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Treatment of Subacromial Pain and Rotator Cuff Tears

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To Gustaf, Oscar, Emmy and
my parents

"If I have seen further than others, it is by standing upon the shoulders of giants"

- Isaac Newton

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2 Abstract

Shoulder pain is very common, affecting 14-21 % of the population at some time during their lifetime. The aims of this thesis were to improve the understanding of various aspects concerning the pathogenesis and treatment of subacromial pain and rotator cuff tears. Patients and healthy individuals were examined and compared in five studies:

Study I) Seventy patients were retrospectively examined, clinically and with ultrasound, 15 years after arthroscopic subacromial decompression. All patients had an intact rotator cuff at surgery. Ultrasound showed significantly fewer rotator cuff tears compared to the prevalence of asymptomatic tears reported in the literature for the same age group. This indicates that arthroscopic subacromial decompression might protect the rotator cuff.

Study II) Forty-two patients were retrospectively examined, clinically and with ultrasound, 39 months (mean) after an acute rotator cuff repair. All patients had pseudoparalysis after trauma, a full thickness tear and no previous history of shoulder symptoms. A delay in surgical treatment of three months and the number of tendons injured did not affect the outcome. Age affected outcome negatively.

Study III) Plasma samples from 17 patients with cuff tears and 16 plasma samples from healthy age- and gender-matched controls were collected and analysed regarding the levels of matrix metalloproteinases and their inhibitors, TIMP1-4. Elevated levels of TIMP-1 were found in the patients with cuff tears compared to controls. Higher levels of TIMP-1, TIMP-3 and MMP-9 were found in patients with full-thickness tears compared to patients with partial-thickness tears.

Study IV) Ninety-seven patients with longstanding subacromial pain, on the waiting-list for arthroscopic subacromial decompression, were prospectively randomised to specific shoulder exercises or control exercises for three months. Thereafter they were clinically examined and asked if they still wanted surgery. The specific shoulder exercises focusing on eccentric exercise for the rotator cuff and scapula stabilisers were found to be effective in reducing subacromial pain and improving shoulder function, thereby reducing the need for surgery.

Study V) All patients including those operated, in *Study IV* were re-examined after one year using clinical assessment scores. The option of surgery was continuously available up to the one-year follow-up. Ultrasound and radiological examinations performed at inclusion were analysed in relation to the choice of surgery. The positive effects of the specific exercise programme were maintained after one year and significantly fewer patients in this group chose surgery. Surgery was significantly more often chosen by patients who had a low baseline shoulder score, and/or a full thickness rotator cuff tear. All patients showed significant improvement in the clinical scores one year after inclusion or one year after surgery.

These results support the concept that subacromial pain has a multifactorial aetiology and that the first line of treatment should be specific shoulder exercises. When conservative treatment fails, an acceptable result can be achieved with arthroscopic subacromial decompression. The rotator cuff status is important to consider when treating and studying these patients.

3 Svensk sammanfattning (abstract in Swedish)

Skuldersmärta är vanligt förekommande och drabbar 14-21 % av populationen någon gång under livstiden. Det främsta skälet till behov av vård för skulderbesvär är smärta från mjukdelarna, bestående av en slemsäck och rotatorkuff-muskulaturen, under skulderbladets tak. Smärtan förekommer ofta tillsammans med nedsatt skulderfunktion. Slemsäcken och rotatorkuffen kan påverkas var för sig, tillsammans och i olika grader. Orsaken till smärtan anses vara multifaktoriell. Syftet med denna avhandling var att med lång- och medellång uppföljning undersöka det kliniska och anatomiska utfallet efter operationerna: artroskopisk subakromial dekompression samt rotatorkuffreparation. Ytterligare ett syfte var att fördjupa kunskapen om vävnadsreglerande proteiner, så kallade matrix metalloproteinaser och dess hämmare, vid kuffruptur. Avhandlingen syftade också till att undersöka effekten av specifik axel träning vid subacromial smärta i relation till det kliniska utfallet och behovet av kirurgi. Vidare undersöktes faktorer som har betydelse för val av behandling. I avhandlingen ingår fem delarbeten baserade på patienter och i studie III även frivilliga friska matchade kontroller. Fynden var i huvudsak följande:

Studie I) Förekomsten av rotatorkuffrupturer var lägre än förväntat hos patienter med subakromial smärta 15 år efter att de opererats med artroskopisk subakromial dekompression, jämfört med rupturförekomst hos symptomfria personer i samma ålders grupp.

Studie II) En fördröjning på tre månader från rupturtillfälle till rotatorkuffreparation påverkade inte det kliniska resultatet. Förekomsten av flera rupturerade kuffsenor inverkade inte heller. Emellertid hade högre ålder negativ inverkan på resultatet. Samtliga resultat identifierades vid medellång uppföljning.

Studie III) Förhöjd nivå av matrix metalloproteinhämmaren TIMP-1 kunde uppmätas i plasma hos patienter med rotatorkuffruptur, jämfört med friska matchade kontroller. Högre nivåer av TIMP-1, TIMP-3 och MMP-9 kunde även påvisas hos patienter med genomgående ruptur, jämfört med patienter med partiell ruptur.

Studie IV) Specifik axel träning under tre månader med fokus på excentriska övningar för rotatorkuffen och skulderbladsstabiliserande muskler minskade signifikant smärta och förbättrade skulderfunktionen. Den specifika träningen minskade därmed behovet av operation i form av artroskopisk subakromial dekompression hos patienter med långvarig subakromial smärta, jämfört med kontrollgruppen.

Studie V) Den specifika träningens positiva effekter var bestående efter ett år och signifikant fler patienter valde även efter ett år att avstå kirurgi i den specifika träningsgruppen jämfört med kontrollgruppen. Patienterna med mest symtom vid studiens början samt de med genomgående kuffruptur valde i större utsträckning kirurgi.

Konklusionerna är att patienter med subakromial smärta framgångsrikt kan behandlas med specifik träning. Vid uttalade symtom och en genomgående rotatorkuffruptur är sannolikheten större att kirurgi i form av artroskopisk subakromial dekompression behövs. Denna kirurgi verkar ha en skyddande effekt på kuffen. Reparation av akuta kuffskador kan dröja tre månader utan att resultatet blir sämre. Matrix metalloproteiner och deras hämmare är involverade vid kuffruptur och dessa proteiner kan mätas systemiskt i plasma, främst vid genomgående ruptur.

4 Abbreviations

AHD	Acromiohumeral distance
ADL	Activities of daily living
AI	Acromion index
ASD	Arthroscopic subacromial decompression
CE	Concentric exercises
CM score	Constant-Murley score
CI	Confidence interval
DASH	Disabilities of the arm, shoulder and hand questionnaire
EE	Eccentric exercises
EQ-5D	European quality-of-life 5-dimensions questionnaire
ELISA	Enzyme-linked immunosorbent assay
FTT	Full-thickness tear
GH joint	Glenohumeral joint
LHB	Long head of biceps tendon
MRI	Magnetic resonance imaging
MMP	Matrix metalloproteinases
PASTA	Partial articular surface tendon avulsion
PTT	Partial-thickness tear
STSL	Superior transverse scapular ligament
TIMP	Tissue inhibitor matrix protein
VAS	Visual analogue scale
WORC	Western Ontario rotator cuff index
US	Ultrasound

5 Introduction

I was inspired to embark on the research projects leading up to this thesis by the many controversies regarding the pathogenesis and treatment of subacromial pain and rotator cuff disease.

Subacromial pain is the most common cause of shoulder pain, causing disability, negatively influencing quality-of-life, and inferring great costs for society. Of patients seeking primary care for shoulder pain, 48-65 % have subacromial pain, and the disorder stands for 31 % of disability payments for dysfunction in the upper extremity (Gomoll et al. 2004, van der Windt et al. 1996, Vecchio et al. 1995, Williams et al. 2004, Wilson d'Almeida et al. 2008). According to the Swedish Board of Health and Welfare (2009) the number of arthroscopic subacromial decompression procedures has increased between 2005 and 2009 despite the fact that several studies have shown similar results between physiotherapy and surgical intervention (Brox et al. 1999, Haahr and Andersen 2006, Ketola et al. 2009)

Subacromial pain is rare before the age of 30 and usually appears in middle age. Rotator cuff tears, both asymptomatic and symptomatic, increase with age (Milgrom et al. 1995, Yamaguchi et al. 2006).

Many different terms are used to describe subacromial pain and it's pathology in the literature; subacromial bursitis, supraspinatus tendinitis or tendinosis, painful arc syndrome, subacromial impingement syndrome and rotator cuff syndrome. The reason for this diversity in nomenclature is the controversy regarding it's pathogenesis. It is accepted that multiple factors are involved in the pathogenesis, but several unresolved issues remain such as: which subacromial structure is first engaged by pathology, and what are the pain-generating mechanisms?

In this thesis the term "subacromial pain" is used and defined as pain thought to originate from structures lying between the acromion and the humeral head, most often associated with some degree of shoulder dysfunction.

In this thesis rotator cuff tears are divided into ***acute*** tears defined as tears appearing after trauma in patients without previous shoulder pathology and with a very restricted range of active motion (pseudoparalysis) (Bassett and Cofield 1983, Oh et al. 2012). The other main form of tear is ***chronic*** developing with time and probably due to multiple factors such as overuse and degeneration (Codman and Akerson 1931, Riley 2008, Seitz et al. 2011). Chronic degenerative cuff affection is the most common but may present with acute symptoms if traumatised: so-called ***acute on chronic tear*.**

Another recurring term in this thesis is ***structural*** outcome. This term describes the status of the anatomical structures such as the rotator cuff tendons, and signs of subacromial degeneration, as evaluated with ultrasound and radiology. ***Clinical*** outcome is a collective term for the clinical assessment tools used in the thesis such as the Constant-Murley score.

6 Background

6.1 Anatomy of the shoulder

6.1.1 Glenohumeral joint

The upper extremity is articulated with the shoulder girdle in the glenohumeral joint (GH joint). The geometrical relationship of the humeral head and the glenoid surface (Figure 1) allows for great range of motion but at the cost of only a minor inherent skeletal stability. Joint stability instead relies on static and dynamic soft tissues acting upon the joint. Glenohumeral muscles contribute to shoulder stability by creating a force vector pointing toward the glenoid (Prescher 2000, Rockwood and Matsen 1990).

The freedom of movement makes the anatomical structures of the shoulder vulnerable and a frequent target of both traumatic and degenerative injuries (Prescher 2000).

The articular capsule (Figure 1) is spacious and has a fold caudally; the axillary recess (Figure 1). This recess allows the humeral head to glide caudally so that the greater tuberosity can slide under the acromion during abduction.

The greater and lesser tuberosities of the humeral head (Figure 2) form the walls of the bicipital groove (Figure 2) and insertion points for the rotator cuff. Anatomical variations of the greater and lesser tuberosities have impact on the biomechanical function of the rotator cuff (Prescher 2000).

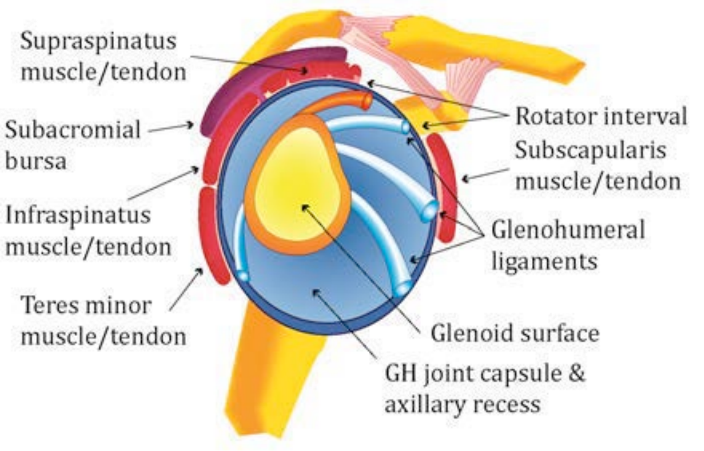


Figure 1 Lateral view of the GH joint, humeral head.
Figure design Lars Adolfsson and Gustaf Hallgren.

