett fångstnät för alla patienter i åldrarna 18–75 år med någon form av skuldertrauma kombinerat med akut debuterande skuldersmärta och bortfall av, för rotatorkuffen, typisk funktion fångades totalt 331 patienter under knappt två års tid. En tidig

magnetkameraundersökning visade att 60 av dessa patienter hade en genomgående ruptur av minst en sena i rotatorkuffen vilket gav en årlig incidens motsvarande 16 per 100 000 innevånare. Den vanligaste skadan var en kombinationsskada som inkluderade ruptur av subscapularis- och supraspinatussenan. Studien visade även att traumarelaterad rotatorkuffskada är betydligt vanligare bland män.

Delarbete II beskriver resultatet efter kirurgisk reparation, som genomfördes med titthålsteknik inom 6 veckor från skadetillfället, för 62 individer med traumarelaterad rotatorkuffskada. Dessa patienter fångades som beskrivits i delarbete I. Resultatet visar att 37% av de reparerade senorna i rotatorkuffen inte läkt fullständigt efter ett år. På gruppnivå förbättrades individerna avsevärt avseende såväl axelfunktion som sjukdomsspecifik patientrapporterad livskvalitet. De som hade en ofullständigt läkt rotatorkuff hade signifikant sämre axelfunktion än de som hade en fullständigt läkt reparation. Arbetets resultat föreslår att en tidig kirurgisk reparation möjligen inte är den viktigaste faktorn för fullständig läkning av rupturerade senor i axelledens senmanschett trots att symptom och funktionsbortfall uppkommit i samband med ett trauma.

I *delarbete III* undersöks senvävnaden från en av de rupturerade senorna i rotatorkuffen (supraspinatus) med histopatologiska metoder för att bland annat undersöka degeneration i senvävnaden. Detta har inte tidigare gjorts i en väldefinierad grupp bestående av enbart individer med traumarelaterad rotatorkuffruptur. I samband med titthålsoperationen togs ett vävnadsprov av supraspinatussenan för att bestämma graden av degeneration. Resultatet jämfördes med en referensgrupp bestående av liknande vävnadsprover från en grupp individer med känd degenerativ skada, långvariga symptom och funktionsbortfall utan trauma. Resultatet visade ingen signifikant skillnad i graden av degeneration eller inflammation mellan grupperna. Däremot fann man en högre andel självdöda celler (apoptos) och högre grad proliferation (nybildning av celler och vävnad) i vävnaden från traumarelaterade skador jämfört med vävnad från spontant degenererade senskador. Resultatet av studien visar att det inte är någon tydlig skillnad i graden av degeneration mellan rupturerade senor som skördats från axlar drabbade av trauma jämfört med de som inte utsatts för trauma.

I *delarbete IV* undersöks faktorer som kan förklara utebliven läkning efter kirurgisk reparation av senor som rupturerat i kuffen efter trauma. Efter en noggrann sambandsanalys testades tio riskfaktorer, inklusive grad av histopatologisk vävnadsdegeneration, för samband mellan fullständig och ofullständig läkning enligt magnetkameraundersökning ett år efter reparationen (delarbete II). Resultaten talar för att ålder, fettomvandling av kuffmuskel och typ eller lokalisation av ruptur är riskfaktorer för ofullständig läkning.

Sammanfattningsvis bidrar denna avhandling med viktig kunskap om trauma-relaterade rotatorkuffskador. Dessa skador är relativt vanligt förekommande, speciellt bland män och skadorna är generellt större än de icke-traumatiska kroniska

skadorna. Det ser inte ut som om tidsfaktorn för reparation är den viktigaste faktorn när det gäller kirurgiskt resultat och läkning, utan andra faktorer så som ålder, fettomvandling av muskulatur och vilken typ av senskada, dvs. rupturens lokalisation verkar vara av stor vikt. Även om den akut skadade individen aldrig haft några större besvär från axlarna visar denna avhandling att det kan finnas bakomliggande degeneration i vävnaden som inte skiljer vävnadskvalitén från kroniska skador. Denna information måste förmedlas till den skadade individen. För den behandlande läkaren och kirurgen är det viktigt att föra ett noggrant resonemang där för- och nackdelar av operation jämfört med icke-operativ behandling eftersom det finns en risk för att senreparationen inte läker.

List of papers

This thesis is based on the following papers, referred to in text by their roman numerals.

Paper I	**High incidence of acute full-thickness rotator cuff tears. A population-based prospective study in a Swedish Community**. Knut E Aagaard, Fikri Abu-Zidan, Karl Lunsjö. Acta Orthopaedica 2015; 86(5): 558-562
Paper II	**Early repair of trauma-related full-thickness rotator cuff tears does not eliminate the problem of healing failure.** Knut E Aagaard, Karl Lunsjö, Richard Frobell. The Bone and Joint Journal 2019; 101-B(5):603-609
Paper III	**No differences in histopathological degenerative changes found in acute, trauma-related rotator cuff tears compared with chronic, nontraumatic tears**. Knut E Aagaard, Hanna Björnsson Hallgren, Karl Lunsjö, Richard Frobell. Knee Surg Sports Traumatol Arthrosc. 2022 Feb 8, doi: 10.1007/s00167-022-06884-w. Online ahead of print.
Paper IV	**Factors associated with healing failure after early repair of acute, trauma-related rotator cuff tears.** Knut E Aagaard, Karl Lunsjö, Richard Frobell, Hanna Björnsson Hallgren. Submitted

Abbreviations

AC	Acromioclavicular
ACT	Acute rotator cuff tear
AP	Anteroposterior
ASAP	Acute Shoulder Assessment Project
ATO	Arthroscopic transosseous
CSA	Critical shoulder angle
CT	Computed tomography
DR	Double row
ECM	Extracellular matrix
EQ 5D	EuroQol 5 Dimensions
FTRCT	Full-thickness rotator cuff tear
GP	General Practitioner
MCID	Minimal clinical important difference
MGHL	Middle glenohumeral ligament
MMP	Matrix metalloproteinase
MRA	Magnetic resonance arthrography
MRI	Magnetic resonance imaging
MSC	Mesenchymal stem cells
PMN	Polymorphonuclear leukocytes
PROM	Patient-reported outcome measure
PT	Physiotherapist
PTRCT	Partial-thickness rotator cuff tear
RC	Rotator cable
RCR	Rotator cuff repair
RCT	Rotator cuff tear
ROI	Region of interest
ROM	Range of motion
SCR	Superior capsular reconstruction
TIMP	Tissue inhibitors of metalloproteinase
TOE	Transosseous equivalent
TRCT	Traumatic rotator cuff tear

Introduction

Shoulder pain is common in the general population and rotator cuff disorders are associated with shoulder pain and dysfunction [1-3]. Despite rotator cuff research that goes more than hundred years back and lately, great advances in surgical repair techniques, we still face challenges in the management of these conditions. In *A Description of All the Bursal Mucosae of the Human Body* from 1788 Alexander Monro draw a tear of the supraspinatus and infraspinatus on one of his sketches [4] and about a hundred years later, Hüter performed the first known cuff tendon re-attachment, after resecting the humeral head [5]. A rotator cuff repair technique with suture actors more like we do today, was described by Perthes when he published a series of three rotator cuff repairs in 1906 [6]. Due to the developments in arthroscopic surgery and day-care surgery settings over the last two to three decades, we have seen an explosive increase in rotator cuff repairs, where US report about 250.000 repairs annually [7].

The aetiology of rotator cuff tearing is understood to be multifactorial including intrinsic factors affecting the tendon biology such as age and genetics and mechanical extrinsic factors such as altered anatomy and trauma with microtrauma or overuse, and sometimes more significant trauma. This thesis will focus on the acute, trauma-related tears, which are often discussed as a separate entity. The typical patient is a middle-aged man who while falling sustains a direct or indirect trauma to the shoulder which results in reduced ability to elevate the affected arm and significant pain. Most guidelines and experts in the field would advocate early surgical repair in young, active patients. One of the reasons for this treatment algorithm is the inevitable approaching muscle atrophy and irreversible fatty infiltration that seem to appear after rotator cuff tearing [8]. Exactly when this irreversible process begins is not clear but early surgery within six to twelve weeks is typically preferred. This stands in contrast to the treatment of the patients with chronic rotator cuff tears without any trauma-related sudden onset of symptoms, where conservative management with physiotherapy in most cases should be first-line treatment [9-11].

The pain induced by the shoulder trauma may in some patients be worse than the loss of function. Patients and sometimes physicians may treat this with pain killers, and follow the ”wait and see protocol”. This will lead to a delay in diagnosing and treatment, and may subsequently lead to inferior final outcome. In 2009, we launched the Acute Shoulder Assessment Project (ASAP) to prevent this to happen.

We encourage all physicians, physiotherapists and other clinicians to refer patients where rotator cuff injuries could not be excluded following the first initial physical examination. Within a week, one of our department physiotherapists would assess the patient and perform a thorough physical examination. Today, this visit will include ultrasound examination. In healthy, physically active patients with ultrasound-verified rotator cuff tears, discussion about treatment options is undertaken and a subacute magnetic resonance imaging (MRI) is ordered to enhance information. The MR images may detect degenerative changes within the joint or the muscles - information that is of great importance in clinical decision-making. With this screening system, we have minimized the time from injury to diagnose, with the intention to initiate the most appropriate individualized treatment at the earliest possible stage.

Background

Anatomy

The rotator cuff comprises four different muscles: the subscapularis, the supraspinatus, the infraspinatus, and the teres minor. They all arise from separate origins on the scapular body (subscapularis from anterior surface and the rest from the posterior surface) and fuse together with the articular capsule of the glenohumeral joint and insert as a tendon cuff on the lesser and the greater tubercles of the humerus. The insertion sites are called footprint of the tendons and even though they mainly have separate footprints, some overlapping is present [12, 13].

Subscapularis

The subscapularis is the largest and most powerful of the four rotator cuff muscles. Based on its cross section it represents more than half of the total rotator cuff muscle mass [14]. It originates in the subscapular fossa along the anterior aspect of the scapular body. The muscle fibres converge into tendinous tissue at the level of the glenohumeral joint and fuse together with the joint capsule and insert with a large footprint on the lesser tubercle. The size of the footprint has been reported to be between 25 to 18 mm (medial to lateral) and 51 to 11 mm (superior to inferior) where a four facets insertion is described (Figure 1) [15, 16]. It consists of a purely tendinous and intra-articular upper part (Facets 1-2) and a musculocapsular lower part (Facets 3-4) [13]. The muscle is mainly innervated by the upper and the lower subscapular nerves which primarily originate from the posterior cord of the brachial plexus (C5-C8). Anatomical variants which include nerve branches from the axillary nerve have been reported [17].

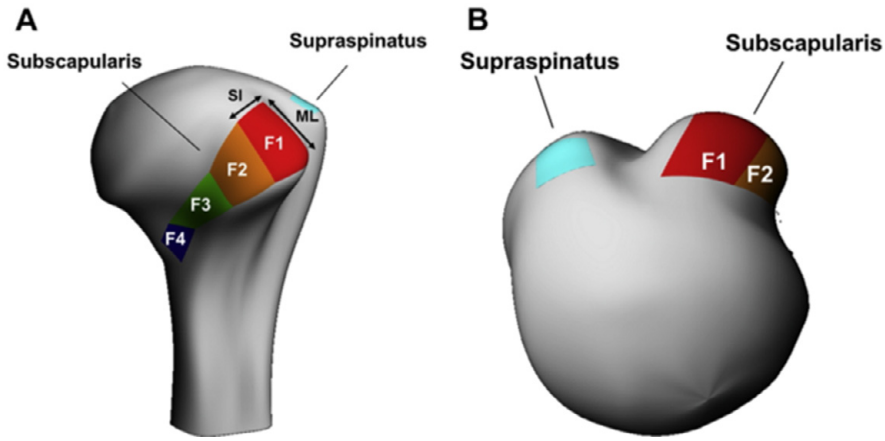


Figure 1. Reconstruction of the proximal humerus and its different facets of the subscapularis tendon insertion, i.e footprint (A from the front, B from above). Published in Arthroscopy, reprinted with permission from Elsivier [16].

Supraspinatus

The supraspinatus muscle lies superior to the spine of the scapula and builds the upper part of the rotator cuff. The muscle fibres converge into tendinous tissue under the acromion and merge together with infraspinatus as it inserts triangularly on the greater tubercle (Figure 2). According to more recent work on anatomy of the rotator cuff, the size of the footprint is about 7 mm in the coronal plane (maximum medial to lateral length) and 13 mm in the sagittal plane (maximum anterior to posterior width) [12]. Parts of the tendon fibres participate in forming the roof of the biceps pulley system. To some extent, parts of the tendon insert on the lesser tubercle [12]. The supraspinatus is innervated by the suprascapular nerve from the upper trunk of the brachial plexus (C5-C6).

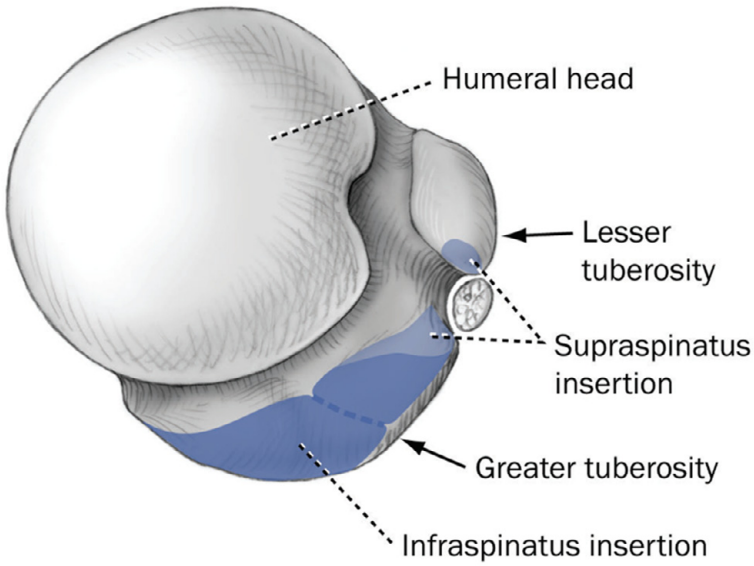


Figure 2. Illustration of the anatomy of superior aspect of the proximal humerus with the supraspinatus (light blue) and the larger infraspinatus (marine blue) footprint. Published in JBJS, reprinted with permission from Wolters Kluwer Health, Inc.

Infraspinatus

This muscle originates inferior to the scapular spine and covers almost the entire back of the scapular body. The fibres converge into tendinous tissue after passing the joint line and merge partially with the supraspinatus as it inserts on the greater tubercle together and, posterior and lateral to the footprint of the supraspinatus (Figure 2). The size of the infraspinatus footprint is much larger than the one from supraspinatus, trapezoid shaped with a medial to lateral length of about 10 mm and an anterior to posterior width of 33 mm [12]. The infraspinatus muscle is like the supraspinatus muscle, innervated by the suprascapular nerve, through motor branches arising from the nerve just after passing the spinoglenoid notch.

Teres minor

The teres minor (teres being Latin for rounded) is both anatomically and functionally closely associated with its superior neighbour infraspinatus. The origin is adjacent to the infraspinatus on the axillary border of the scapula and the insertion site is just inferior to the infraspinatus footprint on the greater tubercle. The size of the footprint has been measured to be 11.4 mm from medial to lateral and 20.7 mm from superior to inferior in the sagittal plane [18]. The anterior and superior part of the rotator cuff insert directly lateral to the articular cartilage surface, in contrast to parts of the infraspinatus and the teres minor, which leave a bare area between the lateral margin of the cartilage and the rotator cuff footprint. This intra-articular bare area has been found to be 14 mm in medial to lateral dimension at the most inferior

aspect of the teres minor insertion. The teres minor muscle is innervated by the axillary nerve from the posterior cord of the brachial plexus (C4 – C6).

Rotator interval, biceps pulley system and rotator cable

The rotator interval forms a triangular gap in the anterior part of the rotator cuff. It is a complex anatomical region which plays an important role in the glenohumeral joint stability. It comprises important ligamentous structures; the coracohumeral ligament, the superior glenohumeral ligament and the anterosuperior capsule. These structures, together with subscapularis and supraspinatus, stabilize the long head of the biceps laterally in the rotator interval and are known as the biceps pulley system [19]. From this area, a thickening deeper part of the capsule is forming a ligamentous transverse structure named Ligamentous semicirculare humeri, or more commonly known as the rotator cable (Figure 3) [20, 21]. It inserts posteriorly adjacent to, or together with the inferior part of the infraspinatus footprint on the greater tubercle. This arch has shown variable thickness and it seems to become thicker with increasing age [22]. Its function is not fully understood, but it is proposed that the cable structure provides a bridging mechanism between the anterior and posterior cuff protecting the cuff tissue laterally [23, 24]. Stress is transferred from medial cuff tissue through the loaded cable structure to the humerus at the important anchoring sites. For this reason, it is described as the suspension bridge of the shoulder, and its involvement or not, in a rotator cuff tear may explain differences in functional outcome of both operative and nonoperative treatment [25, 26].