6.1.2 Scapula

The scapula is a thin sheet of bone mainly functioning as a muscle origin site. Structures of the scapula that are of special clinical interest regarding subacromial problems are the superior margin with the scapular notch, the acromion, the glenoid cavity, the scapular ligaments, and the coracoid process (Figure 2-3).

Medial to the coracoid process on the superior margin is the scapular incisura, a notch that varies in size and depth. This notch is arched by a ligament, the superior transverse scapular ligament (STSL) (Figure 3). The suprascapular nerve runs in the incisura often accompanied by the artery and vein. The ligament is ossified in about 10 % of individuals. The coracoid process is the origin of the short head of biceps and the coracobrachialis tendons, and the insertion of pectoralis minor muscle and ligaments to the acromion and the clavicle (Prescher 2000, Warner et al. 1992, Yang et al. 2011).

The scapular spine bends nearly 90 degrees and forms the acromion (Figure 2). The acromion is normally formed by fusion of several ossification centres during adolescence. In about 7-15 % disturbance of this fusion leads to a variant, os acromiale. An os acromiale can only be diagnosed after the age of 25 since ossification of the acromion is not complete until then (Prescher 2000).

Bigliani et al. (1991) divided the shape of the acromion into three types; Type I (flat), Type II (curved) and Type III (hooked). Bigliani was also the first of many authors to describe an association between a hooked acromion and impingement of the subacromial structures. (Bigliani and Levine 1997, Bigliani et al. 1991, Kesmezacar et al. 2008, Prescher 2000). This concept has however recently been challenged (Kesmezacar et al. 2008).

One scapular ligament of clinical importance is the coracoacromial ligament that forms an arch above the shoulder joint from the lateral border of the coracoid process to the anterior tip of the acromion (Figure 1-3). The coracoacromial ligament is said to function as a tension band and stabiliser of the acromion (Prescher 2000). A relationship between the anatomy of the coracoacromial ligament and impingement of subacromial structures was suggested by Neer in the seventies (1972). Five main forms of the coracoacromial ligament have been identified; quadrangular, Y-shaped, broad band, V-shaped and multiple-banded. In a cadaver study the most common forms were found to be Y-shaped or broad band (Kesmezacar et al. 2008). Several later studies have suggested that geometrical and biomechanical properties of the ligament may play a role in subacromial impingement and tendon degeneration, but this remains unclear (Fremerey et al. 2000, Kesmezacar et al. 2008, Soslowsky et al. 1994). Kesmezacar et al. (2008) could not find any significant correlations between the ligament type and acromial shape or the ligament type and rotator cuff degeneration. They found, however, an association between patients with ligaments composed of more than one bundle and rotator cuff lesions (Kesmezacar et al. 2008).

Other important ligaments are the superior transverse scapular ligament (Figure 3) mentioned above, and the inferior transverse ligament also called the spinoglenoid ligament. The inferior ligament spreads between the lateral margin of the base of the scapular spine and the dorsal side of the glenoid cavity. The suprascapular nerve, artery and vein are kept in the spinoglenoid notch by this ligament, and compression of the nerve there may cause infraspinatus palsy (Prescher 2000, Rockwood and Matsen 1990).

Several muscles that are important for normal shoulder function insert at, or have their origin at the scapula, and disturbance of their function may be involved in subacromial pain and impingement.

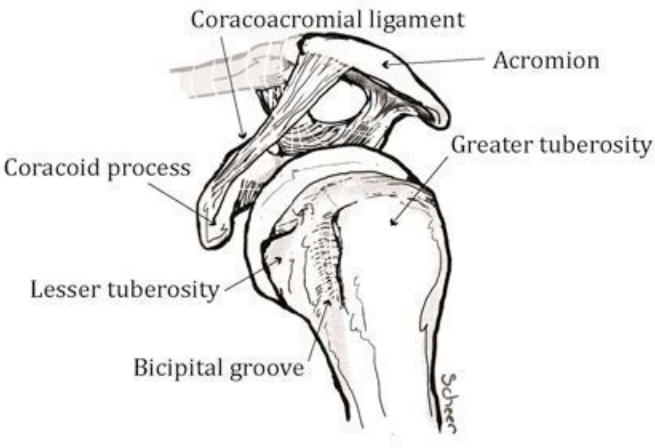


Figure 2 Lateral view of the GH joint and subacromial space.
Figure design Johan Scheer.

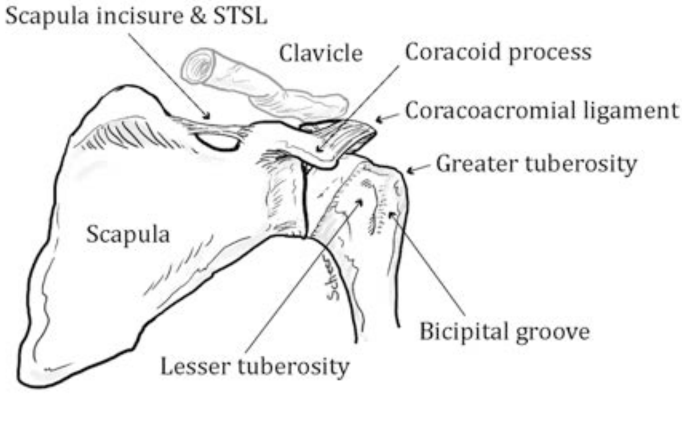


Figure 3 Anterior view of scapula and GH joint, cross section of the clavicle. The scapular incisure medial to the coracoid process and the superior transverse scapular ligament (STSL).
Figure design Johan Scheer.

6.1.3 Acromioclavicular joint

The acromioclavicular joint is the only articulation between the clavicle and the scapula, except for a few individuals (about 1 %) that have a coracoclavicular joint (Lewis 1959). The clavicle joint facet is usually caudally inclined and the acromial facet is cranially inclined. This joint has a rudimentary disc in adults and fibrocartilaginous-covered articular facets. Degenerative changes appear with increasing age and osteophytes often grow in a caudal direction into the subacromial space and may affect the supraspinatus tendon. Osteoarthritis of this joint is diagnosed clinically and with radiology. The acromial branch of the thoracoacromial artery supplies blood to the joint, and innervation comes from the pectoral, axillary and suprascapular nerves (Lewis 1959, Prescher 2000, Rockwood and Matsen 1990).

6.1.4 Bursae

The bursae of the shoulder facilitate gliding between neighbouring structures. Two of the bursae are usually in continuation with the glenohumeral joint; the subscapular bursa and the subcoracoid bursa. Two other clinically important bursae are the subacromial bursa and the subdeltoid bursa, which normally do not communicate with the joint. The subacromial bursa (Figure 1) lies embedded in the subacromial pad of adipose tissue between the rotator cuff and the acromion and “lubricates” shoulder movement especially during abduction and external rotation (Prescher 2000, Rockwood and Matsen 1990).

6.1.5 Deltoid muscle

The largest of the glenohumeral muscles is the deltoid. It has three parts, the anterior third originates from the lateral clavicle, the middle third originates from the acromion and the posterior third originates from the spine of the scapula. Insertion is at the deltoid tubercle of the humerus. The anterior and the middle thirds of the muscle elevate in the scapula plane with some action of the posterior third, especially above 90 degrees elevation. Only the anterior and middle third are involved in elevation of the arm. In horizontal abduction the deltoid accounts for 60 % of strength. The axillary nerve innervates the deltoid muscle and the main blood supply comes from the posterior humeral circumflex artery, both structures run on the deep side of the muscle (Prescher 2000, Rockwood and Matsen 1990).

6.1.6 Rotator cuff

The cuff consists of four separate muscles; subscapularis, supraspinatus, infraspinatus and teres minor (Figure 1, 4). These muscles emerge from the scapula and their tendons blend in, strengthen and cover the glenohumeral joint capsule on the ventral, cranial and dorsal sides and insert at the greater and lesser tuberosities of the humeral head (Figure 4). The area between the tendons of supraspinatus and subscapularis is called the rotator interval (Figure 1) and contains the coracohumeral ligament, which originates from the base of the coracoid process and inserts at the greater tuberosity (Prescher 2000, Rockwood and Matsen 1990).

The ***subscapularis*** muscle originates on the anterior surface of the scapula and the tendon inserts at the lesser tuberosity of the humerus. The muscle is the largest and most powerful of the rotator cuff muscles and functions as the primary internal rotator of the humerus as well as stabilising the humeral head in the glenoid cavity by resisting anterior, posterior, and inferior displacement. Injury or weakness to the subscapularis may lead to increased impingement and/or anterior instability during humeral elevation, abduction, and external rotation (Pennock et al. 2011). The upper subscapular nerve innervates most of the muscle and the lower subscapular nerve innervates the rest. In the majority of cases these nerves come from the posterior cord and in a few cases from the axillary nerve (Tubbs et al. 2007). The subscapularis artery, the largest branch of the axillary artery, supplies the muscle with blood (Rockwood and Matsen 1990).

The ***supraspinatus*** muscle originates in the fossa supraspinatus above the spine of the scapula and inserts at the greater tuberosity of the humerus. Near its insertion the tendon consists of five axial plane layers from the bursal to the articular side (Clark and Harryman 1992). The supraspinatus tendon is at risk for compression and attrition because of it's anatomical position above the humeral head, beneath the acromion and the coracoacromial ligament (Figure 4). The supraspinatus is active in any movement involving elevation of the arm and is important for glenohumeral joint stability, the circumferential insertion at the humeral head and muscle fibres orientated toward the glenoid cavity. In the neutral position of the arm the supraspinatus produces a compression force and because of the circumferential insertion the humeral head is depressed. In abduction of the arm, the vertical force of the deltoid is little and the head-depressing force of the supraspinatus muscle is lost, but abduction and compression forces remain. The infraspinatus and subscapularis muscles provide further depression force on the humeral head, and the ability to resist the shear force of the deltoid, explaining why abduction is possible in the presence of a supraspinatus tear. A recent electromyographic study indicated that in addition to the deltoid muscle and the rotator cuff muscles the adductors, latissimus dorsi and teres major muscle are also important in maintaining GH joint stability during daily activities (Hawkes et al. 2012).

The suprascapular nerve, a mixed motor and sensory nerve, which originates from the superior trunk of the brachial plexus, innervates the supraspinatus muscle. Entrapment of the nerve may occur as it passes through the scapular notch under the STSL (Figure 3) (Blum et al. 2011, Thompson and Kopell 1959, Yang et al. 2011). Blood is supplied by branches of the thoracoacromial artery and the suprascapular artery that join with the posterior humeral circumflex artery on the posterior portion of the cuff. The rotator cuff is poorly vascularised near its insertion site and in approximately two thirds of all supraspinatus tendons there is a hypovascular zone, 1.5 cm from the greater tuberosity called the rotator crescent. This corresponds to a frequently degenerated zone (Blum et al. 2011, Codman and Akerson 1931, Macarini et al. 2011, Prescher 2000, Rathbun and Macnab 1970, Yang et al. 2011).

The ***infraspinatus*** muscle originates below the spine of the scapula, in the infraspinatus fossa, and fuses with the supraspinatus tendon as it inserts at the posterior aspect of the greater tuberosity of the humerus. The infraspinatus muscle is the main external rotator of the humerus. It also works with the other rotator cuff muscles to depress and stabilise the humeral head in the glenohumeral joint, and acts against posterior dislocation. The suprascapular nerve innervates the muscle and it's blood supply comes from the suprascapular artery and occasionally the subscapular artery (Rockwood and Matsen 1990).

The ***teres minor*** muscle originates from the lateral border of the scapula and inserts at the inferior aspect of the greater tuberosity of the humerus. The teres minor is the other external rotator of the humerus and it works with the other rotator cuff muscles to stabilise the glenohumeral joint. Innervation comes from a posterior branch of the axillary nerve and it's blood supply comes from the suprascapular artery (Rockwood and Matsen 1990).

The ***rotator cable*** is a thickening of the coracohumeral ligament, with fibres running perpendicular to the rotator cuff fibres. The rotator cable extends from the coracohumeral ligament through the supraspinatus tendon on the articular side to the inferior border of the infraspinatus tendon (Macarini et al. 2011, Sheah et al. 2009). This structure tends to thicken with age and is thought to be important in preserving normal shoulder function because stress is transferred from the rotator cuff to this thick structure, allowing some patients with a rotator cuff tear to become asymptomatic (Burkhart et al. 1993).

Figure 4 Lateral view of the GH joint with rotator cuff insertion and coracoacromial arc. Figure design Johan Scheer.

6.1.7 Long head of biceps tendon

The long head of biceps tendon (LHB) runs in the bicipital groove in the inter-tubercular tendon sheath. At the cranial end of the groove it becomes intraarticular (Figure 2, 4-5). The tendon crosses the glenohumeral articular cavity over the humeral head and inserts at the supraglenoid tubercle. The morphology of the bicipital groove has been associated with pathology of the tendon; the shallower the groove the more likely pathology, although the bicipital groove is covered with synovium (Elser et al. 2011, Pfahler et al. 1999, Rockwood and Matsen 1990). Biomechanical studies indicate that the tendon contributes to stabilise the glenohumeral joint in all directions, but these studies have limitations and it's function remains poorly understood (Elser et al. 2011, Pfahler et al. 1999). Areas of hypovascularisation of the tendon especially near the glenoid labrum are described and associated with degeneration of the tendon (Kolts et al. 1994, Prescher 2000, Rathbun and Macnab 1970). Patients with malfunction and degenerative changes within the rotator cuff often sustain concomitant degenerative changes of the LHB. The role of the LHB in subacromial impingement is a matter of debate. Dislocation of the tendon from the intertubercular groove appears together with lesions of the subscapularis. Branches of the musculocutaneous nerve innervate the biceps tendon and it's blood supply comes from the brachial artery (Kolts et al. 1994, Prescher 2000, Rockwood and Matsen 1990, Warner and McMahon 1995)

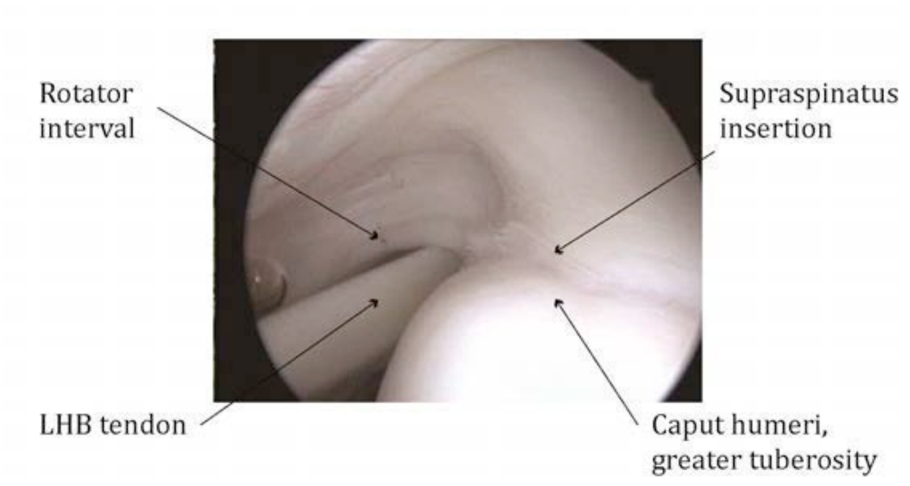


Figure 5 Arthroscopic articular view of normal rotator cuff insertion at the greater tuberosity and LHB tendon.

6.2 Subacromial pain and pathology

The pathology of subacromial pain has a wide spectrum ranging from acute inflammation, subacromial bursitis (Figure 6), to advanced degenerative changes with massive rotator cuff tearing (Figure 8A) (Umer et al. 2012). Bursitis without involvement of other subacromial structures usually appears after a short period of overuse or trauma, and resolves with rest, anti-inflammatory treatment and physiotherapy, according to own clinical experience Trauma without previous history of shoulder symptoms may result in an acute rotator cuff tear (Figure 8 B, D). When pain and disability are persistent, any of the subacromial structures may be involved. Subacromial pain can be provoked at clinical examination by manoeuvres decreasing the subacromial space and impinging the bursa and cuff between the coracoacromial ligament, the anterior part of acromion and the humeral head (Neer 1972, Neer 1983, Valadie et al. 2000). There are many theories in the literature on the aetiology of the pain and it's pathology, but it appears that multiple factors are involved. A classical theoretical model is to divide causes into extrinsic and intrinsic or a combination of both (Armstrong 1949, Codman and Akerson 1931, Neer 1972, Seitz et al. 2011). Mechanical wear or compression from the coracoacromial arch and biomechanical factors are described as extrinsic factors, while age-related degeneration of subacromial structures and genetic predisposition are considered intrinsic factors. Armstrong (1949) introduced the extrinsic compression theory, which was later refined by Neer (1972, 1983) who named it "subacromial impingement" which implies an extrinsic compression due to narrowing of the subacromial space. Extrinsic compression alone does not explain all subacromial pathology (Seitz et al. 2011).

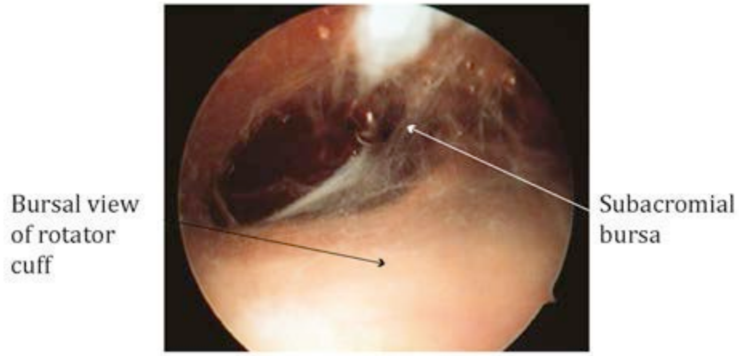


Figure 6 Arthroscopic view of the subacromial bursa.

6.2.1 Extrinsic mechanisms of subacromial pain

Anatomical factors that may affect the subacromial space include: variations in the acromial shape; the anterior slope; the angle of the acromion; and the lateral extension of the acromion over the humeral head. Osseous changes of the inferior acromio-clavicular joint or the coracoacromial ligament may also affect the subacromial space. It is reported that the shape of the acromion is associated with the severity of rotator cuff pathology (Bigliani et al. 1991, Ogawa et al. 2005). Patients with Type I acromion have a better outcome after conservative treatment for subacromial pain than those with Types II and III (Morrison et al. 1997, Wang et al. 2000). Acromial morphology is considered to contribute to bursal-sided partial tears (Yadav et al. 2009). It is t not clear, however, if the shape is congenital or acquired with age and part of a degenerative process (Bonsell et al. 2000, Budoff et al. 1998, Sano et al. 1999). A more horizontal position of the acromion is also associated with subacromial pathology (Vaz et al. 2000). Recently a new biomechanical measure, the lateral acromial coverage of the humeral head designated acromion index (AI) was introduced by Nyffeler et al. (2006). A large lateral extension of the acromion is thought to predispose to rotator cuff tearing by influencing the orientation of the resultant deltoid muscle force vector. The larger the lateral extension of the acromion, the higher the ascending force component by the deltoid muscle contributing to impingement of the rotator cuff against the acromion (Nyffeler et al. 2006). A relationship between AI, rotator cuff tearing and a structural defect after repair has been reported (Nyffeler et al. 2006, Torrens et al. 2007, Zumstein et al. 2008). Kim et al. (2012) also concluded that a higher AI is more frequently seen in patients with full-thickness tears (FTTs) and massive tears than in patients with articular sided partial-thickness tears (PTTs) on magnetic resonance imaging (MRI).

Ossifications of the coracoacromial ligament and subacromial spurs are findings associated with bursal-sided PTTs that may progress to full-thickness tears (Ogawa et al. 2005).

It is most likely that these anatomical factors are not the only cause of all subacromial pathology but more likely predispose a person to cuff pathology appearing after overuse and micro-trauma. This is supported by the fact that the dominant shoulder is affected more often (Yamaguchi et al. 2006).

Biomechanical factors such as abnormal scapular and humeral kinematics can cause superior displacement of the humeral head and extrinsic rotator cuff compression. Postural abnormalities, rotator cuff and scapular muscle deficits, and soft tissue tightness are external factors that influence scapula and humeral kinematics (Seitz et al. 2011).

Co-activation of subscapularis-infraspinatus and supraspinatus-infraspinatus muscles stabilise the humeral head within the glenoid fossa by causing compression forces. These forces are believed to be important for normal shoulder function (Michener et al. 2003, Myers et al. 2009). Patients with subacromial pain have decreased rotator cuff co-activation and increased mid- deltoid activation at initiation of elevation. This alteration in muscle activation may facilitate encroachment of the subacromial structures during overhead elevation. It is unknown whether or not the alteration in muscle activation is present before the patient develops pain or appears as a result of pain, altered scapula or humeral head position or movement (Michener et al. 2003, Myers et al. 2009).

The acromiohumeral distance (AHD) is the space between the acromion and the humeral head. The AHD, when measured during muscle activity, may be useful in detecting defects related to biomechanical factors. There is however limited evidence for this measure's usefulness and inter-observer reliability has been found to be poor (Graichen et al. 1999, Seitz et al. 2011, Zuckerman et al. 1997). Proximal migration of the humeral head in subacromial pain patients usually present during active movement only, and may be counteracted by scapular rotation leading to increase in the subacromial space. If proximal migration of the humerus with the arm at rest is seen, this is regarded as a sign of a major rotator cuff tear (Graichen et al. 2001, Keener et al. 2009, Yamaguchi et al. 2000) (Figure 7).

Figure 7 Patient with progress of subacromial pain and rotator cuff disease to massive cuff tearing over eleven years, illustrating proximal humeral migration. A) Year 2000, subacromial degeneration B) Year 2006, beginning of proximal humeral migration C) Year 2011, pronounced proximal humeral migration four years after failed rotator cuff repair, and development of secondary osteoarthritis, so called cuff arthropathy.

6.2.2 Intrinsic mechanisms of subacromial pain

In the 1930's Codman and Akersson (1931) presented a degenerative process that they thought preceded supraspinatus tendinopathy and tearing. There is, today, a growing body of evidence supporting intrinsic mechanisms as important factors for changes in tendon morphology and performance (Milgrom et al. 1995, Sher et al. 1995, Tempelhof et al. 1999). The overall theory of intrinsic mechanisms assumes that demands on tendon cells at some point are greater than the endogenous ability to repair structural defects leading to degeneration and tearing. Factors suggested to be involved are age, vascularity, alterations in tendon matrix, mechanical properties and genetics (Seitz et al. 2011). Codman and Akersson (1931) and even (1972, 1983), who refined the concept of extrinsic compression theory, included age as an important factor and described a continuum of subacromial pathology having three stages:

Stage I) Reversible inflammation and oedema of the rotator cuff, patient less than 25 years of age.

Stage II) Fibrosis and thickening of the subacromial bursa and rotator cuff, patient between 25 and 40 years.

Stage III) Bony spurs and PTTs or FTTs, patient older than 40 years.

The prevalence of PTTs and FTTs are described to increase with age (Milgrom et al. 1995, Sher et al. 1995, Tempelhof et al. 1999, Yamaguchi et al. 2001). In both biomechanical and histological studies, age has been shown to have negative impact on tendon properties but there is no consensus whether tendon changes are due to aging or are secondary to an inferior healing response to micro-trauma (Seitz et al. 2011, Woo SL 2000).