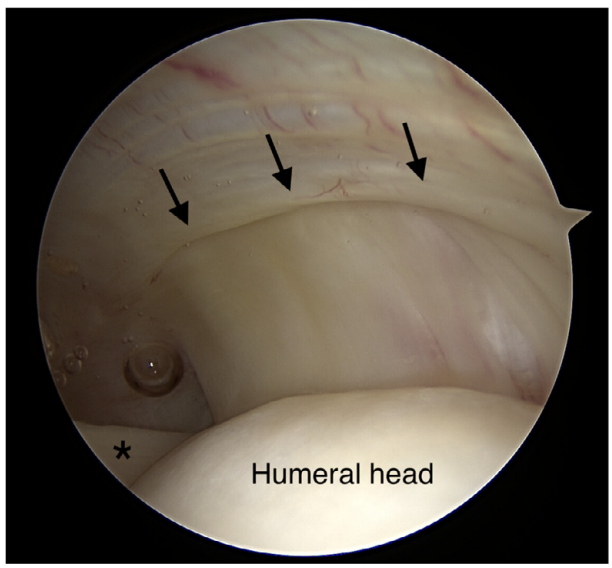


Figure 3. Arthroscopic view in a right shoulder with the rotator cable demonstrated with black arrows and its relation to the long head of biceps (*) (courtesy of Knut Aagaard).

Microanatomy

The supraspinatus tendon has a five-layer structure of the cuff-capsule complex just medial to the insertion site at the greater tubercle [27]. The most superficial layer (1 mm thick) consists of fibres from the coracohumeral ligament. The second 3-5 mm thick layer consists of large bundles of parallel tendon fibres extending from the muscle belly to the insertion on the humerus. In the third layer (3 mm thick) the collagen fibres are smaller, obliquely orientated in relation to layer two and intermingle with fibres from the adjacent subscapularis and infraspinatus. Loose connective tissue containing thick bands of collagen fibres forms the thin fourth layer. It merges with the deep extension of the coracohumeral ligament. Just proximal to the insertion on humerus, anteriorly, thick bands of fibres from the coracohumeral ligament run perpendicular to the primary tendon fibre orientation towards the posterior edge of the infraspinatus tendon. This transverse band is referred to as the rotator cable, as described above (Figure 3) [24, 27, 28]. The fifth layer consists of the 2 mm thick glenohumeral joint capsule with fibres of varying orientation. Histology of the supraspinatus insertion site has shown a fibrocartilaginous tissue consisting of tendon, layers of fibrocartilage and calcified fibrocartilage, and bone [29]. The functional meaning of this fibrocartilaginous transition zone is proposed to avoid a direct tendon-to-bone interface, protecting the tendon attachment from wear caused by bending and twisting forces.

Function

The glenohumeral joint has a greater range of motion (ROM) than any other joint in the human body [30], and shoulder function has been described as the perfect compromise between mobility and stability [31]. The large ROM is due to a wide and loose joint capsule in combination with limited skeletal restraints. The four rotator cuff muscles and their tendons act both as dynamic stabilizer of the glenohumeral joint and as active movers. For the motion of the glenohumeral joint, they play different roles and their function may vary depending on the shoulder position. The main function of the subscapularis is internal rotation in relation to the scapula. The muscle also acts as an adductor. The supraspinatus muscle plays an important role in the abduction of the arm, where it acts together with the deltoid and several other muscles. Historically, the supraspinatus was considered to be the main activator of the abduction however, recent research has shown that the deltoid, infraspinatus, upper and lower trapezium and serratus anterior are all recruited prior to the abduction movement, together with the supraspinatus. Both the infraspinatus and the teres minor act as external rotators of the humerus.

Shoulder motion comprises not only movement of the humerus in relation to the glenoid cavity. The elevation of the arm include motion in all the four shoulder

girdle joints: sternoclavicular, acromioclavicular, glenohumeral, and scapulathoracic articulation. For this motion, a large number of muscles are involved. For the perfect balance, some muscles are working together as agonists and some are acting as antagonists. Helping understanding the complexity, the force couple theory has also been applied to the shoulder movement [32]. For example, the subscapularis works as an internal rotator and its force needs to be neutralized be the activation of the infraspinatus, the antagonist and the external rotator in this force couple, so that the humeral head does not dislocate. During abduction the deltoid and the supraspinatus will together create a resultant joint force directed towards the glenoid. This prevents a superior migration of the humeral head as it is compressed against the glenoid cavity.

Injuries to the rotator cuff may cause a great variety and degree of symptoms. Some patients with small rotator cuff tears (RCT) will have great difficulties regaining full function and pain relief whereas others, with larger tears, may recover quickly and experience only limited restrictions. Besides the different levels of activity, the ability to compensate differs between individuals. When the supraspinatus is gone, you have to rely on the other muscles involved in the abduction and the stabilization of the humeral head preventing the superior subluxation during abduction and forward flexion.

Rotator cuff tears

Epidemiology

Shoulder pain is common in the general population. The point prevalence of shoulder pain in earlier studies differs from 7-27% in patients younger than 70 years of age and 13-26% for patients older than 70 years [33]. The most prevalent cause of shoulder pain and dysfunction is tearing of one or several of the rotator cuff tendons [1]. The rotator cuff is subject to degenerative changes over time and there is strong evidence that the number of tears increases with age [34-37]. However, a tear does not necessarily lead to dysfunction or pain. Milgrom et al. found a linear increase of lesions in asymptomatic individuals after the age of 50, and in their examined population, over 50% of the individuals aged 70 or above had a present partial or full-thickness lesion [38]. In another study by Tempelhof et al. a similar picture was presented: out of 411 asymptomatic volunteers over 50 years old, 23% had a present full-thickness RCT [39]. Yamamoto et al. found a prevalence of full-thickness tears of 20.7% in the general population, with and without shoulder symptoms (mean age 57.9 years) [40]. A 7.6% prevalence was found by Moosmayer et al. when they, by using ultrasound, diagnosed 32 full-thickness RCT in 420 asymptomatic volunteers aged between 50 and 79 years [41].

Pathogenesis

The multifaceted pathogenesis of RCT is still not fully understood. There seems to be consensus that a multifactorial process, consisting of both extrinsic and intrinsic factors, gradually weakens the tendon leaving it more prone to rupture [42, 43]. The extrinsic factors cause damage to the rotator cuff through direct strain on the tendons from the adjacent soft tissue or compression by bony impingement. This compression occurs from a static or dynamic narrowing of the subacromial space due to anatomical or biomechanical abnormalities. For instance, Bigliani et al. showed that the acromial anatomical shape, which they divided into three subtypes: type I (flat), type II (curved), and type III (hooked), is a risk factor for RCT [44]. They found that type III acromion was found in the majority of their examined patients with RCT. Moor et al. have showed a positive relationship between an increased critical shoulder angle (CSA, i.e. the angle between the glenoid fossa plane and a line from the inferior glenoid edge to the lateral edge of the acromion) and RCTs [45]. Recent studies have both reputed [46, 47] and supported these findings [48-50].

Intrinsic factors of rotator cuff tendinopathy and tearing are expressions of degeneration with visible morphological changes. There is growing evidence supporting a number of claims regarding the cause of histopathological changes within the tendons [42]. The natural process of aging is one of the more postulated reasons for degenerative changes, leading to chondroid metaplasia, hyaline degeneration, and reduced cellularity [39, 51]. Vascularity seems to play an important role in the pathogenesis where aging often leads to increased vascularity, theorized as a response to micro-trauma. On the other hand, according to a histopathological study by Matthews et al. the vascularity decreases as the size of the RCT increases [52]. It is still unclear whether avascularity is the reason for or a consequence of the tear. Another acclaimed intrinsic mechanism is tensile overload of the supraspinatus tendon under uniaxial loading, where strain varies with the degree of shoulder abduction. Increased strain is implied to predispose tears in the articular tendinous zone [53]. Further research is necessary to determine the exact role of movement-induced tendon compression and stress-shielding (a decrease in tendon load). Certain joint positions have been shown to induce excessive tensile stress on commonly tendinopathic areas of the tendon which may alter the prevention and treatment using physical therapy in the future [54].

Studies on familiar predisposition have suggested a genetic role in the pathogenesis of rotator cuff disease [37, 55, 56]. Harvie et al. compared siblings and used spouses as a control group. They found a relative risk of 2.42 for full-thickness rotator cuff tear and for symptomatic FTRCTs the relative risk was 4.65 in siblings versus controls. Since the pathogenesis is multifactorial, it has been difficult to find out exactly which genetic pathway plays the most important role. Gene changes associated with apoptosis, extracellular matrix remodelling, angiogenesis, changes

in metabolism, and stress-related genes are understood to contribute to rotator cuff tendinopathies and tearing [57].

Classifications

There are several classification systems used among radiologists and surgeons. Classification is important because different types of rotator cuff tears may need different kinds of treatment. From a patient's perspective, we separate the symptomatic from the asymptomatic tears. Cuff tears are also classified according to the onset of symptoms. Tears are most often divided in chronic, acute, or a combination of both, so called acute-on-chronic. Some authors use acute and traumatic as synonyms, but to be more precise, acute or chronic refers to onset and duration and the more aetiological traumatic refers to various forces from outside the body causing tissue damage. To describe morphology there are many classification systems, some developed for evaluation based on CT or MRI and others developed for intra-operative grading or typing. First, based on whether the tear goes through the whole tendon or not, full-thickness rotator cuff tears (FTRCT) are separated from partial-thickness (PTRCT), either intra-tendinous, bursal-, or articular-sided. Second, tear size based on tendon retraction can be measured in the coronal plane according to Patte in a simple three staging scale [58]. DeOrio and Cofield classified the tears as small (<1 cm), medium (1-3 cm), large (3-5 cm) or massive (>5 cm) according to the maximum measurement in either the coronal or in the sagittal plane [59]. Tear size may also be measured by the number of involved tendons [60]. Third, tear location may be classified into either which tendons that are involved, or more commonly into groups: anterosuperior including subscapularis, rotator interval, long head of biceps and supraspinatus; superior including supraspinatus tendon only; and posterosuperior tears including supraspinatus and infraspinatus and in rare cases teres minor. Global tears include tears of the subscapularis, supraspinatus and infraspinatus tendons. An example of this is the Collin classification in type A-E which however, does not include subscapularis single tendon tear. Finally, rotator cuff tears are also classified or described according to their geometric appearance in crescent, U-shape, reverse L-, L-shape, trapezoidal and massive tear according to Ellman and Gartsman [61]. The shape and the localization of the tear seem to be important due to any disruption of the rotator cable or not [26, 62]. Whereas Yoon et al. found no differences in clinical and structural outcome after repair of anterosuperior cuff tears regarding the presence the rotator cable involvement [63], others have reported an association with fatty infiltration and tear progression and healing failure after repair of chronic tears [64, 65].

Muscle atrophy and fatty infiltration can be calculated and graded in different ways. By using MRI, direct volume estimation has been defined as accurate but impractical [66, 67]. Recently, new application software has been launched and this

may lead to increased usability and popularity. Three additional methods have been used to assess for rotator cuff muscle atrophy, the scapular ratio according to Thomazeau [68], the "tangent sign" described by Zanetti [69], and lastly the 4-graded scale according to Warner, rating both supra- and infraspinatus [70]. In this present project, the tangent sign has been used. Muscle atrophy has been associated with inferior structural and clinical outcome after surgical repair [60, 68, 70-72]. Rotator cuff muscle atrophy may in some cases be reversible after successful repair [71, 73]. The main limitation of the dichotomous classification of Zanetti is that there are many patients with moderate atrophy and this potential important subgroup is difficult to grade correctly [74]. Another critical limitation to atrophy classification systems is the causal relationship between increase in tear retraction and decrease in cross-section area of the supraspinatus muscle on MRI [75]. The latter is the reason we choose not to include atrophy in demographics or analyses in the studies included in this thesis. Furthermore, individuals with rotator cuff tears inevitably develop fatty infiltration of the rotator cuff muscles. This specific muscle degeneration is another defined predictive factor for surgical outcome [70, 72, 76-78], and is originally evaluated according to the CT-based classification of Goutallier [8]. The classification has been adapted to MRI by Fuchs et al. [79]. Historically, fatty infiltration has been considered mainly as a result of either an FTRCT based on the significant unloading mechanism or, a denervation of varying reasons, including traction to the suprascapular nerve. This statement seems to be correct for moderate and high-grade fatty infiltration. However, for low-grade fatty infiltration, there seems to be reason for accepting even age [80] and obesity [81] as cause for this likely irreversible degenerative process. Kim et al. have shown an association with tear size and location [82]. Fatty degeneration of the supraspinatus muscle was more predominant in tears with shorter distance from the biceps. The authors speculate that this might be due to the disruption of the anterior attachment of the rotator cable. In the presence of a supraspinatus tear, the FI starts in the anterior part of the supraspinatus muscle belly. Goutallier is a 5-point score whereas Fuchs is often 3-point score. Similar to atrophy, a positive relationship between increased retraction and level of fatty infiltration has been published however, if there is a causal relationship or just a correlation remains unclear [83]. The subjective 5-scale grading is another limitation which Fuchs et al. has shown that may be reduced by the use of the simplified 3-point score [79].

Histopathology

Tendinitis. Tendinosis. Tendinopathy.

Healthy tendons consist of strong connective tissue due to large amounts of tightly bundled, predominantly longitudinal oriented collagen I fibres. As an example, the Achilles tendon can withstand forces up to more than twelve times the body weight [84]. Full-thickness rotator cuff tears are rare in the younger population and among

the adolescents. Instead tendon tears occur at the skeletal immature insertion site of the tendon and thus, periosteal sleeve fractures and apophyseal avulsions appear [85, 86]. However, during aging several histological changes occur and the tendon is gradually weakened [87]. This degenerative process may be asymptomatic and a rotator cuff tear could be the patient´s first sign of this tendon aging path. Others experience pain and dysfunction at a younger age due to the pathological process referred to as tendinopathy. This umbrella term was advocated by Maffulli et al. in the late 1990s [88], when there was a shift from the use of "tendinitis" to "tendinopathy" or "tendinosis" due to non-inflammation theories. More recent research indicates that inflammation does accompany tendon overuse injuries, and may play an important role in tendon deterioration [89-91]. Currently, the term tendinitis is again used to describe any acute or chronic painful tendon impairment as inflammatory cells and markers are found in histological studies, especially in the early mild to moderate stages of tendinopathy [90, 92]. Tendinosis however, is considered as a chronic degenerative condition, as a result of a combination of mechanical (excessive loading, micro-trauma, impingement), extrinsic (smoking, poor nutrition, alcohol consumption, pharmacological agents), and intrinsic (normal aging, genetics, body weight, other comorbidity) factors [42].

The tendinopathic and degenerative tendon tissue show several similar histological changes: a disorganization of the collagen fibres, an increase of the vascularization and the number of sensory nerves, a breakdown of tissue organization (tendon, endotendon, paratendon), increased cell death (i.e. areas of hypocellularity), hypercellularity (more common in reactive, tendinopathic tissue), increased levels of leukocytes like macrophages and mast cells, and metaplasia with chondroid transformation and increased numbers of adipocytes. To quantify these histopathological changes, different scoring systems have been developed. Both the Movin and the Bonar scores are frequently used as original scores or modified and revised versions and they assess the same characteristics [93]. Originally, the Movin score was developed for achillodynia and the Bonar score for the assessment of patellar tendinopathy [94]. Later, both scoring systems have been in usage for the assessment and classification of different types of tendinopathies, including rotator cuff tendinopathy.

The role of inflammation in tendinopathy is however not clear. As mentioned above, this topic has been disputed in the literature. Historically, there have been significant controversies. Inflammation is a biochemical process which according to Celsius, the Roman scholar, feature calor (heat), dolor (pain), rubor (redness), and tumor (swelling). However, the definition has over the years differed and today, we also need to distinguish the acute inflammation from the chronic. Whereas the acute inflammation often is associated with the infiltration of inflammatory cells, chronic inflammation can be defined as a prolonged, dysregulated and maladaptive response that involves active inflammation, tissue destruction and attempts of tissue repair [95]. There is no exact definition of inflammatory cells, but polymorphonuclear

leukocytes (PMNs which includes neutrophils, eosinophils, basophils and mast cells), monocytes/macrophages, and T-cells are all considered as inflammatory cells [96].

Apoptosis, also known as programmed cell death, is a physiological process in healthy tissue and necessary to maintain proper tissue homeostasis is. This process is also found in many different human disorders, including osteoarthritis [97-99], rheumatoid arthritis [100, 101], neoplasia [102] neurodegeneration [103, 104], and tendinopathy [105, 106]. The relationship between apoptosis and tendinopathy has also been studied, where increased level of apoptosis is believed to be associated with tendinopathy and tearing of the rotator cuff [105, 107, 108]. Hypoxia, mechanical loading, inflammation, and genetic predisposition are described risk factors for enhanced apoptotic tenocyte death [106, 109, 110]. Further, the literature supports an association between pathological apoptosis and tissue degeneration. Chen et al. studied chronic lateral humeral epicondylitis and found a higher apoptotic rate in tendons with an increased degree of degeneration compared to low grade degeneration [111], and tissue remodelling and proliferation are highly associated with pathological apoptosis. In the human patellar tendon, regions with increased matrix remodelling also show higher rates of tenocyte apoptosis and proliferation [112]. The extracellular matrix (ECM) is dependent of living tenocytes producing ECM, where collagen type I represents the main component, together with collagen type III, V, VI, XII, and XIV. Turnover of the ECM is mediated by matrix metalloproteinases (MMPs), which furthermore is regulated by tissue inhibitors of metalloproteinases (TIMP). Elevated plasma levels of TIMP have been reported in patients with rotator cuff tears compared to intact tendons [113]. This may indicate that the development of tearing is not solely local, and that a systemic process cannot be excluded, where genetic factors have been discussed. This systemic theory agrees with histopathological findings in Achilles tendons. Cetti et al. found a widespread bilateral tendon damage in patients with spontaneous Achilles tendon rupture [114].

Yuan and colleagues reported excessive apoptosis in ruptured rotator cuff tendons from patients with a mean age of 61 years, but could not determine whether the pathological level of apoptosis preceded and was causative, or a result of the tear [108]. Lundgreen et al. also found increased tenocyte apoptosis in torn supraspinatus tendons, as well as in intact subscapularis tendons in the same cohort [107]. This indicates a generalized apoptotic activity throughout the whole rotator cuff, not only in the torn tendon. Apoptosis may be p53 dependent or non-dependent. p53 is a powerful tumour suppressor protein; it prevents cancer formation, and is described as “the guardian of the genome” due to its role in conserving stability by preventing mutations [115]. In *Paper III* in this thesis, we used the p53 maker to assess apoptosis in torn supraspinatus tendons.

Imaging

The most commonly used modalities assessing shoulders for rotator cuff pathology are plain radiography, sonography, magnetic resonance imaging (MRI) or arthrography (MRA), and computer tomography arthrography (CTA).

Plain radiography

Conventional plain radiogram has still an important role in the initial clinical assessment of patients with shoulder pain and dysfunction. Obvious disadvantages, like its ineffectiveness of soft tissue imaging, may be outweighed by the easiness of the investigation, the reproducibility, the low cost, and relative safety. Most shoulder surgeons and musculoskeletal radiologists would prefer (1) a true anteroposterior (AP) view, with the humerus both internally and externally rotated; (2) a scapular outlet view; and (3) an AP view with 30 degrees caudal tilt to appreciate the acromio-clavicular joint in particular. In the setting of a traumatic injury, modifications due to pain and different anticipated pathology are made. The two AP views do not need to be true AP, the scapular outlet view is replaced by scapula Y or an axillary view, and the AC joint film does not belong to the standard views. The films will guide in two different ways. First, the findings will diagnose or rule out fractures, osteoarthritis, osteonecrosis, and other bony pathology. Second, increased acromial sclerosis, cortical changes of the footprint area, calcification of tendons or bursa, traction spurs in the coraco-acromial ligament, cranial migration of the humeral head, and finally an acetabularization of the acromion are all important findings when diagnosing the chronicity or the severity of the rotator cuff disease. For example, a reduced acromio-humeral distance of less than 7 mm has been associated with an FTRCT, as well as a negative correlation between tear size and grade of fatty infiltration and the acromio-humeral distance [116].

Sonography

Ultrasound with a high-frequency linear array transducer may provide prompt diagnosis. Several advantages make it a popular diagnostic tool, both inside and outside hospital environment. It is widely available, non-invasive and without ionization radiation. It allows routine dynamic and bilateral examination and direct clinical correlation, and is less time-consuming and more cost-efficient compared to MRI. Furthermore, it has no known side effects [117-119]. The main disadvantages of sonography are substantial limitations in the assessment and grading of muscle atrophy and fatty infiltration, its hands-on aspect, which makes the full diagnostic impact of the study only accessible to the executing sonographer, and its low diagnostic value for con concomitant shoulder pathology such as labral tears, articular damage and scapular fractures [120]. This is the reason we choose MRI for imaging in the studies comprised in this thesis.

For rotator cuff tears and biceps pathology standardized diagnostic criteria have been defined [121, 122]. The diagnostic accuracy has been shown to be high, sensitivities and specificities of 90% and above have been calculated with respect to full-thickness tears [118, 123, 124].

Magnetic resonance imaging

MRI provides the clinician with the most information compared to the other radiological modalities. However, MRI is not the modality of choice in first-line assessment of patients with shoulder pain or suspected rotator cuff pathology. Most often, plain radiography in combination with sonography will give the clinician enough information. MRI may be indicated to assess muscle atrophy or fatty infiltration as a preoperative additional investigation. MRI is also indicated if the diagnosis is not clear after initial x-rays and sonography. "MRI shoulder" is a standardized investigation which includes different images and sequences in three planes: oblique coronal (1), oblique sagittal (2), and axial (3). The sensitivity for detecting partial-thickness tears has been shown to be inferior compared to MRI arthrography. However, regarding full-thickness tears, MRI has a sensitivity and specificity of at least 90%, similar or superior to sonography. In the presence of an acute shoulder trauma, MRI also has a high diagnostic value in diagnosing occult fractures of the proximal humerus and the scapula. The lowest diagnostic accuracy is found detecting subscapularis tears. A recent meta-analysis estimated an accuracy of 0.90, lower than for the other cuff tendons, due to a low sensitivity of 0.60 [125]. Adapting knowledge from arthroscopy findings, together with improved imaging quality, may in the future increase the sensitivity. As an example, the ASAP cohort had several cases of a retracted, medialised middle glenohumeral ligament (MGHL). During arthroscopy, this is known as the hidden ligament and by pulling on the subscapularis tendon, the MGHL is reduced back to its anatomical position. On MRI this can be visualised by a ligamentous structure anterior and medial to the labrum on axial sequences (Figure 4).

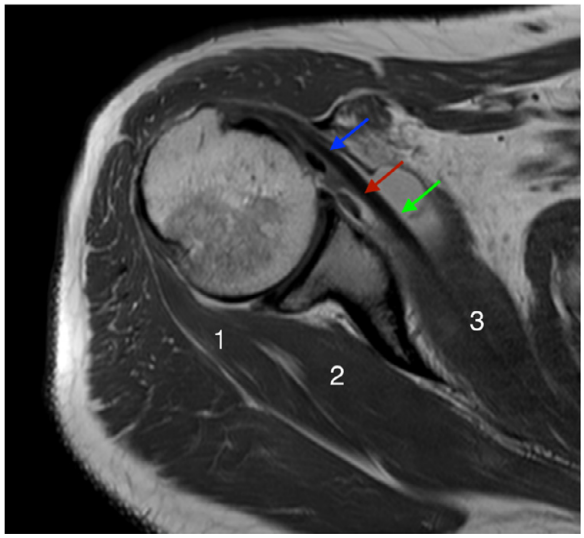


Figure 4. Example of elongated and torn subscapularis tendon (green arrow) with dislocated long head of biceps (blue arrow) with a typical medialised middle glenohumeral ligament (red arrow). Muscle bellies for orientation: (1) teres minor; (2) infraspinatus; (3) subscapularis.

MRI may be difficult to perform on patients with very painful shoulders. Pain relieving medication should be offered. In patients with claustrophobia, tranquilizer or sedatives can be used. Some pacemakers, intracranial magnetic clips, neuro-stimulators, and ocular foreign metallic bodies are examples of potential contraindications.

Acute trauma-related tears have some typical features that might aid the radiologist and the shoulder surgeon to discriminate the genesis from nontraumatic. An oedema (white appearance on T2) within the tendomuscular transition and muscle tissue itself has been reported to be the most frequent phenomenon with a positive predictive value of 93.7% [126] (Figure 5B). In the same study by Loew et al., kinking of the ruptured tendon was also shown to be more common among TRCTs. This term defines a wavelike feathering appearance of the cuff (Figure 6). This feature is believed to be a sign of preserved elasticity of the tissue, leading to less tension if repaired. Further characteristics that are supportive of a possible causal link between a traumatic injury and a RCT, are fluid in the bursa and in the joint [127] and bone marrow oedema at the grater tubercle [128].

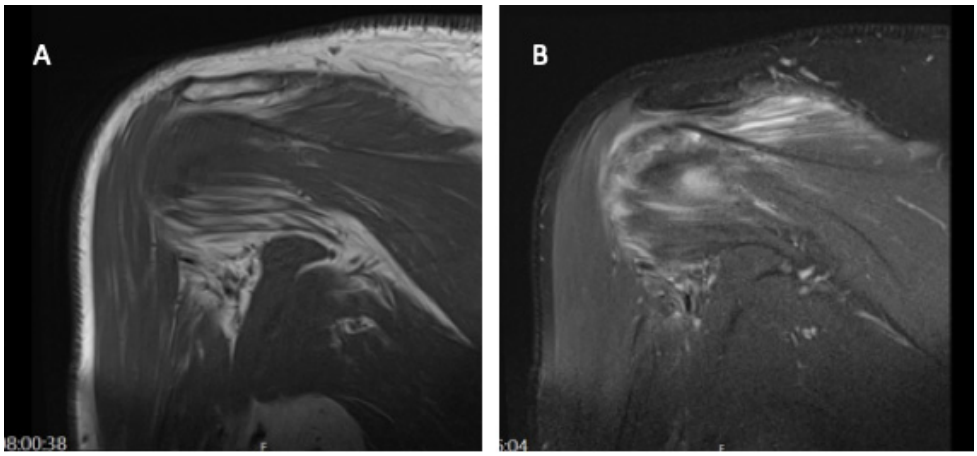


Figure 5. Example of less common fatty infiltration of the teres minor muscle alone in an acute trauma-related rotator cuff tear, visualized in a with T1 (fat appearce white). In B we appriciate the for the acute tear typical muscle edema (white in the infraspinatus muscle), best visuallized with fat supression (pd cor spair) image

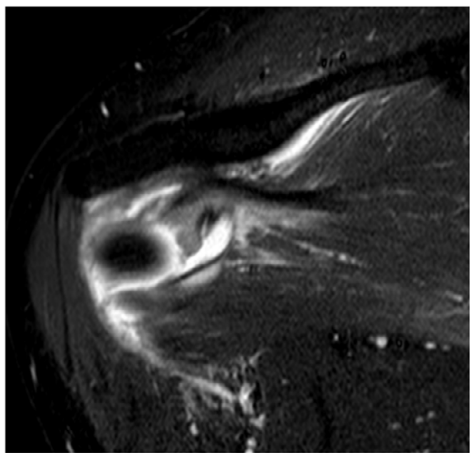


Figure 6. Kinking and wavelike feathering appearance of the infraspiantus tendon in a large posterosuperior cuff tear

Computed Tomography

CT is usually preserved for the evaluation of complex fractures or prosthetic shoulder joints. The ability to visualize the joint in three different planes is valuable for interpretation and preoperative planning. CT may be combined with intra-articular contrast, and the computer tomography arthrography is still in some centres popular for detection of rotator cuff and biceps pathology.

Treatment

Due to the large diversity of symptoms and patient characteristics, like age, level of activity, comorbidities, and physical demands, the treatment of RCTs should be individualized. For chronic tears to date, a small number of randomized controlled trials has been conducted and there is no clear support favouring operative treatment over conservative management [10, 129, 130]. There are studies reporting statistically significantly better outcome scores among repaired patients, but the difference is on or below the threshold for minimal clinical importance. Further, several studies have failed to demonstrate better clinical outcome scores in patients with healed repairs, compared to the patients with healing failure [131, 132]. This might reflect the effect of placebo, or just an adaptation over time. Long-term results are sparse however, trials indicate that patients treated with rotator cuff repair have favourable long-term outcome [133], and that there is a high risk for secondary rotator cuff arthropathy in non-repaired patients [134]. The majority of the trials have been exclusively studying small to medium sized and mostly chronic, nontraumatic tears.

For acute, trauma-related tears, only one randomized control trial has been performed [135]. Ranebo and co-workers studied 58 patients with exclusively trauma-related, small tears with a median tear size of 9.7 mm. One half underwent mini-open cuff repair and the second half received physical therapy. There were no significant differences in clinical outcome scores after one year. The short follow-up, the small number of patients with risk of under-powering, and the small tear size are some limitations of this study. A larger, multi-centre, randomized, placebo-controlled trial is currently ongoing and will hopefully provide further knowledge to this topic. However, even in this trial, large and massive tears are excluded, as well as tears involving the subscapularis tendon [136].

Physical therapy

When conservative or nonoperative management is advised, physiotherapy is the cornerstone of the treatment. Non-steroidal anti-inflammatory drugs (NSAIDS), steroid injections or other treatment modalities are often added to different exercise programs. The rationale of physiotherapy with exercise programs is to (1) strengthen the remaining parts of the rotator cuff; (2) address secondary thoraco-scapular dysfunction with correction of posture and strengthening of periscapular muscles; and (3) address posterior capsular tightness with stretching [137]. Both supervised shoulder rehabilitation programs [138] as well as patient education and home program, have been reported with successful outcome [139].

Surgical treatment

There are many surgical alternatives when operative treatment of a full-thickness rotator cuff tear is chosen, and the far most common method is the rotator cuff repair (RCR). Approach options are open, mini-open or arthroscopically assisted, and

arthroscopic repair. Arthroscopic rotator cuff repair is today one of the most common surgeries performed in orthopaedics and has evolved to become the gold standard according to many authors [140]. However, this evolution has not been driven by superior outcome. Systematic reviews and long-term follow-up (>10 years) after a randomized controlled trial have failed to show any superiority with regards to clinical and structural outcome [141, 142]. Through three to five 1-1.5 cm small incisions around the shoulder, tools for visualization and instrumentation are used for diagnosing, preparing and finally suturing cuff tendon down to footprint. The bone tunnel technique which is most commonly used in the open approaches, was first described Codman in 1911 [143]. Over the years, as the quality of suture anchors improved, the suture anchor technique gain popularity. Single row techniques advanced to double row and transosseous equivalent (TOE) and knotless techniques were developed. There is no strong evidence for the clinical outcome superiority of the double row and TOE repair techniques. Recently, arthroscopic transosseous (ATO) repair has been developed and may gain popularity primarily due to a lower implant cost.

When the cuff tear is considered irreparable, i.e. fatty infiltration of Goutallier grade 3 (on the 5-staged grading) or beyond, reverse shoulder arthroplasty is considered gold standard in elderly patients, with or without pseudoparalysis. In the younger population, tendon transfers or superior capsular reconstruction (SCR) may be indicated. Finally, a biodegradable implantable balloon (spacer) has been developed to reduce subacromial friction, and thus the pain, in patients with massive irreparable RCT without pseudoparalysis. A cost-efficiency trial is ongoing. The latter two surgical options have no long-term evidence.

Adjuncts to surgery

There are many ongoing studies investigating adjunct treatment options. One of the available products which may enhance healing is platelet-rich plasma (PRP). Some in vitro and animal studies have shown promising outcomes, however, these results have not been confirmed in human clinical trials [144-147], and according to the Cochrane review by Moraes et al. there is still insufficient evidence for supporting the usage of PRP as augment in rotator cuff repairs as well as in other soft tissue injuries [148]. Regarding the augmentation with mesenchymal stem cells (MSC), observational trials have been encouraging considering healing enhancement. Yet, randomized controlled trials are needed to demonstrate effectiveness.

Repair healing

What is the goal of rotator cuff repair? From a patient's perspective it would be to become pain free, to fully regain shoulder function, including full range of motion, and good strength in all directions maintained over time. As mentioned above, some trials with one- or two-years follow-up have shown equal PROM regardless of

repair integrity [131, 132]. However, in meta-analyses and in trials with longer follow-up we can see that the patients with intact repairs have superior outcome scores and better strength compared to the individuals with healing failure [149-151]. Thus, from a shoulder surgeon's perspective, the goal should also be to achieve solid healing.