Deficient vascularisation of the rotator cuff is another intrinsic mechanism. Codman and Akersson (1931) were the first to describe the most common site of tearing as the “critical zone”, an area with deficient vascularisation about a centimetre from the supraspinatus insertion at the greater tubercle. Rathbun and Macnab (1970) developed the theory and described a relative avascular zone with the arm in adduction. Lohr and Uhthoff (1990) described a lower arteriolar density on the articular side than on the bursal side of the supraspinatus tendon. This theory of a hypovascular zone and resultant reduced healing capacity predisposing to tendinopathy has been questioned since no avascularity has been found in this zone *in vivo* and it is not known if the avascularity described *in vitro* causes the tear or is a result of full-thickness tearing (Fukuda et al. 1990, Levy et al. 2008, Rathbun and Macnab 1970, Seitz et al. 2011).

The histopathological changes associated with rotator cuff tendinopathy are well documented and it is known that they vary with duration of tendon affection. Acute injuries result in diffuse tendon thickening and matrix changes associated with the healing response, while in chronic tendinopathy there are focal defects and tendon thinning associated with degeneration (Garofalo et al. 2011). Within twelve weeks of symptoms, accumulation of glycosaminoglycans (GAGs) and disorganisation of the collagen fibres, thought to cause tendon thickening, has been demonstrated (Scott et al. 2007). In chronic tendinopathy, a reduction in the total collagen content, fat degeneration and increased tenocyte apoptosis has been found, which is concurrent with reduced tendon thickness (Teefey et al. 2000). This corresponds to the three stages presented by Neer (1972, 1983). Further, histological evidence for disorganised tissue in the mid-substance and on the articular side compared to more organised collagen on the bursal-side layers of the cuff tendons has been proposed to predispose to intratendinous and articular-sided PTTs that may precede FTTs (Fukuda 2000, Fukuda et al. 1990). Cuff tears that begin on the articular side are believed to be related to intrinsic factors (Yadav et al. 2009).

Presence of the molecular changes in the bursa and the rotator cuff, however, are still controversial but it has been shown that alterations in the intracellular and extracellular composition are present. Matrix metalloproteinases (MMPs) and their inhibitors, tissue inhibitors of metalloproteinases (TIMPs), are responsible for extracellular matrix turnover and are involved in cuff degeneration. Increased MMP and TIMP levels have been identified in the subacromial bursa, synovial fluid and cuff tendons in patients with subacromial pain (Lo et al. 2004, Shindle et al. 2011, Voloshin et al. 2005). Inflammatory mediators such as cytokines induce MMP production and oxygen-free radicals, which have an increased expression in the bursa and the rotator cuff in both early and late tendinopathy (Millar et al. 2009, Voloshin et al. 2005). These mediators are known to be involved in catabolic processes and might be important in degeneration. It is however not known where and why the inflammatory process starts. To further highlight the complexity of pathogenesis, factors such as age, gender, hormones, metabolic status, vascularisation and mechanical load also influence MMPs and TIMPs (Henle et al. 2005, Shindle et al. 2011)

Intratendinous degeneration and tearing is also thought to result from shearing between various parts of the tendons. The layers of the supraspinatus tendon in particular are proposed to have distinct mechanical properties and different resistances to loading (Fukuda 2000). Intrasubstance tearing is suggested to develop into an articular-sided tear before becoming a full-thickness tear with continued loading (Reilly et al. 2003). There is biomechanical evidence for the propagation of tearing; the thinner the tendon the less area/load index, and as degeneration increases the tensile strength decreases (Sano et al. 1997). However not all patients progress in their pathology or symptoms and the reason for this is unclear. Altered mechanical loading also modulates MMP expression. Increased strain, shear or compression forces can induce matrix remodelling, furthermore local loss of tension, as in full-thickness tearing, may lead to apoptosis and tendon degeneration (Jones et al. 2006). The supraspinatus tendon is under high stress and collagen remodelling is increased compared to other tendons under less stress (Riley 2008, Riley et al. 2002).

Genetic predisposition also plays a roll in cuff tendinopathy according to Harvie et al. (2004) who found an increased risk for tears in siblings of patients with symptomatic cuff tears. A long list of genes are reported to be involved in the development of tendinopathy, for example polymorphism of collagen genes are found in persons with achilles tendinopathy (Mokone et al. 2005). A genetic discrepancy in synovial inflammation, apoptosis and regeneration potential has been discussed. Furthermore the association between pain and tearing may be influenced by genetic factors (Gwilym et al. 2009, Shindle et al. 2011). It has been suggested that painful tendinopathy and painless tendon tear are two somewhat different entities, perhaps explained by genetic differences resulting in different structural proteins and proteolytic enzymes (Corps et al. 2006, Raleigh et al. 2009).

6.3 Rotator cuff tears

Rotator cuff tears are theoretically divided into different types depending on the affected part of the tendon, aetiology and/or symptoms. There are several controversies in the literature but the general belief seems to be that treatment, healing potential and prognosis are correlated to the type of tear. Rotator cuff tendons may tear partially (PTT), which in this thesis is considered a non-penetrating tendon defect, and may be on the bursal side in the mid-substance or on the articular side (Figure 8 C) (Finnan and Crosby 2010). Full-thickness tear (FTT) is a loss of continuity throughout the tendon (Figure 8 D) and a complete tear is when the FTT extends the whole width of the tendon

(Figure 8 B). Massive tears are defined differently in the literature based on the area of the defect or the number of tendons detached (Bedi et al. 2010a). In this thesis a massive tear is defined as complete avulsion of more than two tendons.

6.3.1 Acute rotator cuff tear

Many patients with a rotator cuff tear have a history of a trauma, in previous studies 40-88 %, but most traumatic cuff tears do not fulfil the criteria of an acute tear (Fukuda 2000, Lahteenmaki et al. 2006, Sorensen et al. 2007). A traumatic acute rotator cuff tear has been defined as one appearing in patients with no previous history of shoulder symptoms that presents with pseudoparalysis (less than 45 degrees of motion in both active forward elevation and abduction) after trauma. These tears are rare and Basset and Cofield (1983) identified tears according to the above criteria in only 2.3 % patients. In another study by Lähteenmäki et al. (2006) only 5.3 % of the patients fulfilled these criteria.

Acute tears may be PTT or FTT, most often painful and in younger patients (Cofield 1985, Moosmayer et al. 2010). Codman and Akerson (1931) postulated that trauma can lead to rupture of healthy rotator cuff tendons, but most often acute ruptures occur in cases where aged tendons are weakened by overuse or degeneration. It has been questioned if "True acute tears" even exist since many traumatic tears are probably "acute on chronic tears" (Codman 1990, Codman and Akerson 1931). Even so, this small subgroup of tears is considered acute, and immediate repair has been recommended (Bassett and Cofield 1983, Lahteenmaki et al. 2006).

One form of acute tear without pseudoparalysis is the partial anterior bursal-sided supraspinatus tear, located posterior to the LHB at the anterior rim of the greater tuberosity, but not in the "critical zone". The clinical features are acute symptoms including pain and shoulder dysfunction after trauma in young patients (Oh et al. 2012). Oh et al. (2012) found a higher frequency of inferiorly directed spurs associated with these tears and surgical treatment was effective in reducing pain and improving function.

The Swedish national guidelines (Swedish National Musculoskeletal Competence Centre 2006) state that surgical repair of acute tears should be performed within three weeks but there is little scientific support for this guideline. Bassett and Cofield (1983) showed in their long-term follow-up (mean seven years) that function was better with early repair but pain relief was acceptable regardless of time between injury and surgery.

6.3.2 Degenerative rotator cuff tear

Tears that are believed to have a degenerative origin may be PTT or FTT (Figure 8 A, C). Degenerative tears may be symptomatic, including pain and loss of shoulder function but may also be asymptomatic in the meaning that the tear is not causing pain or dysfunction as appreciated by the individual with the tear (Seitz et al. 2011).

Natural history studies on asymptomatic tears have demonstrated a prevalence of 5-80 % within an age range of 30-99 years, including both PTTs and FTTs (Milgrom et al. 1995, Yamaguchi et al. 2001). Moosmayer et al (2009) presented a prevalence of FTTs in a Norwegian population of 2-15 % within the age range 50-79 years. In a Japanese population Yamamoto et al. (2010) found a prevalence of FTTs of 21 % having a mean age of 58 years. Despite numerous cadaveric and imaging studies, the prevalence of cuff tear is uncertain and may differ between populations. One thing, however, is certain: the prevalence of both asymptomatic and symptomatic cuff tears increases linearly with age (Milgrom et al. 1995, Reilly et al. 2006, Tempelhof et al. 1999, Yamaguchi et al. 2001). Asymptomatic tears are most often limited to the supraspinatus tendon and the tear size is small to moderate (< 3 cm). Why these tears are, and possibly remain asymptomatic is not understood (Moosmayer et al. 2009). One theory is that an intact rotator cable prevents biomechanical failure by distributing the load on the thinner tendon at the "critical zone" to the thicker structure of the rotator cable thus limiting propagation of the tear (Macarini et al. 2011, Sheah et al. 2009). Burkhart et al. (1993) named this theory the "suspension bridge model" where an intact rotator cable and rotator cuff tendon force couples preserve the biomechanics despite an FTT.

Ultrasound (US) and magnetic resonance imaging (MRI) are the imaging modalities of choice for identifying both PTTs and FTTs (Figure 14 B-C) and they have documented equivalent accuracy (Fukuda et al. 1990, Teefey et al. 2004, Yamaguchi et al. 2000). There are several different rotator cuff tear classification systems based on arthroscopic findings. These consider the location, depth and area, but the inter-observer reliability is poor when determining depth and area (Adolfsson and Lysholm 1993, Crawshaw et al. 2010, Finnan and Crosby 2010, Fukuda et al. 1990, Henkus et al. 2009).

6.3.3 Partial-thickness tears

PTTs with degenerative origin most often appear in the mid-substance or on the articular side of the tendon (Figure 8 C) causing increased load on the remaining fibres and increased risk for further tearing (Fukuda 2000, Sano et al. 1999, Yadav et al. 2009). Yamakado (2012) found histopathologic degeneration in 93 % of patients with partial articular surface tendon avulsion (PASTA), supporting a degenerative origin.

PTTs on the bursal side are, in some studies, reported to be more painful than intratendinous or articular-sided tears. Subacromial bursitis present with bursal-sided tears causes increased levels of substance P and reaction with nerve endings is suggested to explain the increased pain in this condition (Fukuda 2000, Gotoh et al. 1998). PTTs are also reported to be potentially more painful than FTTs because of the tension created on the remaining intact fibres (Strauss et al. 2011). The finding of a prominent rotator cable may be indicative of a PTT since the rotator cable is believed to compensate for degeneration at the cuff insertion (Macarini et al. 2011).

There is no consensus on any single management plan for symptomatic degenerative PTTs. Initial conservative treatment with specific physiotherapy for six to twelve months and subacromial corticosteroid injection to relieve pain is recommended. Standardised long-term follow-up studies evaluating conservative treatment, however, are lacking (Finnan and Crosby 2010). PTTs have the potential to progress in tear size over time but the symptoms do not necessarily do so, and physiotherapy may prevent this (Finnan and Crosby 2010).

There are several studies supporting surgical repair of PTTs (Itoi and Tabata 1992b, Reilly et al. 2003, Shin 2012), but methodologically they are low-level scientific reports (Moosmayer et al. 2010). These studies show that the potential for healing without repair is very low, and that a high proportion of PTTs progress to FTTs (Finnan and Crosby 2010, Fukuda 2000). Histological findings in tendons with PTTs show small tears to have higher cellularity and blood vessel proliferation, which is associated with healing potential, whereas larger tears have fewer and smaller fibroblasts, suggesting that the reparative process has diminished and cells are in an inert state (Matthews et al. 2006).

Biomechanical data, such as increased tendon strain on the remaining fibres of tendons with a PTT, support the use of surgical repair to prevent tear progression (Mazzocca et al. 2008). Surgical interventions include tear debridement to stimulate healing, suture of the tear, and acromioplasty to prevent progression (Fukuda 2000). A recent review on PTTs (Finnan and Crosby 2010) concludes that when conservative treatment fails, surgical intervention can provide pain relief and restore shoulder function. The authors underline however that there is limited scientific evidence supporting the efficacy of surgery (Finnan and Crosby 2010). The same review concludes that when surgery is indicated; debridement should be performed in patients with less than 50 % of the tendon thickness torn, ASD if there is a bursal-sided tear, and suture of the tear when more than 50 % of the tendon thickness is torn. Open or arthroscopic trans-tendon repair, takedown to FTT repair, and trans-osseous repair have all been described as effective techniques (Fukuda 2000, Slabaugh et al. 2010, Strauss et al. 2011, Uchiyama et al. 2010).

Intratendinous tears are difficult to diagnose and to treat since they do not have any communication with either the subacromial bursa or the glenohumeral joint. As with other PTTs, there is no consensus, but the treatment options are the same as for bursal- and joint-sided tears; conservative or surgical treatment including ASD with or without resection and suturing. Little has been written in the literature about intratendinous tears, but a recent study describes successful outcome after ASD, explorative longitudinal split, resection of laminated fibres and suturing (Uchiyama et al. 2010).

6.3.4 Full-thickness tears

FTTs may be complete with no intact fibres or incomplete with some intact fibres left beside the full thickness tear (Figure 8 A-B, D). FTTs are correlated with increased tissue remodelling factors such as matrix metalloproteinases in the tendons and the synovium resulting in more synovial inflammation and matrix degradation than with PTTs. It is likely that synovial inflammation and tendon degradation have an effect on each other leading to progress in tear disease (Shindle et al. 2011).

FTTs have no healing potential without repair, but on the other hand the frequency of recurrent tear, or repaired tendons failing to heal, is reported to be very high, between 20-80 % (Shindle et al. 2011) for chronic tears. The indication for surgery should therefore be limited to disabling symptoms in chronic cases.

The cause of failure is poorly understood but probably multifactorial; histopathological changes in the tendons, pull-out of anchors, breakage of sutures, osteoporotic bone, decreased healing potential with increasing age, and, if infraspinatus and/or subscapularis are involved, loss of force couples (Boileau et al. 2005, Burkhart et al. 1993, Castagna et al. 2008).

Subacromial bursal inflammation is associated with cuff tearing. In the acute phase the bursal inflammation may be regarded as an attempt to heal the tear since the bursa has great reparative ability but as time passes this “reparative burst” decreases (Chillemi et al. 2011). This is one reason to avoid anti-inflammatory drugs and subacromial corticosteroid injection directly after an acute tear. Others claim that the bursal tissue should be preserved as far as possible during surgery (Chillemi et al. 2011).

Muscle atrophy and fatty infiltration of the muscle belly are associated with large and massive tears and described as a predictor of poor functional outcome after both conservative and surgical repair (Laron et al. 2012). MMPs play an important role in the remodelling of skeletal muscle and development of atrophy, with altered protein expression leading to fibrosis. Expression of MMP-2, -9 and -13 has been shown to increase significantly with muscle atrophy and tendon degeneration (Laron et al. 2012, Shindle et al. 2011). A recent study showed that gene expression related to tissue remodeling, in particular MMP-1 and MMP-9, differed between rotator cuffs that healed and those that failed to heal after arthroscopic repair (Robertson et al. 2012).

The reason for this change in protein regulation in cuff tearing may be partly due to the change in mechanical load on the muscle. As tear size, muscle degeneration and dysfunction progress, fatty infiltration increases. Little is known about the adipogenic differentiation of muscle stem cells, but it has been correlated with tendon and muscle degeneration, changes in the pennation angle, denervation of the muscle, oxidative stress, and aging (Laron et al. 2012).

One animal study indicated that separation of fibre bundles due to an increased pennation angle might lead to infiltration of fat cells filling the space between reoriented muscle fibres. This study also showed that these fatty changes could be reversible if tension returns to the muscle-tendon unit, implying that cuff repair may decrease fatty infiltration (Gerber et al. 2004). Affection of the suprascapular nerve by entrapment or traction caused by tearing of the supraspinatus tendon may contribute to supraspinatus and infraspinatus fatty infiltration (Laron et al. 2012, Mallon et al. 2006).

Whether or not cuff repair influences atrophy and fatty infiltration remains uncertain, but there are studies indicating that successful repair of massive degenerative tears may arrest or lead to recovery of these muscle changes (Yamaguchi et al. 2012).

Several studies have shown that repairs that heal and remain intact result in better elevation and abduction strength, but that the absence of healing does not necessarily affect pain relief and patient satisfaction negatively (Boileau et al. 2005).

A recent systematic review could not definitely state that the clinical outcome of patients with healed cuff repair was better than non-healed because of conflicting results and methodological factors (Slabaugh et al. 2010). The only significant difference related to surgical technique, according to another systematic review, was that double-row repair leads to a significantly lower structural failure rate compared to single-row repair in tears greater than one cm (Duquin et al. 2010). Short- to midterm follow-up after rotator cuff repair shows successful results as regards pain relief and shoulder function, but there are still only a few long-term studies (Borgmastars et al. 2010). Borgmästars et al. (2010) however, reported in their long-term follow-up (mean 20 years) that pain relief was consistent but the range of motion and strength assessed had decreased to scores less than preoperatively, indicating that the degenerative process progresses despite surgical repair. The material in this study was, however, partly historical since free tendon grafting is very rarely used today.

Even patients with FTTs can be symptomatically managed with conservative treatment by relieving inflammation and restoring muscle balance, but they usually have some remaining muscle weakness (Fukuda 2000, Moosmayer et al. 2009). Moosmayer et al. (2010) performed a randomised controlled study comparing cuff repair with physiotherapy. Patients with traumatic and atraumatic small and medium-sized FTTs without pseudoparalysis were included and the follow-up time was one year. With intention-to-treat analysis the surgically treated group was significantly improved compared to the physiotherapy group, but 82 % of the patients in the latter group reached an acceptable result after physiotherapy alone. The remaining patients in the physiotherapy group were effectively treated with secondary repair indicating that physiotherapy is an option for the initial management of small and medium-sized FTTs (Moosmayer et al. 2010).

When conservative treatment is unsuccessful, ASD with or without tear debridement is an option for chronic degenerative small- to medium-sized tears. Massoud et al. (2002) reported 75 % satisfactory outcome at follow-up (mean 41 months) after decompression alone. An unsatisfactory outcome in this study was related to manual work and symptom duration of more than one year (Massoud et al. 2002). Norlin and Adolfsson (2008) reported that subacromial pain patients with small FTTs at the index procedure had a mean of 94 points in Constant-Murley score (CM) score (100 points representing a normal shoulder function and no pain) at long-term follow-up. These and the results of several other studies give support to ASD as a successful procedure for small to medium-sized tears, perhaps because there is an intact cable structure (Burkhart et al. 1993, Norlin and Adolfsson 2008, Shin et al. 2012).

With surgical treatment of rotator cuff tears, subacromial decompression is traditionally included to increase access to the cuff and to diminish the contribution of extrinsic factors. As our knowledge of intrinsic mechanisms in the pathogenesis of tears increases a debate has developed as to whether decompression should be performed routinely or not during cuff repair (MacDonald et al. 2011, Shin et al. 2012).

Recent studies have reported no difference in shoulder pain, function and quality-of-life in patients undergoing arthroscopic cuff repair with or without decompression, at two-year follow-up after surgery (MacDonald et al. 2011, Shin et al. 2012). But Shin et al. (2012) showed a higher reoperation rate in the group without decompression. The follow-up time was only two years in both studies and the effect of decompression may appear later. Another aspect is that bursal resection was performed in all patients in both studies in order to visualise the cuff. Bursal resection is thought to play an important role in the reduction of cuff degeneration.

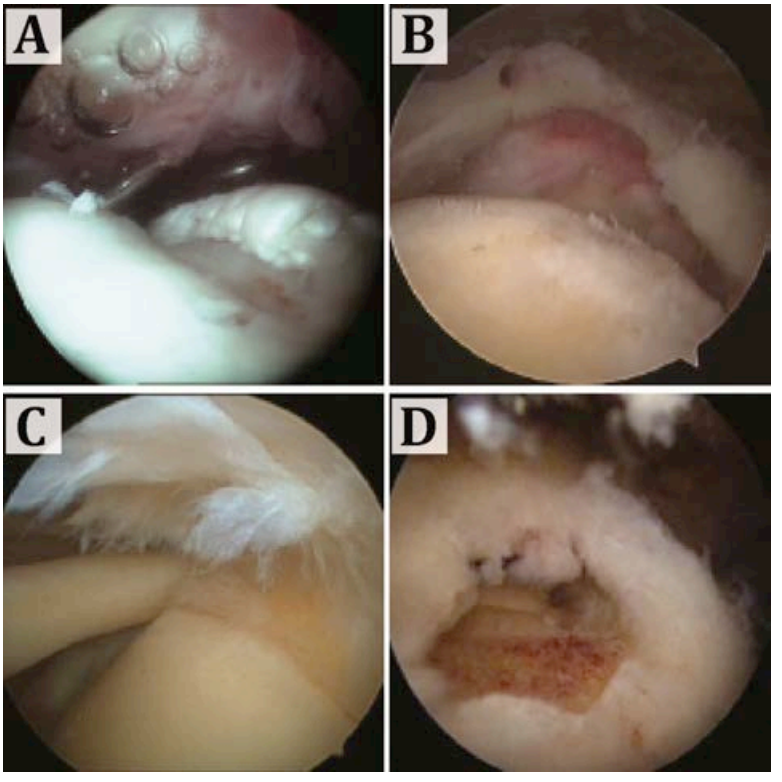


Figure 8 A) Complete degenerative chronic FTT of the supraspinatus tendon with rounded remaining's of the tendons at the greater tuberosity, articular view. B) Complete L-shaped acute supraspinatus FTT with bleeding and rough edges, articular view. C) Articular-sided view with biceps tendon and degenerative PTT of the supraspinatus. D) Incomplete acute FTT of the supraspinatus tendon, subacromial view.

7 Aims of this thesis

The overall aim of this thesis was to improve the understanding and treatment of the shoulder disorders; subacromial pain and rotator cuff tears.

The specific aims were:

Study I. To investigate the structural condition of rotator cuff tendons 15 years after ASD, and relate this to clinical outcome scores.

Study II. To investigate the structural and clinical outcomes of surgical repair of acute rotator cuff tears in previously asymptomatic patients, and to relate these outcomes with delay in repair, age at repair and the extent of the initial cuff injury.

Study III. To measure the plasma level of MMPs and their tissue inhibitors (TIMPs) in patients with rotator cuff tear and to compare the levels with those in healthy controls. A second aim was to examine any relationship between tear size and MMP and TIMP levels.

Study IV. To examine if a specific exercise programme, targeting the rotator cuff and scapula stabilisers, could improve shoulder function and pain to a greater degree than control exercises in patients with subacromial pain and thereby decreasing the need for arthroscopic subacromial decompression.

Study V. To investigate if the positive short-term results after a specific exercise programme (*Study IV*) were maintained after one year and to examine if baseline clinical score, rotator cuff status and radiologic findings influenced the choice of surgery.

8 Participants

All participants were recruited at the Department of Orthopaedics, Linköping University Hospital. The healthy controls in *Study III* were recruited by advertising at the Linköping University Hospital. All participants were able to understand written and spoken Swedish. Written informed consent was obtained after the participants had been given verbal and written information about the study before inclusion. The studies were performed with approval of the local Institutional Review Board at the University Hospital of Linköping (*Study I*) or the regional board of ethics in Linköping: Dnr. M128-09 (*Studies II* and *III*) and Dnr. M124-07 (*Studies IV* and *V*).

8.1 Patients and control participants

Study I: Between 1989 and 1993, 183 ASD procedures were performed on patients with a history of more than six months of subacromial pain. At the time of surgery, 89 of the 183 patients who underwent ASD had an intact rotator cuff. Seventy of these patients (32 men) were willing to undergo clinical and ultrasonographic examination at a mean of 15 years later. Of the others, twelve refused to participate, six had left the area, and one had been subjected to non-related shoulder surgery, and these were excluded. Mean age at follow-up was 60 (range 38-80) years.