Spontaneous healing of torn intra-synovial tendons, in contrast to extra-synovial like the Achilles tendon, does not occur [152]. The tendon stump needs to be pulled back to a bony surface, secured with sutures or other fixation material and protected from excessive load or traction before healing has occurred. The repair healing follows the typical wound healing process which essentially can be divided into the inflammatory initial phase, followed by proliferation and finally the remodelling phase [153-156]. The inflammatory phase is usually about a week long and is characterized by hematoma, deposition of fibrin, cytokines and growth factors release, and migration of fibroblasts and endothelial cells [157-159]. Profuse synthetic activity characterizes the following proliferation phase, which lasts for a few weeks [160]. Fibroblasts proliferate and start to rebuild connective tissue by producing and cross linking fibrillar collagens. Remodelling will then last for months and during this phase collagen III is replaced by collagen I, the cellular activity and the vascularity are reduced. A histologically unorganized scar tissue with inferior biomechanical qualities compared to healthy tendon tissue will now be found at the healing site [155, 160, 161]. The healing process of the repair is completed.

In clinical studies, when healing of repaired cuff tendons is examined, most authors have been using MRI or ultrasound. No tissue samples are taken as evidence of biological healing. Structural integrity visualized by MRI or ultrasound are proxies for healing, yet not the same as healing. Imaging will show tendon stump repaired and fixed at insertion site, but MRI or ultrasound cannot provide information about actual biological healing or not. For structural integrity, Sugaya et al. have developed a classification system where most authors define Sugaya grade 1,2, and 3 as intact repairs equal to healing and grade 4 and 5 equal to non-healing, healing failure or re-tear [162-165]. The term re-tear implies a preceded healing and should therefore only be used if this can be shown to be the case.

Little is known about the relationship between histopathological changes and healing capacity. Regarding tendon degeneration, Chillemi et al. showed that chondral metaplasia, collagen disorganization, poor or absent neoangiogenesis, and fibrosis were negative factors for cuff repair healing [166]. The cohort in this study differs a lot from the ASAP cohort. Half of the patients were repaired more than one year after trauma or onset of symptoms, and none of the patients had repair within six weeks.

On the opposite side of the repair interface, bone quality may also contribute to healing capacity. Bone vascularization of the greater tuberosity seems to affect

tendon healing. Using CD34-anibodies to evaluate microvascularization in bone samples, Bonnevialle et al. showed that a lower rate of microvessels significantly reduced the healing potential after repair [167].

Rationale for this thesis

Rotator cuff tears are common in the general population and many of these tears are caused or related to a specific shoulder trauma. Surgical management is advocated in active, healthy individuals with large tears and or impaired shoulder function. Late diagnosis leads to delayed repair with substantial risk of inferior clinical outcome. By introducing the Acute Shoulder Assessment Project, we wanted to prevent late or missed rotator cuff tear diagnoses. Through repeated information to all physiotherapists and general practitioners about the risks of late referrals, we minimised the delay to assessment and discussion about treatment. The incidence of acute TRCT prior to this project was not known, but the screening system within the ASAP made it possible to investigate and calculate. And if we are able to provide early diagnosis, what is the outcome after sub-acute surgical repair? Will they all heal? If there is still a high number of healing failures, maybe the tendon tissue quality is compromised even though the impaired shoulder function developed acutely and was related to a specific shoulder trauma? And finally, if the answer cannot be found in the histopathology, what other risk factors are there for healing failure?

Aims

The general aim of this thesis was to generate increased knowledge on acute, trauma-related full-thickness rotator cuff tears (TRCT) in previously asymptomatic patients.

Specific aims in each study

Paper I: To describe the epidemiology of TRCT and estimate a population-based incidence of TRCT.

Paper II: To investigate the structural integrity of TRCT, as visualised on MRI, after early arthroscopic repair with healing as primary outcome and PROMs as secondary outcome.

Paper III: To study histopathological changes of the supraspinatus tendon after TRCT, primarily to grade the level of degeneration as determined by the Bonar score, and secondarily to study levels of inflammation, proliferation, apoptosis, and hemosiderin staining. A cohort of non-traumatic, chronic rotator cuff tears was used as a control group for comparison.

Paper IV: To identify risk factors associated with healing failure in TRCT treated with early arthroscopic repair.

Materials and methods

The ASAP cohort

The Acute Shoulder Assessment Project was launched in 2009 after a pilot study conducted the year before. All general practitioners (GPs) and physiotherapist (PTs) in the catchment area of Helsingborg Hospital (in 2011 268,000 inhabitants) received written information about the project. From November 2010 until March 2014, we prospectively enrolled 463 participants with acute onset of shoulder pain, directly related to a specific shoulder trauma, and with limitations in active arm elevation. The patients were referred either from GPs or PTs at the local primary care units, or from Emergency Department physicians, after an initial physical examination and plain radiographs. Patients aged 18-75 were included. Patients with severe comorbidities, previous treatment for shoulder symptoms including pain and dysfunction, glenohumeral osteoarthritis, or rheumatoid arthritis were excluded. PTs at our institution examined the patients within ten days after the initial clinical assessment.

The participants were divided into three groups. Group I comprised patients with suspected full-thickness rotator cuff tear where active ROM was limited and one or more of the clinical cuff tests were positive. A sub-acute MRI was conducted within two weeks and when a full-thickness rotator cuff tear (FTRCT) was diagnosed, surgery was discussed and offered. Group II included participants who were not under suspicion of a rotator cuff tear, nor had other specific shoulder diagnoses. They presented good active ROM and were diagnosed with a bleeding or a simple sprain. A follow-up telephone interview by a shoulder surgeon after three months was conducted, and if symptoms persisted, an additional physical examination followed in the out-patient clinic. MRI was ordered if the clinical examination could not rule out a RCT. The third and last group comprised patients who all were diagnosed with other specific shoulder diagnoses, explaining their symptoms and dysfunction. The most common injury was an AC-joint sprain. The flowchart of the participant enrolment in the ASAP is shown in Figure 7.

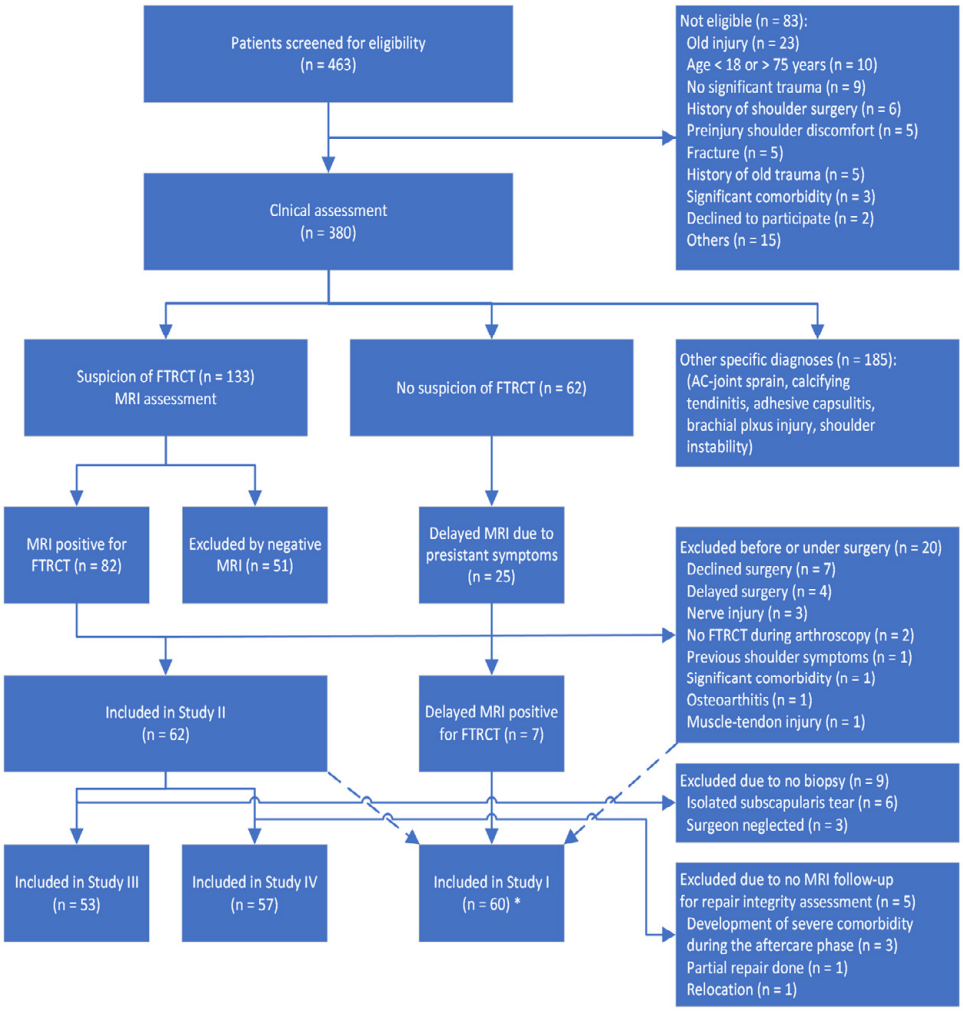
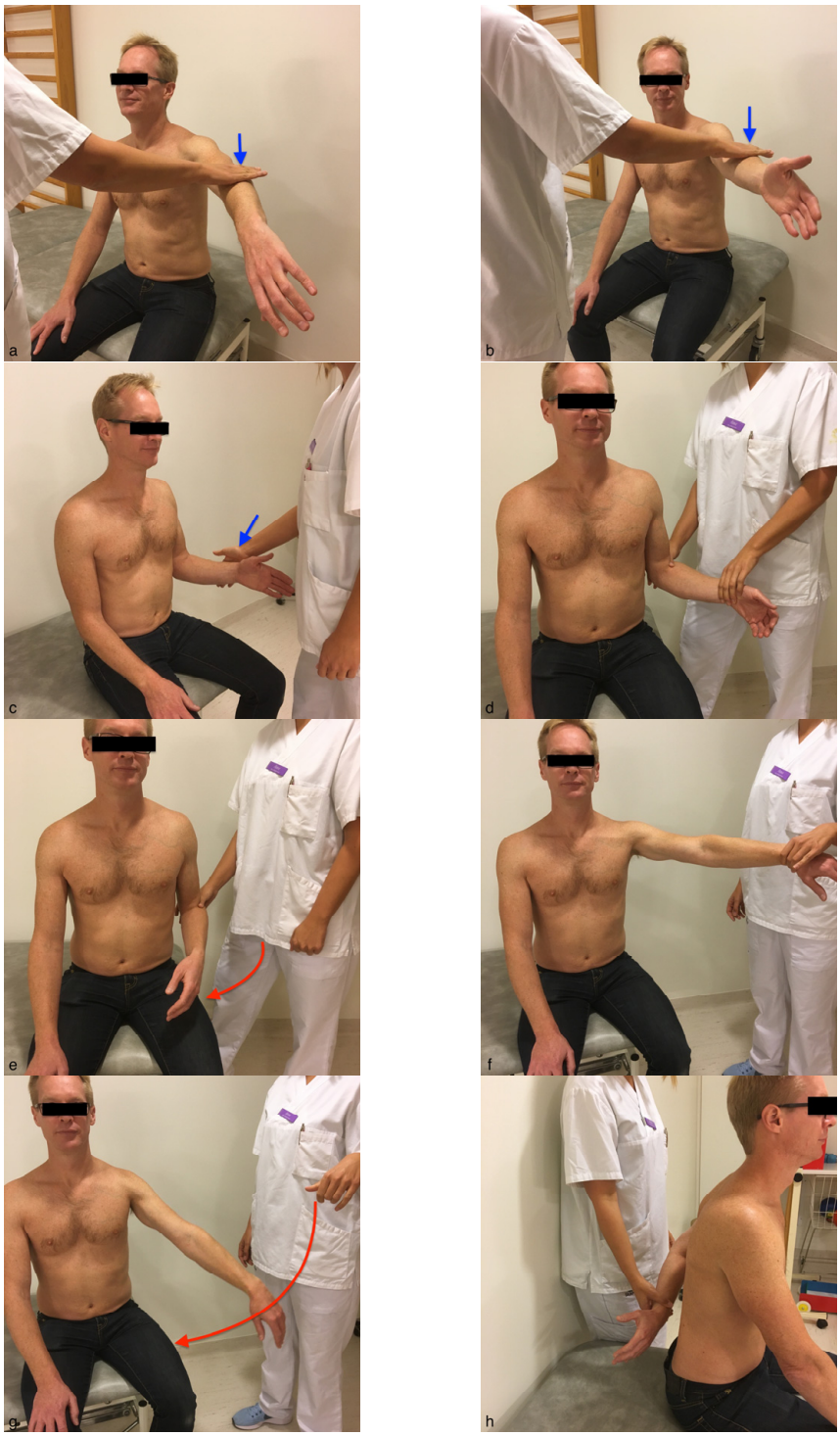


Figure 7. Flowchart of ASAP. * Participants enrolled over a period of two years.

Assessment by the physiotherapist

The physical examination followed a standardized protocol and tests as follow (Figure 8 a-o): Posterosuperior rotator cuff tests that were performed included: empty can, full can, painful arc, isometric external rotation force, external rotation lag, and drop arm. For the subscapularis muscle, the internal rotation lag tests and the belly press were conducted. Additionally, the following tests for AC joint pathology were performed: O'Brien's, cross body, and "patient's index finger localizing AC joint when showing pain origin", and finally the Speed's test for biceps pathology.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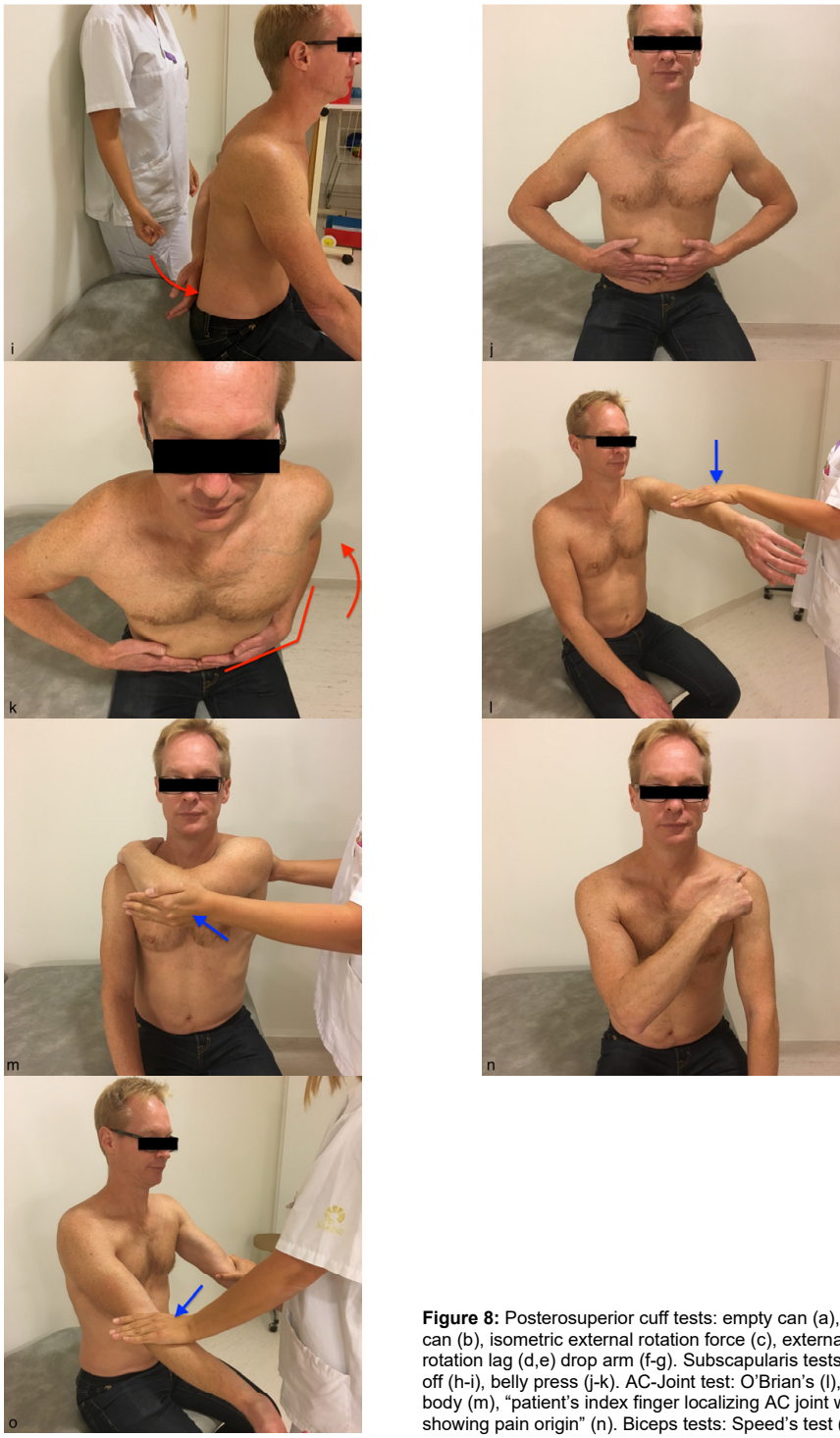

Figure 8: Posterosuperior cuff tests: empty can (a), full can (b), isometric external rotation force (c), external rotation lag (d,e) drop arm (f-g). Subscapularis tests: Lift off (h-i), belly press (j-k). AC-Joint test: O'Brian's (l), cross body (m), "patient's index finger localizing AC joint when showing pain origin" (n). Biceps tests: Speed's test (o).

Imaging

Magnetic resonance imaging

All MRI examinations were performed on a 1.5 T scanner (Siemens Medical Systems, Erlangen, Germany). A dedicated shoulder array coil was used. The arm was placed at the side of the body with the thumb pointing upwards. Seven different sequences, all with a slice thickness of 3–4 mm, a 16 cm field of view and one number of excitations was obtained; one oblique sagittal, four oblique coronal, and two axial sequences. The details are published in *Paper I*.

Specific methods

Paper I

The ASAP cohort was established and the incidence of acute, trauma-related rotator cuff tears estimated. Demographics of this specific cohort was described and other shoulder injuries was registered.

Paper II

Surgery

All procedures were performed under general anaesthesia in the beach chair position, with an interscalene block in most cases. The surgery started with diagnostic arthroscopy and probe measurement of the cuff tear in the coronal plane. In case of biceps instability or tear, tenodesis or tenotomy was performed according to the surgeon's preference. Arthroscopic repair of ruptured tendons was performed using single-row technique. Modified Mason–Allen and margin conversion techniques with side-to-side sutures were also utilized. All operations were performed with Fastin RC 5.0 mm anchors for subscapularis repair and biceps tenodesis on top of the sulcus intertubercularis, and triple loaded Healix 4.5 mm and 5.5 mm anchors (DePuy Synthes Sports Medicine (Mitek), Raynham, Massachusetts) for supra- and infraspinatus repair. Acromioplasty was performed in all cases except for subscapularis single tendon repairs.

Rehabilitation protocol

Postoperatively, all patients underwent rehabilitation in primary care according to an evidence-based standardized protocol. The arm was put in a sling without abduction pillow for four weeks, or six weeks if the entire infraspinatus was involved. During the first four weeks, passive range of motion (ROM) with

elevation up to 145° was allowed. From the fifth week, the patients started with active assisted ROM. The active ROM started at week seven in patients with single tendon repairs and at week ten in those with multiple tendon repairs, followed by strengthening exercises. Clinical evaluations of shoulder function were performed by a PT in our department at three, six, and twelve months, where compliance with rehabilitation was discussed and the individual need for additional sick leave was re-evaluated.

Structural outcome

The integrity of each repaired tendon was assessed according to Sugaya using MR images acquired at one-year follow-up. In agreement with previous studies, we categorized grades 1 to 3 as intact and grades 4 to 5 as having a defect in structural integrity. In classifying into the binary outcomes of this trial, all repaired tendons within the rotator cuff were classified as intact, whereas healing failure was denoted by at least one repaired tendon showing a grade 4 or 5 defect. Interobserver reliability of such classification at one year was assessed by comparison of these results with those of a second, experienced musculoskeletal radiologist, blinded to clinical information and to the results from the first assessment.

Clinical outcome measurements

Constant-Murley Score (CS)

When evaluating a possible change of shoulder function over time after intervention, we used the Constant-Murley Score. It is recommended by the European Society of Shoulder and Elbow Surgery (ESSSE) and is one of the most common shoulder-specific scoring instruments. Based on a 100-point scale composed of a number of individual parameters, CS comprises four subscales: pain (15 points), activities of daily living (20 points), strength (25 points) and ROM (40 points). The higher the score, the greater the shoulder function. A subjective first part evaluates severity of pain, activities of daily living and working in different positions and is responsible for 35 points. The next 65 points are results of objective measurements of ROM and strength. Interobserver reliability was calculated in the original study [168] and a more complete assessment of its reliability in patients with shoulder pathology was later performed by Conboy et al. [169]. The score has moderate evidence for reliability and limited evidence for responsiveness [170, 171]. A minimal clinical important difference (MCID) of 10.4 points has been suggested [172]. Due to age- and gender-related differences in strength and shoulder motion, a relative (also called age- and gender-adjusted, or normalized) CS was developed. For comparison with other populations, we presented both the relative and the absolute CS in *Paper II*.

Western Ontario Rotator Cuff (WORC) index

The Western Ontario Rotator Cuff (WORC) index is a condition-specific self-reported instrument to assess quality of life [173]. It contains 21 items representing five domains, each to be answered on a visual analogue scale. The five domains are Physical symptoms, Sports/Recreation, Work, Lifestyle, and Emotions and the values in millimetres are converted into percentages. Higher percentages indicate proximity to normal shoulder function. The WORC index can be presented as the whole score, as we presented our results in *Paper II*, or for each domain if that provides valuable information. The Swedish version has been tested and found to be reliable, valid and responsive as an instrument for outcome measurement for patients undergoing rotator cuff surgery [174].

EQ-5D-VAS

To evaluate the overall health, we used EQ-VAS. This is a generic, self-reported non-disease-specific instrument and the second part of the EQ-5D questionnaire, the health status component of the EuroQol assessment (EuroQol Group, Rotterdam, The Netherlands) [175]. The EQ VAS is the evaluation part of the EQ-5D where the respondent is asked to mark out the health status on a 20 cm vertical scale with bottom rate 0 as "worse possible health you can imagine" and highest rate 100 as "best health you can imagine". EQ VAS has shown weak but significant external responsiveness (= ability to capture clinically meaningful change over time) in a test of external responsiveness against shoulder surgery score in rotator cuff patients [176], this in contrast to EQ-5D.

Paper III

All patients in this study were extracted from the ASAP. Surgery was performed at a median of 30 (IQR, 25 to 37) days after the shoulder injury. During arthroscopy, and before any radio frequency instruments was used, a biopsy of the most lateral part of the torn supraspinatus tendon was harvested in a standardized fashion using a meniscus upbiter basket punch (Figure 9). The tissue material was then fixed in neutral buffered formalin, transported to the Department of Pathology at Lund University where it was dehydrated and paraffin embedded. Sections of 2 μm were obtained and stained with haematoxylin–eosin (HE) and alcian blue (AB). Sections were then scanned by Nano Zoomer S360 (Hamamatsu, Japan) and evaluated for tendon degeneration. Out of the 62 patients that underwent surgery, six had intact supraspinatus tendons (isolated subscapularis tendon tears) and in three cases the surgeon neglected to harvest a supraspinatus tendon biopsy leaving 53 samples for histopathological analysis. In addition, similar tissue samples were harvested from ten age- and sex-matched individuals with no history of shoulder trauma undergoing surgery for chronic rotator cuff tears. These samples formed the control group referred to as the chronic tears in *Paper III*.

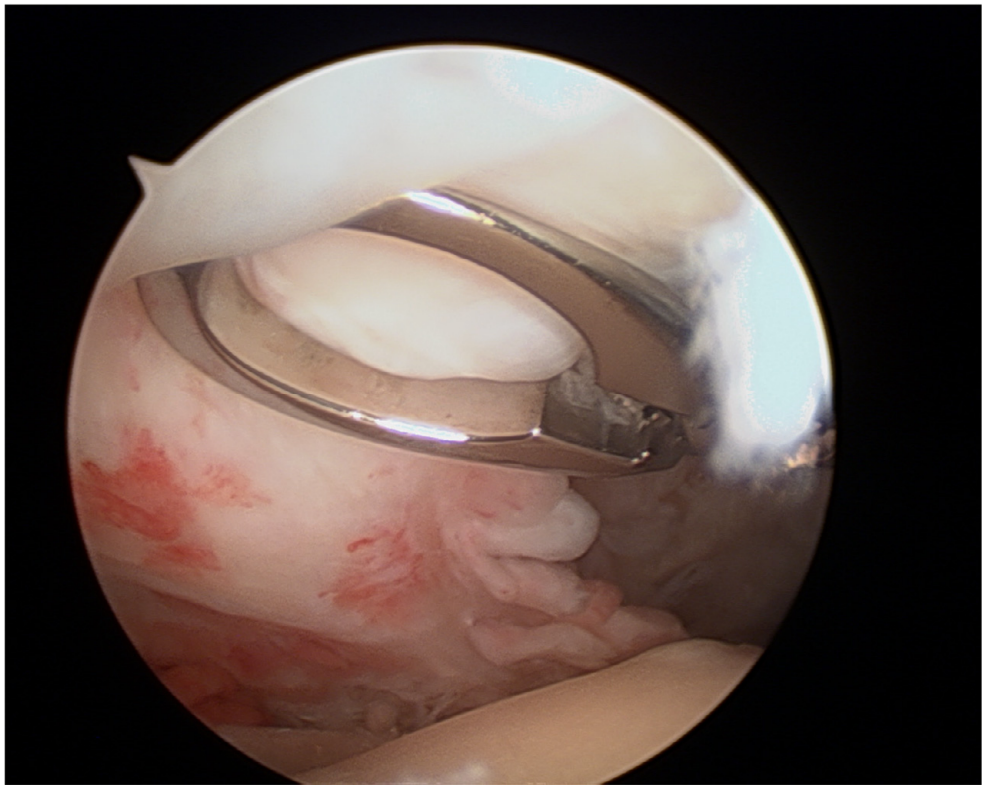

Figure 9: Meniscus upbiter used for harvesting tissue biopsy of the suprapsintus tendon stump, viewing with a 30 degrees scope from the glenohumeral joint in a right shoulder. Note the ecchymosis on the smooth undersurface of the tendon, as proposed sign of a trauma-related tear.

Tendon degeneration as determined by histopathology - the Bonar score

The Bonar score was used to evaluate the extent of tendon degeneration [177]. This score comprises a semi-quantitative grading scale that emphasizes seven pathological qualities in tendinosis: fibroblastic alterations (hyper-/hypocellularity), increased glycosaminoglycan content, collagen disorganization or disarray, hypervascularity or vascular remodelling, cell morphology, calcification, and intratendinous adipocytes. HE stains of 2-µm sections were obtained for assessment of the morphology. AB stains were performed for identification of sulfated glycosaminoglycans (GAG). The first five qualities were graded from 0 to 3 (normal to worst pathological appearance), and the presence of calcification and adipocytes are each given 2.5 points. A completely normal tendon would score 0 and accordingly, a maximally degenerated tendon would score 20 (3 x 5 + 2.5 x 2, Table I, Figure 10). We used the latest modified Bonar score with previously reported good inter-observer reliability (r^2=0.71) [177]. All tissue samples were analysed by an experienced pathologist at the Department of Pathology, Lund University.

Immunohistochemistry

The immunohistochemical tests were conducted at the Department of Pathology, Lund University. To evaluate the degree of inflammatory response, the expression of the pan-leucocyte marker CD45 was studied [178]. The pathologist manually marked out the borders of the entire section where counting of stain positive cells was conducted by computer-based software (Sectra IDS7 Px, Sectra, Sweden) [179]. The inflammatory index was defined as the number of all CD45 positive cells per mm^2.

Tendon proliferation response and activity was estimated by calculating the proliferation index [180], defined as the percentage of all Ki-67 positive cells within all fields of a given region of interest (ROI) that showed positive labelling. The pathologist visually inspected the entire section and localized a "hotspot" (i.e. the area of maximum staining) which defined the ROI. Within this ROI, counting of cells was conducted by computer-based software (Sectra) [179].

For the assessment of apoptosis, the expression of p53 was studied. The apoptotic (p53) index was calculated and defined as the percentage of all positive p53 cells within all fields of a given tissue sample that showed positive labelling (number of positive cells/total number of all cells x 100). Here, the hotspot technique (described above) was used by the pathologist for defining the ROI.

To study any traces of acute tissue damage with bleeding, we analysed hemosiderin deposition. Histochemical staining with Perls' Prussian blue was used. No intensity scores were used, thus any detected deposits within all fields of the tissue sample were considered positive.

Table I. Bonar Score: updated and with clarification of terms and grades. Published in J Sci Med Sport, reprinted with permission from Elsivier [177].

	Grade 0	Grade 1	Grade 2	Grade 3
Cell morphology Four fields of view, 200×	Inconspicuous elongated spindle shaped nuclei with no obvious cytoplasm at light microscopy	Increased roundness: nucleus becomes more ovoid to round in shape without conspicuous cytoplasm	Increased roundness and size; the nucleus is round, slightly enlarged and a small amount of cytoplasm is visible	Nucleus is round, large with abundant cytoplasm and lacuna formation (chondroid change)
Collagen arrangement Polarized One field of view, 100×	Collagen arranged in tightly cohesive well demarcated bundles with a smooth dense bright homogenous polarization pattern with normal crimping	Diminished fibre polarization; separation of individual fibre bundles but with maintenance of overall bundle architecture Non homogeneous polarization	Bundle changes; separation and loss of demarcation of fibre bundles, giving rise to expansion of the tissue overall and clear loss of normal polarization pattern	Marked separation of fibre bundles with complete loss of architecture
Cellularity One field of view, 100×	Mainly discrete cells	Hyper cellular[a], in runs and/or increased cell numbers	Areas of hypo[a] as well as hyper[a] cellularity	Area of assessment is mostly a-cellular
Vascularity ≤10 fields of view, 400×	Inconspicuous blood vessels coursing between bundles	Occasional cluster of vessel, <2 per 10 high power fields	2–3 clusters of capillaries power 10 high power field	Areas with greater than 3 clusters per 10 high power fields, and/or areas of pathological a-vascularity
Ground substance One field of view, 100×	Not stainable ground substance	Stainable mucin between bundles but bundles still discrete	Stainable mucin within bundles with loss of clear demarcation of bundles	Abundant mucin throughout the section with inconspicuous collagen staining

a Hypocellular: < 20 nuclei per field; hypercellular: >30 nuclei per field. Plus 2.5 points for each of: calcification; adipocytes (intratendinous). Total score: a tendon with the most pathology will score 20. A tendon with no observable pathology will score 0.

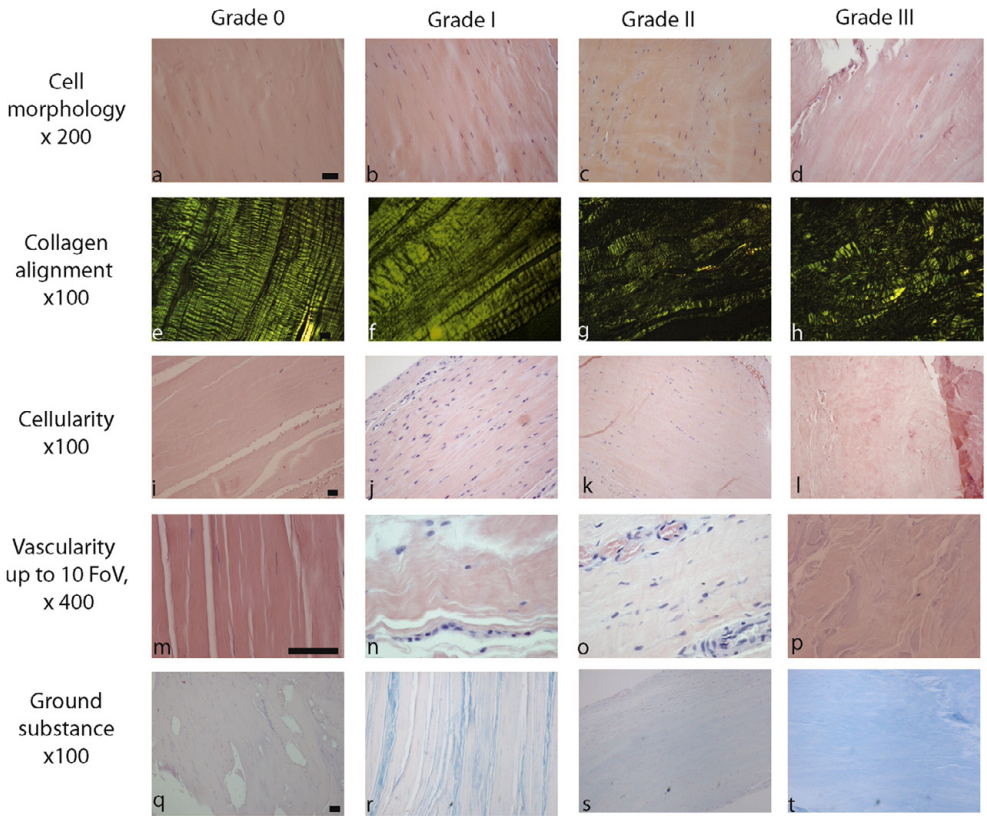

Figure 10. Pictorial representation of the Bonar score. Example micrographs of each grade are shown. The slides in the first four rows are stained with haematoxylinand eosin. The slides in the ground substance row are stained with Alcian blue. Magnification is reported for each row. Scale bars = 50 µm. Published in J Sci Med Sport, reprinted with permission from Elsivier [177].