Study II: Between 2004 and 2009, 53 patients with acute rotator cuff tear were operated with repair and open subacromial decompression (1 ASD). Forty-two patients (32 men) fulfilled the inclusion criteria and were willing to undergo clinical and ultrasonographic follow-up examination at a mean of 39 (range 12–108) months. The inclusion criteria were: trauma to the shoulder; sudden onset of symptoms; asymptomatic shoulder before trauma; pseudoparalysis; full-thickness rotator cuff tear of at least one tendon with an acute appearance when sutured; and no sign off previous cuff tear or other cuff pathology. Patients with previous or gradual onset of symptoms in the injured shoulder, partial cuff tear only, or displaced fracture were excluded. Mean age at injury was 59 (38–79) years.

Study III: Between 2009 and 2010, 17 consecutive patients (14 men) were recruited. Inclusion criteria were: subacromial pain and shoulder dysfunction over the last 6 months or more, and a PTT or FTT of the cuff verified by ultrasound. Exclusion criteria were: radiological or clinical signs of osteoarthritis in any joint,; systemic joint disease; a fracture non-union; Dupuytrens disease; frozen shoulder; tendinosis or rupture of any tendons other than in the rotator cuff; disorders of the spine; idiopathic scoliosis; spondylitis; cerebral or cardiovascular disease during the past year; abdominal or bowel disease; surgery or trauma during the past year; any infection during the last month; malignancy; treatment for the last month with medications that may affect MMPs or TIMPs (tetracycline, bisphosphonates, anti-inflammatory drugs, statins); sub-acromial corticosteroid injection during the last six months; or vigorous physical activity during the last 24 hours. During 2010, 16 age- and gender-matched (13 men, three women) control subjects with no history of shoulder disease or any of the exclusion criteria were recruited. Mean age of all participants was 57 years (range 39-77).

Study IV and *V*: Between 2008 and 2010, 102 consecutive patients diagnosed with subacromial pain and on the waiting list for arthroscopic subacromial decompression were included. Inclusion criteria were: lateral shoulder pain at rest and/or during arm elevation; at least six months with the current symptoms; and poor results after three months of conservative treatment. In addition three of the following four criteria had to be positive: Neer impingement sign (Neer 1972); Hawkins-Kennedy test (Hawkins and Kennedy 1980); Jobes test (Jobe and Jobe 1983); or Patte's test (Leroux et al. 1995). Furthermore a positive Neer's impingement test (relief after subacromial injection of local anaesthetic agent) (Neer and Welsh 1977) was compulsory. Exclusion criteria were: malignancy; osteoarthritis of the glenohumeral or acromioclavicular joint; previous fractures, os acromiale; surgery of the shoulder girdle; polyarthritis; rheumatoid arthritis; fibromyalgia; instability in any joint of the shoulder girdle; frozen shoulder; symptoms from the cervical spine; pseudoparalysis; or subacromial corticosteroid injection during the last three months. This study cohort was used in both *Study IV* (three-month follow-up) and V (one-year follow-up) according to Figure 9. Within two weeks after inclusion the patients were randomised to a specific exercise programme or a control exercise programme. Shortly after randomisation prior to allocation, five patients were excluded: two patients were misdiagnosed and developed a frozen shoulder and three patients declined participation due to lack of time. Both treatment groups were comparable at baseline, except for significantly more male patients in the specific exercise group. All 97 patients were compliant from baseline until three-month follow-up and were included in the three-month statistical analysis. Two patients of the 97, one in each group, could not participate in the one-year follow-up due to non-shoulder-related illness. Mean age at inclusion was 52 (range 33-65) years in both exercise groups.

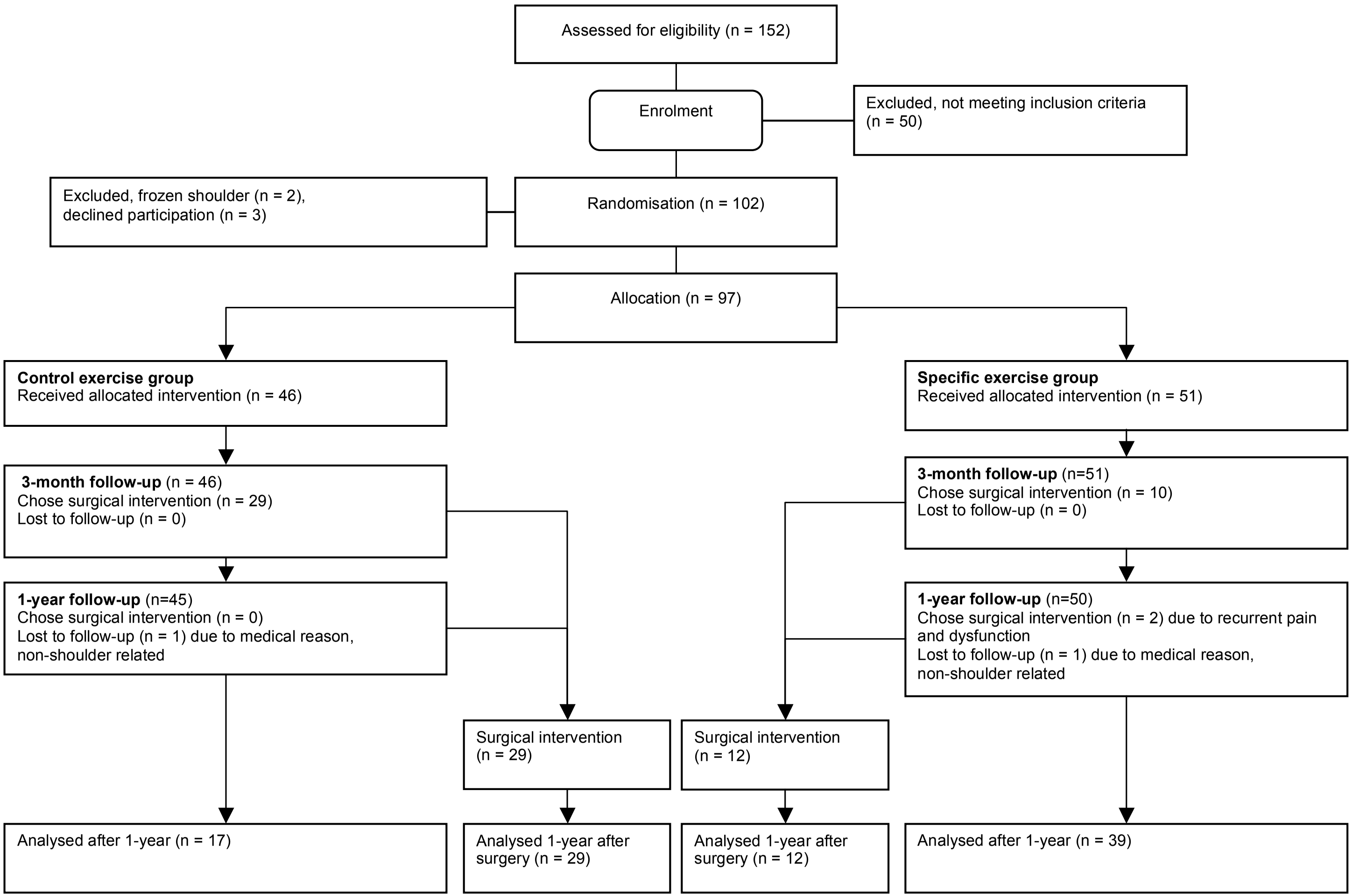


Figure 9 Flow chart according to consolidated standards of reporting trials (CONSORT-statement) with the numbers of approached and excluded patients and allocation of the randomised treatment and the analysed patients.

9 Methods

9.1 Outcome assessments

9.1.1 Constant-Murley score

CM score (*Studies I, II, III, IV, V*) is a shoulder-specific assessment tool, containing both subjective and objective measures having a maximum of 100 points representing no symptoms. It includes four main items and they contribute differently (proportions in brackets) to the total score: subjective pain (15 %) and ADL (20 %), objective range of motion (40 %) and strength in abduction (25 %) (Appendix 1). In this thesis the score was used in accordance with the original version of the CM score (Constant and Murley 1987) with the assessor asking the patients about their subjective pain and symptomless ADL level. Pain free range of motion was measured with a goniometer in the standing position. Abduction strength was measured with a myometer (Nottingham Mecmesin Myometer®), patient in standing position with the arm in the scapular plane and 90° of elevation, hand and forearm pronated. The strength test should be pain free and the highest value out of three was used. In the current studies a digital myometer, validated by Johansson and Adolfsson (2005), was used to measure the abduction strength instead of the mechanical spring balance used in the original version of the CM score.

In the early 1990s the European Society for Surgery of the Shoulder and Elbow recommended that CM score should be used in shoulder research (Coghlan et al. 2008).

The intra-tester reliability of the CM score has been reported to be high but for inter-tester reliability the level of agreement has been reported to vary (Constant and Murley 1987, Roy et al. 2010). Some aspects of validity are not fully evaluated concerning the CM score. Still, the CM score has been shown to have excellent responsiveness for different shoulder conditions such as subacromial pain and rotator cuff tear (construct validity) with the exception of patients with shoulder instability. The CM score has also been shown to be more responsive than DASH and as responsive as WORC for subacromial pain and rotator cuff tearing (Roy et al. 2010). There is also a strong correlation with the Western Ontario Rotator Cuff Index (WORC) (>0.70) but weaker with the Disability of the Arm, Shoulder and Hand (DASH) questionnaire (0.30-0.70) (Roy et al. 2010, Walton et al. 2007). Interpretation of the clinical relevance of difference in CM score has not yet been evaluated for subacromial pain patients, which makes interpretation and comparisons of results difficult.

Gender and age influences the CM score, with the mean score being significantly higher for men and after 50 years of age the score decreases approximately 0.3 points per year (Roy et al. 2010, Walton et al. 2007).

9.1.2 Disability of the Arm, Shoulder and Hand

Disability of the Arm, Shoulder and Hand (DASH) (Studies I, II, IV, V) is a region specific (whole upper extremity) self-administered questionnaire used to assess self-rated disability and symptoms, from both arms at the same time, as experienced during the preceding week (Beaton et al. 2001). The DASH consists of 30 items asking about the degree of difficulty performing both specific tasks, and general pain estimates. Each item has five response alternatives, ranging from “no difficulty” to “unable to perform activity". The sum of the estimates is transformed into a score between 0 and 100, where zero represents no disability and symptoms. There are optional modules for work and sports/music not used in this thesis. DASH has been translated into many languages, and the Swedish version has been found to be reliable and valid (Atroshi et al. 2000).

Rate your ability to do the following activities in the last week by circling the number below the appropriate response

	NO DIFICULTY	MILD DIFICULTY	MODERATE DIFICULTY	SEVERE DIFICULTY	UNABLE
Open a tight or new jar	1	2	3	4	5
Write	1	2	3	4	5

Figure 10 Excerpt from the English DASH questionnaire, items, 1 and 2.

9.1.3 The Western Ontario Rotator Cuff Index (WORC)

The Western Ontario Rotator Cuff Index (WORC) (Study II) is a disease-specific outcome instrument developed for clinical trials evaluating treatment of patients with degeneration of the rotator cuff (Kirkley et al. 2003). The instrument is self-administered and consists of 21 items divided into physical symptoms (6 items), sports/recreation (4 items), work function (4 items), lifestyle function (4 items) and emotional function (3 items). The instrument includes instructions to the patient, explaining the items. The response format is a 10 cm visual analogue scale with a description at each end such as "no pain" to "extreme pain". The total score is recommended to be used and it can be presented in its raw form or converted to a percent score. The best total score is 100 % and represents no decrease in shoulder-related quality-of-life, 0 % is the worst score.

WORC has been tested reliable and valid on patients who were treated for rotator cuff tendinosis with no or small FTT (Kirkley et al. 2003) and correlates well with DASH, Patients Global Impression of Change scale (PGIC) and CM score (Kirkley et al. 2003, Roy et al. 2010).

9.1.4 Visual Analogue Scale

A Visual Analogue Scale (VAS) was used in Studies IV and V to rate the patient's perceived pain intensity at rest, during arm activity, and at night during the previous 24 hours. This is a frequently used one-dimensional instrument to assess pain. The scale is presented to the patient as an ungraded, 100 mm long horizontal line, with vertical bars at each end. The anchor points were labelled "No pain" and "Worst imaginable pain". In this thesis, a plastic ruler on which a vertical marker was moved to a point along the line that best represented their perception of pain was used to quantify pain.

VAS has been shown to be reliable in evaluating pain intensity in clinical practice and has been tested valid for both chronic and experimental pain (Carlsson 1983, Price et al. 1983, Williamson and Hoggart 2005). VAS has also been shown suitable and valid for measuring differences in pain over time (Williamson and Hoggart 2005). The major concern with VAS is that the patient's perception of "worst imaginable pain" is based on personal experience and ability of abstract thinking.

9.1.5 EuroQol Instrument

The EuroQol Instrument (EQ-5D and EQ VAS) (*Studies IV, V*) a nondisease- specific instrument for describing and evaluating health-related quality-of-life. It was developed by the EuroQol Group (1990), an international, multidisciplinary network of researchers. The EQ-5D consists of five dimensions; 1) Mobility 2) Self-care 3) Usual activities 4) Pain/discomfort 5) Anxiety/Depression within three severity levels; "no problem", "moderate problem" or "severe problem". The second part of the instrument is the EQ VAS, a visual analogue scale with anchor points "Worst imaginable state of health" and "Best imaginable state of health". To facilitate interpretation and comparison, the EQ-5D Index has been developed which includes negative values. The English version has been evaluated for reliability, validity and responsiveness in patients with rheumatoid arthritis (Hurst et al. 1997).

9.1.6 Patients Global Impression of Change

The Patient Global Impression of Change scale (PGIC) (Study IV) is a framework for identifying clinically significant changes in the patient's condition. This scale has important implications in providing clinically relevant information about the effect of a treatment intervention in an individual patient (Hurst and Bolton 2004). The original version of PGIC includes seven steps but in *Study IV* the change in symptoms following treatment was graded using a five point Likert scale; 1) worse 2) unchanged 3) small improvement 4) large improvement 5) recovered. A five-step scale was used to ease for the patients. Support for using five-step global assessment scale was found in the literature (Preston and Colman 2000).

9.1.7 Hospital Anxiety and Depression scale

The Hospital Anxiety and Depression scale (HAD scale) (*Studies IV, V*) is a frequently used instrument (Zigmond and Snaith 1983) in the literature. It is rapid and easy to administer, it measures anxiety and depressive symptomatology in physically ill patients. Analysis has shown that these two factors give good internal consistency and are significantly correlated to patient age and quality-of-life (Zigmond and Snaith 1983). In *Studies IV* and *V* the HAD scale was not used as an outcome measure but as a baseline-screening tool for mental distress. The test has been found reliable and valid in detecting the severity of depression and anxiety in the setting of a hospital outpatient clinic (Zigmond and Snaith 1983).

9.2 Imaging modalities

9.2.1 Radiology

Radiology of the shoulder and the acromioclavicular joints (*Studies II, IV, V)* was used mainly to exclude patients with glenohumeral and acromioclavicular osteoarthritis, os acromiale and signs of previous fracture. In addition subacromial calcification, proximal humeral migration (Figure 7 A-C) and signs of subacromial degeneration were identified. Subacromial degeneration was considered present with one or more of the following findings: sclerosis, cysts and spur formations on the greater tuberosity and/or under the acromion (Figure 12). The degenerative findings were dichotomised into two categories; yes (one or more signs) and no (zero signs). In *Studies IV* and *V* these findings were analysed in relation to rotator cuff status and the choice of surgery (yes/no) up until one-year follow-up. Standard views were used including anteroposterior, lateral, axillary and acromioclavicular. All radiological examinations and interpretations were performed at the Department of Radiology, Linköping University Hospital by experienced radiologists. In *Study V* two shoulder specialists also assessed the radiographs independently of each other to ensure correct interpretation.

Figure 12 Anteroposterior view of shoulder with subacromial sclerosis and spur formation defined as subacromial degeneration.

9.2.2 Ultrasound

Ultrasound (US) (*Studies I, II, III, IV, V*) was the method of choice in all studies to evaluate the integrity of the rotator cuff. Many authors recommend US as the primary imaging technique for soft tissues of the shoulder because it is a rapid and cost- effective method, with excellent sensitivity and specificity in diagnosing rotator cuff tears. The overall accuracy may reach 96 % and studies show a comparable accuracy with MRI for diagnosing cuff tears (Harryman et al. 1991, Oh et al. 2009, Teefey et al. 2004, Tempelhof et al. 1999). The main advantages are the ability to perform a dynamic examination and side-to-side comparison. The equipment used was a high-resolution ultrasound, Acuson Sequoia 512 ultrasound instrument (Siemens, Malvern, PA) with a variable 8-10 MHz linear array-transducer. All patients (*Studies I, II, III, IV, V*) and healthy controls (*Study III*) were examined at the Department of Radiology, Linköping University Hospital by the same radiologist, who is experienced in shoulder US. In *Studies II, III, IV* and *V* the study subjects were also examined with ultrasound, by the main author (HBH) to ensure correct interpretation. At all times the US examination was performed step by step according to a standardised protocol with the patient in the correct position. The transducer was orientated parallel to the tendons to visualise the fibres in a longitudinal plane, and was then rotated 90° for a transverse view (Figure 13 A-D). The rotator cuff was divided into intact tendons, PTTs and FTTs (Figure 14 A-C). PTT was defined as a localised absence of the tendon seen in two orthogonal imaging planes as a mixed hyperechogenic and hypoechogenic region on the bursal side, joint side, or intratendinously but not penetrating the entire tendon. FTT was defined as non-visualisation of the tendon throughout it’s thickness. Another advantage of US examination is that the orthopaedic surgeon can use it in their office. The main author

(HBH) performed US examinations and when comparing her findings of 129 examinations to an experienced radiologist an accuracy of 93 % was found.

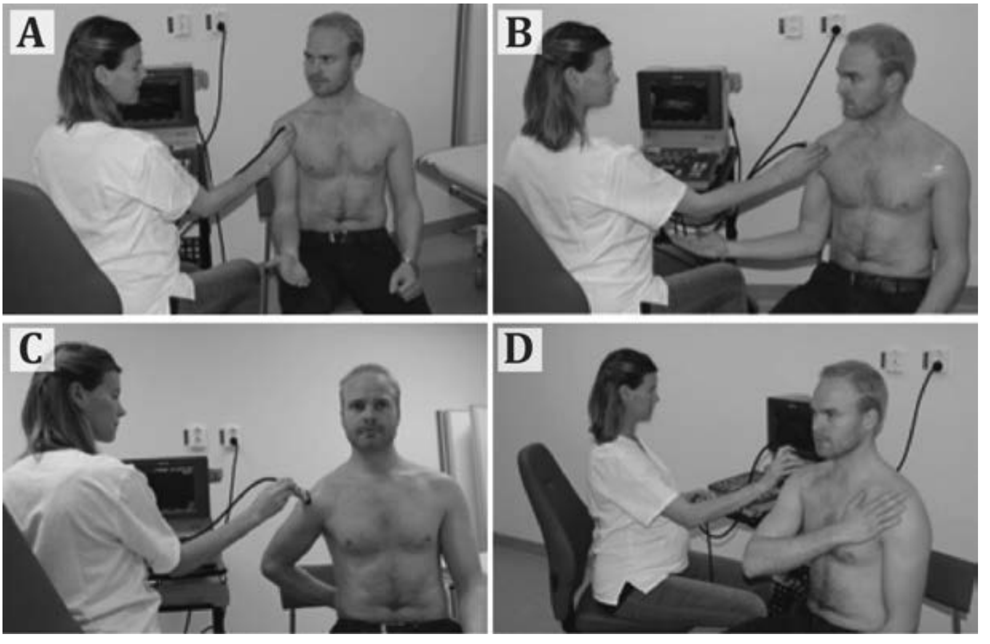


Figure 13 Standard sequence of biceps and rotator cuff US examination. A) US transducer placement for imaging the LHB which is used as an reference landmark, patients palm facing up resting on thigh B) US transducer placement for imaging subscapular tendon medially to the LHB, patients arm in external rotation, palm facing up C) US transducer placement for imaging supraspinatus tendon, patients arm in internal rotation with hand on back pocket D) US transducer placement for imaging infraspinatus and teres minor tendons, patients hand on opposite shoulder.

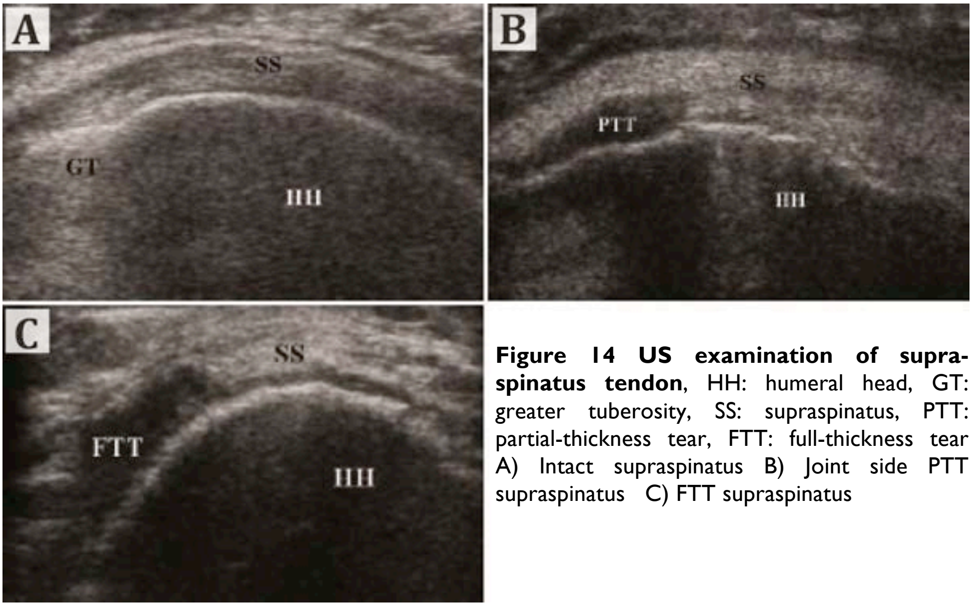


Figure 14 US examination of supraspinatus tendon, HH: humeral head, GT: greater tuberosity, SS: supraspinatus, PTT: partial-thickness tear, FTT: full-thickness tear A) Intact supraspinatus B) Joint side PTT supraspinatus C) FTT supraspinatus

9.3 Clinical assessment

A standard interview and physical examination was used to clinically diagnose subacromial pain and rotator cuff tear (*Studies I, II, III, IV, V*). In *Study IV* and *V* the clinical assessment was performed at inclusion and repeated at the three-month and one-year follow-ups, the assessor (HBH) was blinded to allocation and not involved in any of the treatments except for the initial corticosteroid injection.

The bilateral shoulder examination included active and passive range of motion measured with a goniometer. The rotator cuff tendons and muscles were tested separately with bilateral manual resistance against isometric contractions. Pain and/or weakness were considered positive findings. Further tests or manoeuvres used in clinical practice to diagnose disorders with subacromial origin are described in the following section. The theory behind these tests is to stress the tissues thought to be involved in the pain-generating mechanism by tension or compression.

Figure 15 Neer impingement sign.

Neer impingement sign The patient's arm is passively elevated in the scapular plane combined with internal rotation in the GH joint, at the same time the examiner prevents thoracoscapular movement by fixating the acromion with a depressive force (Figure 15). This manoeuvre causes the greater tuberosity to encroach on the subacromial space under the anterior and medial parts of the acromion and any spur present. When the bursa and or the rotator cuff are inflamed pain occurs and the Neer impingement sign is positive (Johansson and Ivarson 2009, Neer 1972).