Paper IV

To study the risk factors for healing failure, we used the data from the cohort in *Paper II*. Besides patients' demographics, including age, BMI, diabetes mellitus, gender, and smoking, tendon degeneration as determined histopathological with the Bonar score, fatty infiltration as measured on preoperative MRIs, tear location with regards to integrity of the rotator cable, and tear size (number of ruptured tendons and tendon retraction), were all analysed. Both tear location and tear size were determined during surgery. Isolated crescent tears of the supraspinatus and crescent tears involving the most anterior part of infraspinatus were, together with single-tendon subscapularis tears, classified as rotator cable (RC) stable tears. All other tears involving the anterior and/or posterior cable structures were considered RC unstable [26, 62, 64, 181]. The tendon retraction was measured with an arthroscopic calibrated probe. The selection of the analysed factors was based on drawing of a causal-relation diagram (dagitty.com) [182, 183].

Statistical methods

Paper I

The annual incidence of FTRCT was calculated using the total number of all diagnosed FTRCTs divided by 2 (the study duration was two years) divided by the number of individuals in the same age group (18-75 years) living in north-western Skåne (189,370 individuals). Based on previous research, we defined a population at risk as inhabitants aged between 40 and 75 years who lived in the catchment area of Helsingborg Hospital in 2011, according to the National Population Registry (Statistiska Centralbyrån). For the population at risk, the denominator in the calculation was 118,302 individuals.

Paper II

Since the majority of the variables were non-normally distributed we presented medians and IQR, and used Mann-Whitney U test for statistical comparison. Interobserver reproducibility was tested using kappa statistics. Analyses was performed using SPSS version 24 (IBM Corp., Armonk, New York). A power calculation based on an 80% proportion of intact tendon repair with a precision of ± 10% lead to a sample size of 62 participants.

Paper III

More than 50% of the variables were non-normally distributed and thus, median and interquartile range (IQR) are reported for all variables and nonparametric tests were used for statistical analyses. The Mann Whitney U test was used for between-groups comparisons, and linear regression analyses was used to study the relationship between degeneration and immunohistochemistry outcomes in the study group. Fisher exact test was used to compare the frequencies of positive hemosiderin labelling between the two groups. Intra-observer reliability was tested using the intraclass coefficient (ICC) calculation with 2-way random-effects model. As suggested, an ICC below 0.50 was considered poor reliability, between 0.50 and 0.75 moderate, between 0.75 and 0.90 good, and above 0.90 excellent reliability [184]. Significance level of 5% was considered to determine statistical significance. Statistical analyses were performed using SPSS version 24 (IBM Corp., Armonk, New York).

Paper IV

Descriptive statistics were used to define distributions of continuous variables, frequencies, and proportions of categorical variables. Variables previously suggested to influence healing [55, 165, 185-197] were included in a directed acyclic graph model (daggitty.com) to study causal relations [182, 183]. Compliance to rehab protocol, genetic factors, and bone mineral density were included as uncontrolled variables (light grey in Figure 11) whereas surgeon's experience and the rehab protocol (white in Figure 11) are fixed variables and thus labelled adjusted. Factors with potential influence on outcome (blue in Figure 11: ancestor of outcome) were compared between intact repair group and healing failure group using Mann-Whitney U and $\chi 2$ tests. Fisher's exact test was used instead of $\chi 2$ in instances of a 2-by-2 table with a five or under frequency value in at least one cell. SPSS version 24 (IBM Corp., Armonk, New York) was used for all statistical analysis. P values of < 0.05 were considered significant.

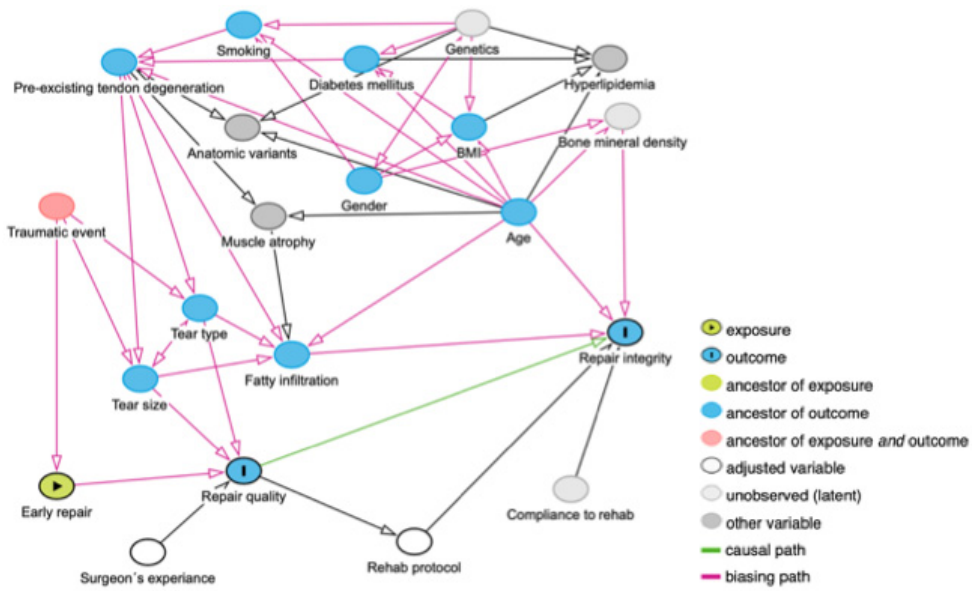

Figure 11. Directed acyclic graph (DAG).

Ethical considerations

The project was performed in accordance with the ethical standards of the Helsinki Declaration and approved by the regional ethical review board in Lund, Sweden, registration numbers DNR 2011/119, 2015/36, 2016/796.

All participants voluntarily consented to take part in the project after receiving thorough information, including the differences from standard treatment procedure. There were frequent follow-ups with physiotherapists and surgeons and a supplementary MRI-scan was conducted one year after surgery.

MRI-scans, in contrast to plain radiography and CT-scans, do not include ionizing radiation that is associated with the risk of DNA damage and carcinogenic mutations. There is no current scientific evidence that suggests that MRI is associated with increased mortality or any increased cancer incidence.

Thesis results

Paper I

During the first two years of the ASAP, the physiotherapists examined 331 patients (60% men) with acute soft-tissue shoulder injuries. Seventy-two patients were excluded because they did not meet the inclusion criteria or declined to participate. The study group (65% men) was made up by 259 participants with a median age of 51 (18–75) years. Eighty-eight participants with suspected FTRCT were diagnosed by MRI (n=85) or ultrasound (n=3, used because of claustrophobia). Patients with MRI-verified FTRCT were recommended arthroscopic rotator cuff repair and 47 of the 55 FTRCTs in Group I underwent surgery at a median time of 28 (20–48) days after the trauma. All 47 patients had arthroscopy-verified FTRCTs with acute appearance. Eight patients declined surgery. The remaining 33 patients in Group I had other lesions (Table II).

Table II. Patients of Group I who did not have FTRCT (n=33)

MRI DIAGNOSIS	n	MEDIAN AGE (RANGE)
Fracture of greater tubercle	8	56 (35-75)
Bone marrow edema after dislocation	6	61 (47-69)
Tendinosis	6	60 (47-67)
Partial-thickness rotator cuff tear	5	60 (45-71)
Fracture of surgical neck	3	69 (56-71)
Bone marrow edema	2	45 (41-49)
Calcifying tendinitis	1	55
Bursal bleeding	1	47
No pathology	1	41
Total:	33	56 (35-75)

Group II comprised 120 participants with other specific diagnoses listed in Table III.

Table III. The different diagnoses in Group II (n=120)

DIAGNOSIS	n	MEDIAN AGE (RANGE)
AC joint sprain	60	35 (18-70)
Glenohumeral dislocation	25	47 (29-71)
Contusion	17	35 (19-66)
Calcifying tendonitis	5	51 (44-62)
Brachial plexus traction	3	41 (34-52)
Thoracic contusion	3	51 (32-69)
Pectoralis major tear	2	37 (29-44)
Neck distortion	2	21 (20-22)
Initially missed fracture	2	51 (31-71)
Frozen shoulder	1	53 (53)
Total:	120	39 (18-71)

In Group III which included 51 patients, 20 of them rated their shoulder function to be ≥80%, and they were assumed not to have FTRCT. Seven patients could not be reached by telephone, were contacted by mail, and were encouraged to return for an update clinical examination if they still felt shoulder discomfort. None of them returned during the first three years after enrolment in the study, and they were considered not to have an FTRCT. Twenty-four patients rated their shoulder function to be <80% and were examined by a shoulder surgeon. MRI was performed in all but three patients, and five patients were diagnosed with FTRCT.

The estimated population-based incidence of acute FTRCT was 16 (CI: 11–23) per 105 inhabitants for the age group 18–75 years. The annual incidence of FTRCT for the population at risk (aged 40–75 years) was 25 (CI: 18–36) per 10^5 inhabitants. The prevalence of acute FTRCT in the study group was 60/259 (23%, CI: 18–28)

The most common lesion was a combined subscapularis and supraspinatus tendon tear, followed by an isolated subscapularis tear. The subscapularis tendon was involved in 38 of 60 of the rotator cuff tears (63%, CI: 52–76), and 36 of the 60 patients (60%, CI: 48–72) had FTRCTs that involved two or more tendons.

The injury mechanism included fall from the same level (63%) followed by fall from a height (20%) and no fall (17%). 21% were sports-related injuries, which were mainly caused by skiing. Of the 259 participants, 54% suffered from direct trauma to the shoulder, 30% from indirect trauma, 5% from combined trauma, and 11% were unknown. The same pattern was also seen in the FTRCT patients. Thirty patients had direct trauma, 19 had indirect trauma, and three had combined trauma. The dominant side was affected in 40 of the 60 FTRCTs. We diagnosed eight patients with occult fractures. This diagnosis was more common in younger patients, while FTRCTs were more common in older patients. MRI revealed five partial-thickness RCTs found in patients aged 40 – 75 years. The majority of those who had FTRCTs were males (82%).

Paper II

Repair healing, or structural integrity as visualized on MRI, was the primary outcome in this study including 62 patients with trauma-related cuff tear. A total of 57 patients (92%) had MR images available at the one-year follow-up. Intact structural integrity (i.e. healing of all repaired tendons) was found in 36 of the 57 patients (63%). Overall, 13 patients (23%) displayed a defect in the structural integrity of one or two of the repaired tendons (i.e. at least one repaired tendon displayed healing) and a defect in the structural integrity of all repaired tendons was found in eight patients (14%). The latter two groups were classified as healing failure for further analysis. We found excellent agreement in discriminating between intact repairs and healing failure between the two assessors (kappa 0.88, 95% CI, 0.75-1.0).

Patient-related outcome measures were secondary outcomes. The median WORC index increased continuously over the two-year period from 30.8 points (IQR 20.1 to 38.6) at baseline to 85.0 points (IQR 60.6 to 95.7) at two years. Patients with intact repairs did not report statistically significantly higher WORC index at 12 or 24 months than patients with healing failure, median 86.6 points (IQR 64.9 to 93.4) *vs* 78.4 points (IQR 59.0 to 89.7; p = 0.112) and 87.4 points (IQR 61.9 to 96.7) *vs* 82.4 points (IQR 49.6 to 92.8; p = 0.104), respectively. Median EQ VAS increased continuously from 65 points at baseline (IQR 50 to 71) to 83 points at 24 months (71 to 92). There was no statistically significant difference in EQ VAS between patients with intact repairs and those with failure of healing at 12 or 24 months, with a median 84 points (IQR 70 to 90) *vs* 80 points (IQR 75 to 92; p = 0.819) and 85 points (IQR 75 to 95) *vs* 80 points (IQR 65 to 91; p = 0.239), respectively. The age- and gender-adjusted median Constant-Murley score increased from 26.5 points at baseline (IQR 21.2 to 37.4) to 83.1 points at 12 months after surgery (IQR 71.9 to 97.5). Patients with intact repairs had statistically significantly better median relCS scores at 12 months than those with healing failure, 91.6 points (IQR 70.4 to 101.1) *vs* 78.1 points (IQR 66.3 to 88.0; p = 0.031); this difference was also clinically relevant.

Paper III

In the histopathological part of the thesis, our primary objective was to study the degeneration in the tendon tissue, as measured by the Bonar score, and secondary to study the level of inflammation, proliferation, and apoptosis. The median Bonar score for patients with trauma-related tears and patients with chronic tears was 10.5 (IQR, 7.5-14.5) and 11 (IQR, 5-12.8), respectively, with no statistically significant difference between the groups. There were large variations with regard to the

inflammatory index in both groups, and no statistically significant between-groups difference was found (2.3 (IQR, 0.1-10.1) vs. 4.5 (IQR, 0.1-13.6)). The proliferation and the apoptotic (p53) indices were statistically significantly higher in patients with trauma-related tears compared to patients with chronic tears ($p = .001$ and $p = .003$ respectively). In the study group with trauma-related tears, the linear regression model showed a statistically significant relationship between higher Bonar score and higher inflammatory index ($B=0.11$, 95% CI [0.06, 0.16], $p < .001$) and higher apoptotic (p53) index ($B=0.13$, 95% CI [0.01, 0.25], $p = .042$). A positive labelling for hemosiderin was found in 18 of the 53 (34%) tissue samples of patients with trauma-related tears compared to 1 of 10 (10%) in patients with chronic tears (n.s).

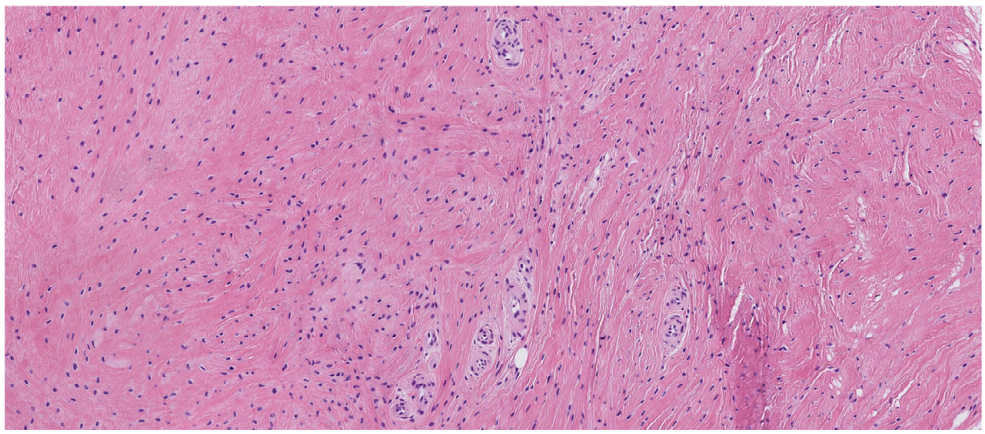

Figure 12. Example of severe histopathological changes in a chronic, nontraumatic supraspinatus tear with hypervascularity, hypercellularity, rounding of tenocytes, and separation of collagen fibre bundles.

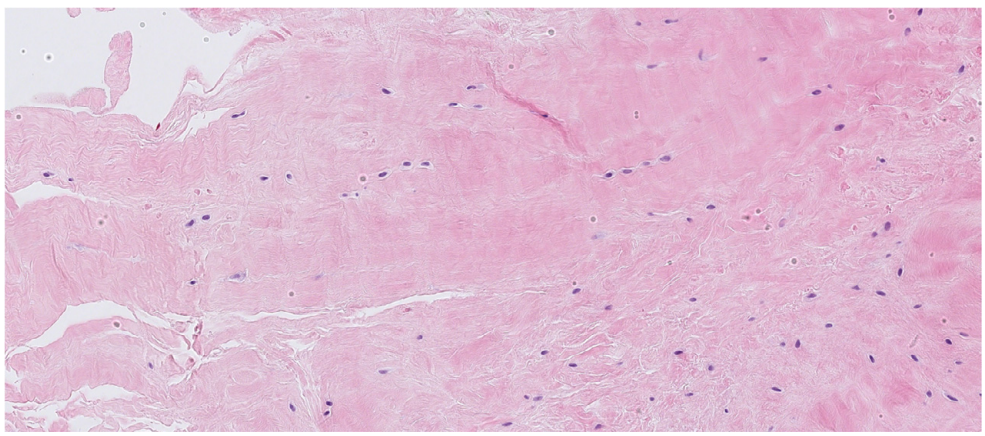

Figure 13. Example of mild histopathological changes in a acute, trauma-related supraspinatus tear with no pathological vessels, normocellularity, some rounding of tenocytes, and maintained overall collagen bundle architechture.

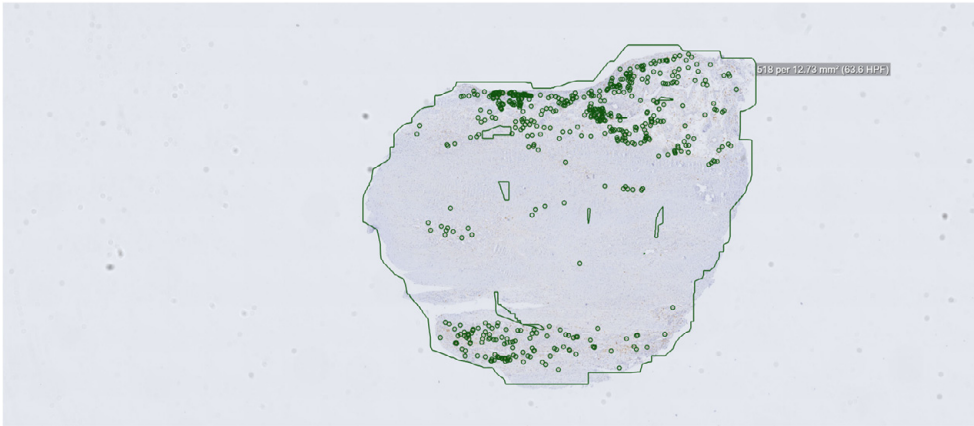

Figure 14. Immunohistochemestry with the CD45 marker used for the inflammatory index. The histopathologist manually marked out the borders of the entire section where counting of stain positive cells was conducted by computer-based software (Sectra IDS7 Px, Sectra, Sweden) [179]. The inflammatory index, defined as the number of all CD45 positive cells per mm^2, was in this specimen 40.7.

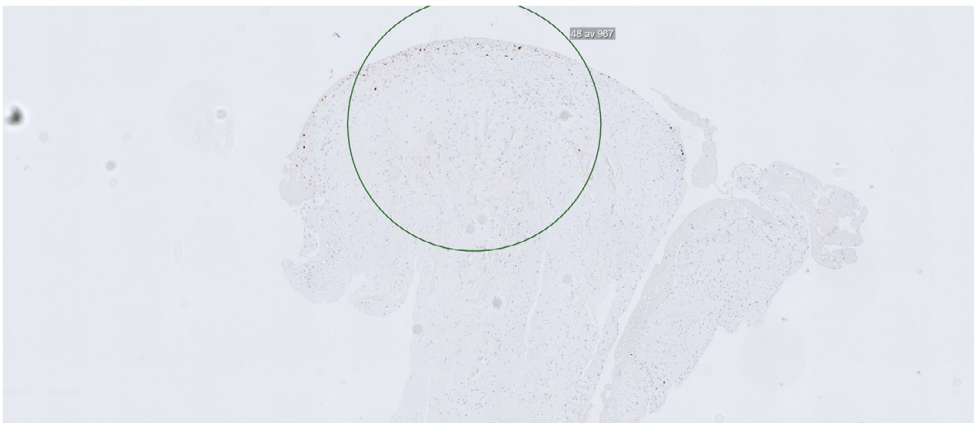

Figure 15. Immunohistochemestry with the Ki67 marker used for the proliferation index. The hotspot defining the ROI (region of interest) has visually been marked out by the histopathologist and the computer software counted 48 +cells within the ROI comprising a total of 967 cells, calculating a proliferation index of 5.0% in this supraspintus tendon sample from the control group.

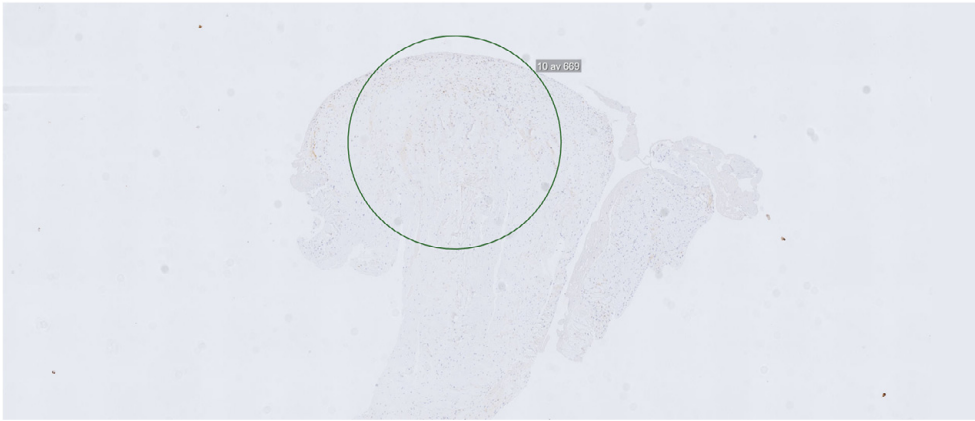

Figure 16. Immunohistochemestry with the marker for apoptosis (p53). As described above, the computer software counted 10 + cells within the ROI comprising a total of 669 cells, calculating an apoptosis (p53) index of 1.5% in this supraspintus tendon sample from the control group.

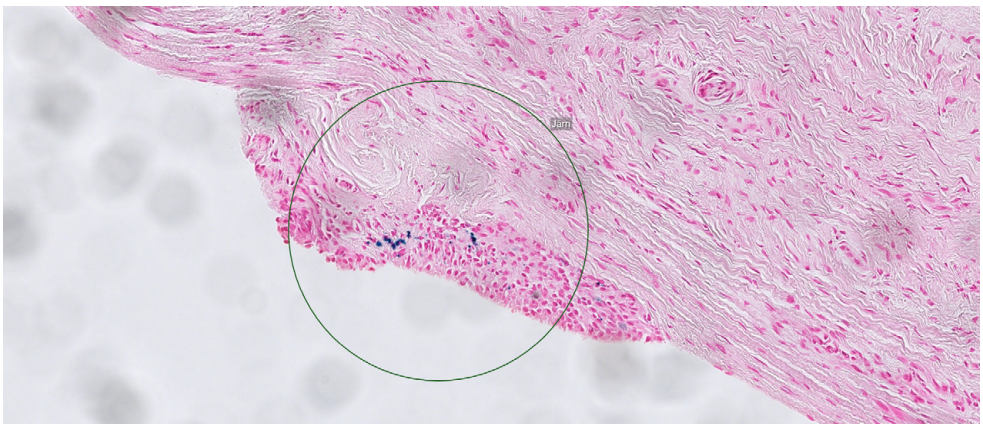

Figure 17. Hemosiderin deposits identified with Perls' Prussian blue stain. Iron in hemosiderin turns blue to black when exposed to potassium ferrocyanide.

Paper IV

The cohort in this study was the same as in *Paper II*. Out of the ten analysed risk factors, a higher degree of fatty infiltration of the supraspinatus muscle (p=0.01), a tear location including disruption of rotator cable integrity (p=0.01), and older age (p=0.03) were significantly associated with healing failure of a repaired rotator cuff. However, tendon degeneration as determined by histopathology was not associated with healing failure at the one-year follow-up (p=0.63).

Discussion

Rotator cuff tears have been studied for decades and still, several important aspects are not fully understood. The overall objective of this thesis was to study trauma-related rotator cuff tears, a subgroup of injuries where individuals without previous shoulder complaints, suffer from a fall or a pulling of the arm, and experience sudden pain and loss of function. In the outpatient clinic, we had observed that some of these patients unfortunately had a delay in their diagnoses. The initial examination, including x-rays, showed no signs of fracture and often physiotherapy was recommended under the diagnosis of a sprain. Referral to a shoulder surgeon followed after several months with little improvement where delayed surgery, if possible at all, often resulted in dissatisfying outcome for both surgeon and patient. The Swedish national guidelines from 2006 recommend early surgical intervention in the physically active part of the population. However, these guidelines have not yet been updated and were based on limited research.

This clinical problem left us with many questions and after an initial literature review, we realized that the knowledge on this topic was insufficient. How common are trauma-related rotator cuff tears? In which age group do we find them and what is the typical size of such tears? In *Paper I* we studied the epidemiology of this acute shoulder injury. A new screening system was developed, where physiotherapists examined patients within the first week after acute, soft-tissue injuries of the shoulders, with the intention to successfully detect trauma-related rotator cuff tears at a very early stage. The new organisation enabled subacute surgery. We hypothesized in *Paper II* that early surgery within six weeks after injury would provide increased healing properties and thus, better clinical and structural outcome. And if not, what other factors affect healing more than timing? Almost one hundred years ago Codman stated that rotator cuff tears have a traumatic cause, yet an underlying degenerative process of the tendon could not be excluded. The level of this underlying degeneration was studied in *Paper III*. We confirmed Codman's postulate, and searched further for risk factors for incomplete healing in *Paper IV*.

Thus, this thesis was designed to address clinically relevant questions of importance for many patients. Significant findings have been published and some of the answers have regenerated new research questions and hypotheses. From the outside, screening for injuries in the general population, we continued to the inside of the shoulder via the camera and the lens in a small tube, and before working through the microscope into the tendon tissue.

Epidemiology and aetiology

The result from our epidemiological study showed that acute, trauma-related FTRCTs are common in the general population, with an annual incidence of 25 per 10^5 of the population at risk. We calculated that medium sized Swedish hospitals (with catchment area of about 250.000) will diagnose around 30 acute FTRCTs annually where surgical intervention needs to be discussed. With a previously suggested prevalence of 32% [198] and the 23% found in the ASAP cohort, approximately hundred patients will need additional assessments beyond initial clinical examination and plain x-rays. Hospitals and orthopaedic departments may use these numbers as aid in managing outpatient clinics. At Helsingborg Hospital we are equipped with a shoulder unit, enabling close collaboration between physiotherapists and orthopaedic surgeons. After a pilot study, performed nearly15 years ago, patients with trauma to the shoulder having negative plain radiographs are referred from the Emergency Unit to specific PTs in our shoulder unit. Referred patients undergo clinical assessment within a week after trauma according to a specific predetermined protocol. We believe that PTs are suitable as first-line diagnostic assessor since they have extensive training in the musculoskeletal field, and provide safe, effective, and evidence-based care.

The skewed gender distribution found in the ASAP cohort is similar to demographics from other acute tendon ruptures. Achilles tendon tears had a male predominance of 84% in the study by Vosseller et al. [199]. Pectoralis major tears and distal biceps tendon ruptures are even more rare among women [200, 201]. Sex-related differences in muscle strength and tendon quality, injury mechanism, and physical constitution may be causal factors, next to a possible male dominance in traumatic injuries in general. Regarding trauma-related FTRCTs, our result confirms findings in the systematic review by Mall et al., where 77% of the tears were found in the male population. This male predominance differs from the demographics of chronic nontraumatic tears, where an equal male-to-female ratio has been found [37, 40].

The association between higher age and increasing prevalence of rotator cuff tears has been known for many years. Asymptomatic individuals were studied already in the nineties using MRI, suggesting a prevalence of FTRCT of 28% and 4% for those older and younger than 60 years, respectively [36]. In a natural history study by Yamamoto et al. symptomatic and asymptomatic FTRCTs were found in 21% of individuals a prevalence increasing with age [40]. The median age of individuals with FTRCTs in our study was 60 years, which is comparable to the findings in previous studies with similar cohorts analysing acute tears following shoulder trauma [135, 202, 203].

The specific location of a rotator cuff tear is not considered in itself to be a reliable indicator of aetiology. However, some tear patterns or locations such as

anteroposterior tears are often considered to be trauma-related [204]. Mall et al. also concluded that the tear size and location of FTRCTs differ in chronic, nontraumatic tears and acute, trauma-related tears [205]. Compared to results from a study (MOON Shoulder Group) on exclusively nontraumatic tears, we found larger tears and increased multiple tendon involvement [206]. In the MOON Shoulder Group cohort, subscapularis was involved in only 7%, compared to 63% in our study.

Fatty infiltration of the rotator cuff muscles indicate an asymptomatic preceding degenerative process over time [207]. Twenty percentage of the individuals in our cohort had fatty infiltration in the supraspinatus muscle, grade 2 or more according to Fuchs, despite being a cohort comprising trauma-related tears in individuals without any history of shoulder dysfunction prior to the trauma. Measuring and staging of fatty infiltration has been shown to be difficult and studies have reported moderate reliability [208-210]. Advanced techniques for fat quantification have been developed and even though some of these are immature and not yet for use in daily practice, we expect that this will improve the reliability and the accuracy of the quantification in the near future.

Surgical treatment

Given the large median tear size and a study cohort with participants aged up to 75 years, we did not expect to find a 100% healing rate of repaired tendons despite surgery being done at an early stage. Nevertheless, we were surprised to find a healing rate of only 63%.

For uniformity, all cuff tears were repair with arthroscopic surgery. All three involved surgeons are experienced in shoulder arthroscopy. It is possible that a superior healing rate could have been achieved had we individualised the approach. Isolated subscapularis tears may have been treated with deltopectoral incision, whereas selected posterosuperior tears may have been approached with a deltoid split.

The timing of repair after trauma-related cuff tears is debated, with selected trials reporting superior clinical outcomes after early repair [211, 212], whereas other studies have failed to demonstrate such differences [202, 205, 213, 214]. There is no consensus on the term “early” or “delayed” with regards to time interval between injury and surgery. Today, most authors would agree that a delay of three to four months does affect the clinical outcome negatively. As an example, the ongoing randomised, placebo-controlled Accurate trial includes patients operated within four months after the injury [136]. The work in this thesis was designed to follow the Swedish national guidelines from 2006 (currently under revision) where repair was recommended within six weeks from injury [215]. Our prospective trial was not designed to compare early versus delayed repair and thus, drawing conclusions on the

timing of repair from our data is not possible. The results from this thesis suggest that tendon healing alone may not be a valid argument for early surgical repair.

The healing failure rates after rotator cuff surgery have historically been reported with a large variation from 6.5% [135] to 94% [216]. This is likely a result of the heterogeneity in the cohorts analysed. Most reports on repair integrity have studied chronic cuff tears, and the vast majority of the studies with poor structural outcome have cohorts including older patients with massive tears. I have found five reports, four retrospective and one randomized control trial, on rotator cuff integrity after open or arthroscopic repair of acute, trauma-related tears [135, 202, 203, 213, 217]. Four had similar tear sizes as our patients and reported healing rates of 65-77% which agrees well with our result. The randomised controlled trial by Ranebo et al. reported a healing rate of 93.5% but included smaller tears with a mean tear size of 10 mm (range 4-21). Tear size and increasing number of involved tendons have been suggested as risk factor for healing failure [55, 190-192, 218, 219] and this will be discussed further under *risk factors for healing failure.*

For the vast majority of the patients in our study, clinical outcome scores increased continuously over the first year. The median WORC score in our cohort was 85%. at two years. This is higher compared to 77% and 75% in previous studies using WORC as one of the outcome scores [202, 213]. The one-year improvement in absolute Constant score was better than for the early repair group in the systematic review by Mukovozov et al. (42.4 *vs* 33.5 points) [220]. A possible reason for that may be our early baseline assessment, examining and scoring patients at a median of twelve days after injury. Comparing final follow-up Constant scores instead of improvement over time, should be done with caution due to reduced inter-rater reliability [221] yet, our CS were similar to previous reports [202, 213]. Nevertheless, by defining successful, i.e. “good” or “excellent”, treatment as a relative Constant score above 70 points, 77% of the repairs were successful [168, 222]. This is lower than our expectations. Despite the low number of individuals, it is interesting to note that four patients with healing and three patients with healing failure reported poor outcome according to this grading (< 56 points).

Patients with intact repairs presented better Constant scores compared to those with healing failure. No significant difference between patients with intact repairs and healing failure was found for patient-reported outcome measures (PROMs) such as WORC and EQ VAS. The association between structural integrity and patient’s satisfaction and functional outcome is disputed in the literature. Some studies report better PROMs and functional scores among intact repairs [202, 213, 223] whereas other studies failed to find significant difference with regard to repair integrity [131, 218, 224, 225]. In summary, several reports support our findings that patients with intact repairs have better strength and shoulder function compared to patients with healing failure, but not necessarily better PROMs or self-reported satisfaction. Whether this will persist over longer time periods is unclear. Moosmayer et al. published ten-year follow-up results for their randomized controlled trial indicating

that the clinical outcome scores had increased in favour of the repaired compared to the unrepaired group [133]. These results suggest better function in shoulders with intact repairs compared to unrepaired cuff tears or repairs with healing failure in the long-term perspective. However, future comparative studies with extended follow-up are needed.

Histopathological changes

The presence of a underlying tissue degeneration and weakening of the rotator cuff tendons, also in previously asymptomatic individuals suffering from acute trauma-related tears, has been assumed since 1931 when Codman postulated his believes [226]. Several proxies for degeneration have been suggested, such as macroscopically evaluation during surgery, fatty infiltration of the torn cuff muscles, signal alterations of the tendon tissue and grade of tendon retraction evaluated with MRI or ultrasound. Yet, it is not known if they are in fact true proxies for degeneration nor, to our knowledge, has it ever been studied with histological analysis. In the study and evaluation of tendon tissue degeneration, two classification systems are currently used to quantify tendinopathy: the Bonar score and the Movin score, both with or without validated modifications and updates [94, 177, 227]. Maffulli et al. found a high correlation between the two scores [93]. We used the Bonar score to analyse more than 50 supraspinatus tendon samples harvested from patients in the study group in *Paper II*. We found a high degree of histopathological degeneration. The Bonar findings were not significantly different when compared with samples from nontraumatic chronic tears.

Hemarthrosis or bursal bleeding are considered to be factors of a causal link between a traumatic injury and a tendon tear [228-230]. We hypothesized that the TRCT in our ASAP cohort would show signs of acute bleeding, whereas no traces of bleeding were expected to be found in the chronic group. Interestingly, a positive hemosiderin labelling was only found in one-third of the biopsies from the trauma-related tears. Parts of the rotator cuff which are prone to rupture are scarcely blood supplied and most likely, a haemorrhage is not obligate [231-233]. This is in contrast to evulsion-like ruptures which leave a bleeding, bare footprint. Another possible explanation of the low rate positive labelling is that the staining with hemosiderin is not sensitive enough. Post-hoc analyses indicated however, that the vast majority of the MRIs indicated joint effusion. The MRIs were conducted within two weeks after the injury and despite the difficulty of discriminating between inflammatory joint effusion and bleeding on MRI, the effusions detected on MRIs are assumed to be hemarthrosis. Unfortunately, a routine evaluation and documentation of any hemarthrosis when introducing the trocar during surgery, was not done. Nevertheless, hemosiderin staining of the tendon tissue sample from the acutely injured shoulder joint does not seem to be the best method for detecting

hemarthrosis; analysis of the joint effusion exudate may have demonstrated higher sensitivity. Further, a significant number of the individuals in the study group suffered a shoulder dislocation and the hemarthrosis may have been caused by a Hill Sachs lesion. In conclusion, the cause of the bleeding as indicated and the consequences remain unknown. It is worthwhile to note that nine out of ten in the chronic group showed no traces bleeding and that a larger control group may have changed the outcome.

Tissue damage and haemorrhage initiate inflammation - the first step of an attempt for healing [153, 234, 235]. The patients in both the study group and the control group, showed large variation in the inflammatory index. There are many possible reasons for that. First, the underlying level of inflammation before the injury was unknown. Second, biopsy harvesting was not consistent considering days after injury. Third, the magnitude of the tendon injury, bleeding, and joint effusion which are all fundamentals of inflammation, diverged within the cohort [157, 159]. At the time of the surgery, i.e. biopsy harvesting, some patients had already peeked in the inflammatory phase, whereas others might have had a possible prolonged inflammation, with possible negative effects on healing. This is known from studies on Achilles tendon tearing, where its negative effect on healing has been shown, as it disturbs the following proliferation and remodelling phases [234]. Also, severe inflammation in normal wound healing is associated with excessive scarring [236]. Consequently, a disturbed, pre-existing inflammation with additional inflammatory response induced by injury and surgery may have a negative impact on healing, and may also induce adherences and shoulder stiffness. From the traumatic hemarthrosis of the knee joint we know that chondrocyte apoptosis is triggered by the monocyte- and macrophage-generated oxygen metabolites following erythrocytes breakdown [237]. Yet, we have found no evidence in current literature to support any causal relation between traumatic hemarthrosis and osteoarthrosis in the shoulder joint.

The proliferation in the patients with trauma-related tears was significantly higher than in those with chronic tears. We believe this may be a result of the biochemical response to the trauma. The inflammatory response had been replaced by the proliferative phase. Whether this elevated level of proliferation is a positive factor for healing, or in fact a risk factor for healing failure, remains unknown. We performed post hoc analysis that failed to show any association between proliferation index and healing failure in our study group however, the study was not designed to answer this question. Interestingly, no correlation was found between tendon degeneration and proliferation. Maybe the Bonar score did not detect certain degenerative changes within the tendon tissue, qualities found in aging and deteriorative tissue, that negatively influenced the proliferation capability. Another explanation is that factors, other than the degree of degeneration, regulate the proliferative activity.

Yet, the results indicate that higher Bonar score correlate with elevated inflammatory- and apoptosis indices. The positive correlation between increased

degeneration and higher apoptotic index has previously been shown [108, 238]. This is in contrast to other publications reporting increased apoptotic index in patient with higher degree of tendon degeneration [106-108, 180, 239], our trauma-related tears displayed significantly increased apoptotic index compared to the chronic group. A causal link between tissue injury and increased p53-dependent apoptosis is possible, similar to the chondrocyte apoptosis in the knee joint caused by hemarthrosis.

Risk factors for healing failure

Understanding that the tissue degeneration was not unlike the degeneration in chronic nontraumatic tears, we continued to search for risk factors of healing failure in trauma-related tears. Similar to studies on chronic tears, we found that older age and increased fatty infiltration (FI) of the supraspinatus muscle negatively affected healing [185, 192-194, 240]. Third risk factor for healing failure was a disruption of the rotator cable attachments. Tear type and location have not attracted as much attention as age, FI and other common risk factors nevertheless, disrupted rotator cable has also been suggested as a negative predictor for healing [64], as well as functional outcome [25, 26].

It is well-documented that age correlates with repair integrity. Exactly through which biological processes is not clear. However, fatty infiltration, bone mineral density or bone quality, impaired angiogenesis, and tendon tissue degeneration are all factors closely related to ageing [241-244]. Multivariate analyses conducted in retrospective studies with larger cohorts of chronic tears, or limited number of investigated variables, have suggested that age, tear size, follow-up duration and FI of supraspinatus are independent risk factors for healing failure [55, 192]. An independent risk factor does not necessary implicate a direct causal correlation. A causal effect is said to occur if variation in the independent variable is followed by variation in the dependent variable, when all other things are equal (ceteris paribus). In *Paper IV,* we used directed acyclic graph (DAG) as an example of causal diagram that can provide a starting point for identifying variables that must be measured, or at least discussed, and controlled to obtain unconfounded effect estimates.

One of the reasons for the more aggressive treatment strategy towards surgery is the assumed lower grade of degeneration and thus, better healing potential in trauma-related tears. Interestingly, we failed to display histopathological degenerative changes in the supraspinatus as risk factor for healing failure. This agrees with the findings reported by Sethi et al. They found no correlation between the Bonar score, gross appearance of the rotator cuff and repair healing in their study group with demographics suggesting chronic tears [245]. Yet, conflicting findings have also been published. Proxies for tendon degeneration, such as surgeon-rated tissue

quality [223, 246, 247], inflammatory and matrix remodelling biomarkers [248] have been reported as potential risk factors.

Although smoking has a well-known negative influence on different tissue qualities, including increased apoptosis and histopathological changes in rotator cuff tissue [180], we did not find any correlation to healing failure in this cohort. Since the study group encompassed 6 (10%) smokers, an underpowered analysis is the most probably reason.

The rotator cable, first described by Burkhart et al. in 1993, is critical for mechanical properties such as force transmission within the rotator cuff [24]. This followed a year after Clark and Harryman published an anatomical study on the rotator cuff and outlined a fibrous tissue originating from the coracohumeral ligament running along the perpendicular axis of the posterosuperior cuff [27]. Disruption of its anterior attachment has been described associated with fatty muscle infiltration, tear progression [65], and healing failure after repair of chronic tears [64]. In contrast to tear size and location, disruption of RC attachment was found to be a risk factor for healing failure in our study. The impaired function of the suspension bridge seems to be more important than the actual size of the tear. Restoration of anatomy and anchoring of the rotator cable are important to protect the load and stress, similar to the conclusion in the biomechanical study by Nguyen et al. [249].

Fatty infiltration (FI) has been studied extensively and acknowledged as an important risk factor since Goutallier et al. first demonstrated this almost 30 years ago [8]. In *Paper IV,* we analysed FI as a global index as well as separately in each individual muscle. In agreement with several studies on degenerative tears [77, 165, 192], we reported a correlation between increased FI of the supraspinatus and healing failure. This association is possibly of high importance for healing failure in repaired supraspinatus tears; an odds ratio of 9.3 for healing failure was calculated in a recent meta-analysis [250]. Whether FI affects structural outcome through other pathways or directly by reduced muscle strength and secondary superior migration of the humeral head, leading to impingement and repair damage as suggested by Goutallier [77], remains unknown. Unfortunately, the sample size in our study group was too limited for further analyses.

We draw a directed acyclic graph (DAG) to map all a priori assumptions surrounding possible causal effects on repair healing. The model was used to avoid bias, where selected variables including directed causal paths, were based on previous studies combined with a clinical perspective [165, 189, 240, 251, 252]. It resulted in numerous variables and graphical complexity and yet, the reality is most likely even more multifaceted. The relationship between FI, muscle atrophy, tear location, size, and age are drawn in the DAG model. However, the quantity of the causal effect of different variables is unknown.

Adverse events

Arthroscopic surgery is generally associated with a low rate of infections. We experienced one case of deep infection which was treated with arthroscopic debridement and antibiotics, without further complications. One patient was not compliant with the restrictions in the rehabilitation protocol and suffered an anchor loosening, diagnosed four weeks after surgery. The patient was treated with revision surgery. Non-treatment related adverse events included one patient with subdural haematoma due to a fall six weeks after surgery and another patient was diagnosed with rheumatoid arthritis during the initial post-operative phase.

Nomenclature and semantics

In this thesis I use the term *acute, trauma-related* rotator cuff tears when describing tears that have a clear traumatic genesis and acute in terms of patients seeking medical care in the days following the injury. In the literature we sometimes find different terms with similar meanings. In general, *traumatic* is used to describe significant direct or indirect shoulder trauma in the younger population resulting a tear. The rationale behind the use of this term is partly medicolegally, but also based on the idea that a traumatic rupture has occurred in a previously healthy tendon. I believe this implies certain challenges and would strongly recommend trauma-related instead of traumatic. The term *traumatic* is often used to discriminate from *chronic* tears. This may be misleading and a more correct dichotomous usage would be *trauma-related* (or traumatic) versus *nontraumatic* and *acute* versus *chronic*. The term *acute on chronic* tear should be limited to acute extension of a known tear or in a shoulder with preceding impaired function. Further, with the outcome of the histopathological study showing a substantial level of degeneration in our study group with trauma-related tears, the term *degenerative tear* is misrepresentative. Almost all rotator cuff tears show some amount of tissue degeneration.

Limitations

The work in this thesis has potential limitations. Studying the epidemiology of soft-tissue injuries, certain methodological limitations need to be elucidated. First, even though Helsingborg Hospital is the only institution which offers emergency orthopaedic care in our catchment area, individuals may have travelled to other parts of the country. Second, despite a rigorous effort to contact all health care providers in the catchment region and provide them with detailed information, certain physicians or physiotherapist may have missed this or forgotten to refer. Third, it is

plausible that some individuals with trauma-related tears of various motives did never sought health care. Fourth, we did not obtain MRI scans of all individuals in the examined and screened population. Thus, we cannot exclude that the physiotherapist incorrectly classified some participants as intact rotator cuff, which also would have had negatively impacted the incidence estimation.

Although this project was specifically designed to exclusively study trauma-related rotator cuff tears with a clear history of a specific trauma, the pre-injury status of the tendon is unknown. This problem is universal in the normal clinical setting and is not a limitation specific to our studies. The possibility that some of the patients had asymptomatic tears prior to their trauma. Still, a partial repair due to severe retraction of the supraspinatus tendon was only necessary in one patient. The ASAP participants who were treated surgically, underwent arthroscopic repair using a single-row technique. The three surgeons involved were all experienced in the field of arthroscopic shoulder surgery. As discussed above, it remains unknown if some of the patients with larger tears may have seen a superior outcome with double-row or transosseous equivalent techniques, mini-open or open surgery. Also, the between-group analysis, intact repair versus healing failure, may introduce a risk of type II error due to small sample sizes and thus, the results should be interpreted with caution.

We used the Bonar score, originally developed for patellar tendinopathy to determine the degree of tendon degeneration. The score has been validated for use in rotator cuff tendinopathy, but has to our knowledge not been used to specifically examine trauma-related cuff tears Although the single observer, a senior musculoskeletal expert, presented good to excellent agreement in the intra-observer reliability testing, a possible overestimation of pathological changes cannot be excluded. Adding a second observer might have demonstrated some changes but at the group level, this is considered unlikely. There are many different markers and methods studying indices for inflammation, proliferation, and apoptosis. By choosing other methods, different outcome may have been obtained. Still, we based our selection of makers on previous rotator cuff work and tendon-related studies with a previously reported valid reproducibility.

Statistical limitations are implicit when studying risk factors or predictors of outcome with a relatively small sample size. It limits our ability to draw firm conclusions due to potentially underpowered statistical analyses where multivariate testing were inappropriate. Still, the presented results provide well-founded hypotheses for future trials.

Conclusions

The results of this thesis suggest that acute TRCTs are common shoulder injuries, especially in men. They are usually large and often involve the subscapularis tendon.

Early repair of TRCT resulted in a healing rate of 63%. Although clinical outcomes improved considerably throughout the two-year follow-up for the full cohort, pre-operative counselling should reflect that early repair does not necessarily protect against healing failure. The results suggest that early repair may not be the most important factor for healing and the importance of other factors need to be further investigated.

Previously asymptomatic patients suffering from trauma-related rotator cuff tears need to be informed about a likely underlying tendon degeneration, comparable to tendon degeneration found in chronic, nontraumatic tears, and associated tissue weakening. The effect is therefor, when deciding on treatment for this group of patients, it is important to note that other factors such as tear type and size, patient's shoulder function and activity level may be more relevant than a trauma-related, acute onset of symptoms.

Older age, increased fatty infiltration of the supraspinatus muscle, and a tear location including disruption of rotator cable integrity were suggested to increase the risk of healing failure after early arthroscopic repair in patients with trauma-related full-thickness rotator cuff tears. No relationship between histopathological degenerative changes within the supraspinatus tendon and repair integrity was found.

Future perspectives

We found no differences in histopathological degenerative changes compared to chronic, nontraumatic tears yet, our findings with elevated levels of apoptosis and proliferation suggest that the biology of trauma-related tears is different from nontraumatic, and this may affect the treatment. The increased p53 index indicates a pathological apoptotic process that may be mediated and possibly therapeutically targeted. The raised proliferation suggests that the tissue has responded to injury. Future research should study the progress and peak of the proliferation and see if a mediation would be beneficial, due to the second hit during surgery with additional proliferative activity.

Future expanded understanding of the biology of the condition and the healing process will hopefully reduce the risk of nonhealing. Nevertheless, the important first step is to recognise who to repair. Which tear needs surgical treatment? Only one randomized controlled trial has been conducted comparing repair and physiotherapy of trauma-related tears and this trial only studied small to medium sized tears. The ongoing Accurate multicentre study, a randomised, placebo-controlled trial, investigating the efficiency of arthroscopic repair of TRCT, will hopefully add some important information. Additional studies are needed, especially the treatment of larger tears. Is there a defined cut-off with regards to the size? Or is the location or the type of the injury of greater importance? In our fourth paper we showed that a loss of integrity of the rotator cable was a risk factor for healing failure. Several authors have shown that measurement of cuff size on MRI involves certain difficulties and impaired reliability. Instead of working on improvements in size measurements, focus should perhaps be redirected to imporve the accuracy in detecting any disruption of the rotator cable attachments. Doubling magnetic strength from 1.5 (most commonly used today) to 3-T improves image quality. This will increase the sensitivity of assessment of the rotator cable. Almost thirty years have passed since the rotator cable first was described. However, information about the rotator cable as a prognostic factor remains scarce. Natural history studies on rotator cable integrity are needed. Additionally, it would be useful to target best possible fixation in future trials.

We showed that fatty infiltration is one of the risk factors even in repair of trauma-related tears. Future biologic strategies to target fatty infiltration is clearly one of the most interesting therapeutic models. But even advances in diagnostics will hopefully improve outcome. Innovations like quantitative assessment of FI and

muscle volume of the rotator cuff muscles using 3-dimentional 2-point Dixon MRI has shown promising results regarding both intra- and inter-rater reliability. Enhanced information will improve clinical decision-making.

Increased knowledge of risk factors and biology, next to innovations in imaging and improvements of surgical techniques, are important contributors for continuous development in the assessment and treatment of rotator cuff tears. However, future research should also target patient selection. Essential differences in patients' pre-injury level of activity, demands, and expectations need to be better addressed and studied. Activity scales are critical complements to existing outcome measurement instruments, as they provide "what patients are doing". An activity level scale for upper extremity disorders, the ABAS scale, has recently been developed. I am currently, together with the developers, studying the association between the ABAS scale and general health questionnaires and disease-specific outcome measurements.

The ASAP participants were primarily followed for two years. I plan to continue studying the cohort. Patients with healing failure presented inferior Constant scores relative to those with intact repairs, however, there was no difference in PROMs. If this will remain over time is one of the research questions planned for a long-term follow-up study.

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