Hawkins-Kennedy impingement sign The patient's arm is positioned with 90° of elevation in the GH joint as well as in the elbow. The GH joint is then forcibly rotated internally by lowering the forearm while supporting the elbow. The examiner prevents thoracoscapular movement by fixating the acromion with a depressive force (Figure 16). This manoeuvre causes compression of the bursa and cuff beneath the lateral and anterior acromion resulting in pain i.e. positive test when pathology is present (Hawkins and Kennedy 1980, Johansson and Ivarson 2009, Snyder 2003).

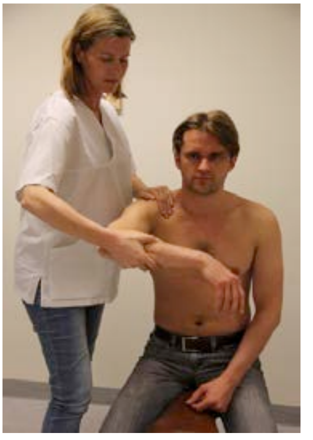


Figure 16 Hawkins-Kennedy impingement sign.

Neither of the above two impingement tests can alone absolutely differentiate between biceps-, labral-, bursal or cuff pathology. Both tests are considered sensitive, Neer, 75-89 % and Hawkins, 91-92 % but the specificity is low, Neer, 30-40 % and Hawkins, 25-44 % (Beaudreuil et al. 2009).

Painful arc of abduction The patient stands with the arm in external rotation (palm facing up) and abducts the arm in the scapula plane (90° abduction and 30° horizontal adduction) and reports any occurrence of pain. A test is positive if pain is experienced between 60˚ and 120˚ of abduction. This test has been reported to be one of the most specific and accurate tests for the clinical diagnosis of a FTT (Kelly et al. 2010).

Figure 17 Jobe supraspinatus test.

Jobe supraspinatus test The patient's arm is extended internally rotated (thumb facing downward) and elevated to 90° of abduction in the scapular plane. The examiner instructs the patient to maintain the position and resist a downward pressure (Figure 17). The test is positive if pain or weakness appears (Jobe and Jobe 1983, Johansson and Ivarson 2009). When weakness is used to define a positive test the sensitivity is good, 77-95 %, but less specific, 65-68 %. If pain exacerbation is used to define a positive test the sensitivity is less (Beaudreuil et al. 2009). In isolation the test is helpful in diagnosing large or massive rotator cuff tears but less accurate in diagnosing minor cuff pathology (Holtby and Razmjou 2004).

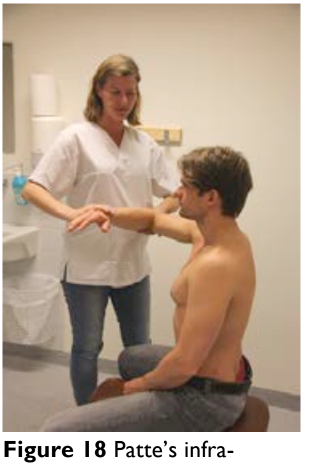


Figure 18 Patte's infra-spinatus and teres minor test.

Patte's (infraspinatus and teres minor) test The patient's arm is positioned in 90° of elevation in the GH joint, the elbow in 90° flexion and the GH internally rotated. The patient is then instructed to activate external rotation against the examiners resistance. The examiner prevents thoracoscapular movement by fixating the acromion with a depressive force (Figure 18). The test is positive if pain and weakness are reproduced indicating infraspinatus pathology. The test has a sensitivity of 76-79 % and specificity of 57-67 % (Beaudreuil et al. 2009, Johansson and Ivarson 2009, Leroux et al. 1995).

Belly-press test This test was used to evaluate subscapularis pathology during resisted internal rotation. The patient is instructed to place the palm of the hand against the abdomen just below the level of the xiphoid process. The elbow should be in line with the trunk in the sagittal plane and the patient is asked to press maximally into the abdomen by internally rotating the shoulder without altering the position of the elbow (Figure 19) (Gerber et al. 1996). The test result is considered positive when the elbow falls behind the midline while the patient generates force by extending the shoulder instead of internally rotating the humerus. This test has been validated and reported to have a sensitivity of 40 % and a specificity of 98 % (Barth et al. 2006, Gerber et al. 1996).

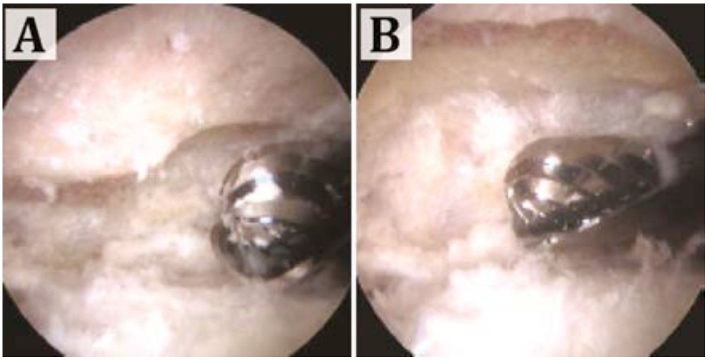
Figure 19 Belly-press test.

A positive **Neer's impingement test** (Neer and Welsh 1977) was compulsory for inclusion in *Study IV.* This test involves a positive Neer impingement sign, the subacromial injection of local anaesthetic agent followed by a negative Neer impingement sign. This test is considered to have a high sensitivity for bursal affection but the specificity is reduced in the case of a cuff tear since the anaesthetic diffuses through the tendon to the GH joint (Beaudreuil et al. 2009). At the inclusion visit in *Study IV* the injected anaesthetic agent was mixed with corticosteroid and injected with using external anatomical landmarks for orientation. A lateral posterior approach (Rowe 1988) and a 21-gauge (0.8 × 50 mm) needle was used. The injection was performed without ultrasound guidance.

9.4 Surgical procedures

9.4.1 Arthroscopic subacromial decompression

ASD (*Studies I, II, V)* was performed with the arthroscopic technique as described by Ellman (1987) (Figure 20). In *Study II* an open or arthroscopic technique was used in combination with cuff repair, the open technique is described together with the cuff repair procedure (Figure 21). All procedures were performed at the Department of Orthopaedic Surgery, Linköping University Hospital by specialised shoulder surgeons. Surgery was performed according to a standard protocol including laxity testing under anaesthesia and arthroscopic examination of the GH joint via a standard posterior portal. After examination of the GH joint for signs of osteoarthritis, cuff tears, biceps pathology or other significant intra-articular pathology, inspection of the subacromial space was performed via the same posterior portal. A lateral portal was routinely used for the probe and shaver. The subacromial space was visualised by resecting the subacromial bursa with a shaver whereby the bursal side of the cuff could be inspected. Finally, resection of the anteroinferior aspect of the acromion was performed with a burr (Figure 20) thereby detaching, without resecting, the coracoacromial ligament (CAL). Occasionally the shaver and burr were switched with the arthroscope between portals for better access to the subacromial structures. No additional debridement of torn rotator cuff fibres, resection of labral tears or calcific deposits, biceps tenotomy, or lateral clavicle resection was done. All surgical findings were documented on a sheet specially designed for shoulder arthroscopy. The wording decompression refers to both bursal and bone resection.



Figures 20 Arthroscopic decompression with burr after bursal resection with a shaver. A) Initial decompression B) Finishing decompression with smoothening of the undersurface of the acromion

9.4.2 Rotator cuff repair

Rotator cuff repair (*Study II*) was performed using an open technique with the exception of one patient operated percutaneously with arthroscopic assistance. All patients were sitting in the beach chair position and under general anaesthesia. Two different surgical exposures were used; the anterosuperior (deltoid split, 29 patients) when preoperative imaging diagnosed a supraspinatus or infraspinatus tear, and the anteromedial (deltopectoral, 12 patients) when subscapularis was involved in the injury. The anterosuperior skin incision was made in the Langer's lines horizontally along the lateral border of the acromion exposing the acromion and the origins of the anterior and middle heads of the deltoid muscle. With the superior incision the deltoid was split and two to three centimetres of the medial portion was detached from the acromion. Bursal resection and open acromioplasty of the anterior undersurface of the acromion were performed to expose the rotator cuff tear. The rotator cuff ends were mobilised from adhesions using blunt dissection and stay sutures were placed at the free ends. The reattachment site at the greater tuberosity was decorticated to stimulate tendon-to-bone healing. The cuff tears were repaired with suture anchor fixation or osteosutures and modified Mason-Allen sutures (Gerber et al. 1994, Mason and Allen 1941) at the greater tuberosity (Figure 21). Depending on the appearance side-to-side sutures were also used when possible. The deltoid was reattached to the acromion with osteosutures before skin closure. The anteromedial skin incision was made over the deltopectoral interval, which was dissected until the clavipectoral fascia was revealed and divided at the lateral aspect of the conjoined tendon. Bursal resection, acromioplasty and cuff tear mobilisation were performed in the same manner as described above and the subscapularis tendon was reattached to the lesser tuberosity with suture anchors or osteosutures.

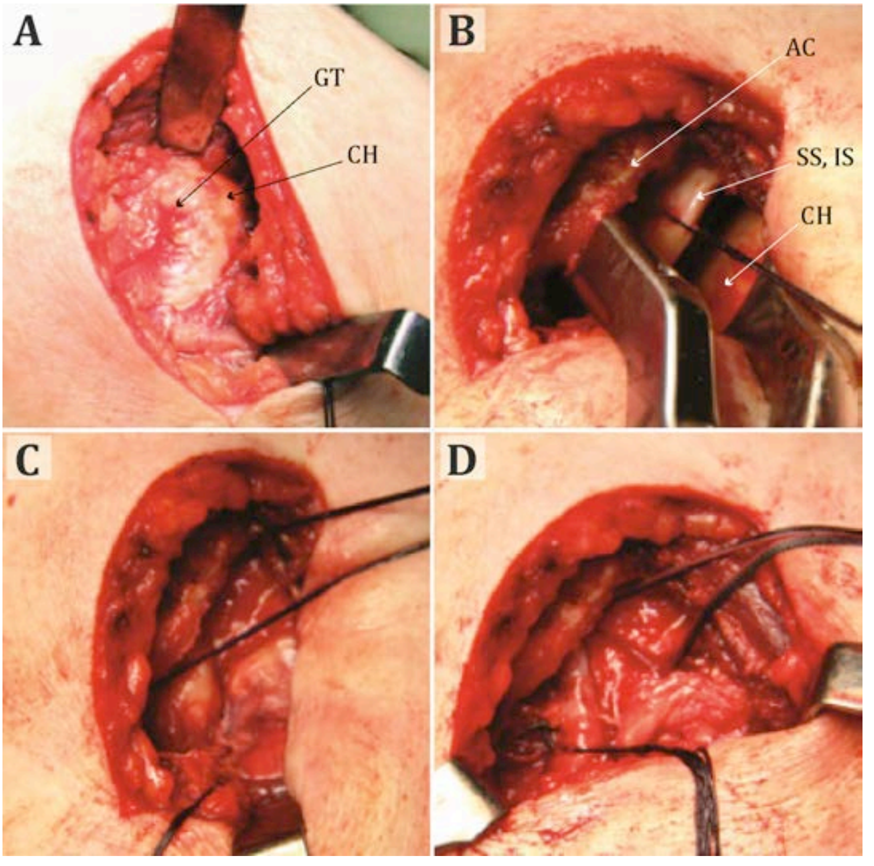


Figure 21 Open rotator cuff repair, anterosuperior skin incision. Patient with acute infraspinatus FTT and chronic supraspinatus FTT, pain and pseudoparalysis four weeks after trauma. GT: greater tuberosity, CH: caput humeri, SS: supraspinatus, IS: infraspinatus, AC: acromion. A) Remains of the SS and IS on the bare GT B) retracted SS and IS released and pulled forward with suture under AC C) two rotator cuff anchors placed at footprint on GT D) anchor sutures tied one at a time starting with the most dorsal.

9.5 Physiotherapy interventions

9.5.1 Specific exercise programme

The specific exercise programme in *Studies IV* and *V* consisted of six different exercises: two eccentric exercises for the rotator cuff (supraspinatus, infraspinatus, and teres minor), three concentric/eccentric exercises for the scapula stabilisers (middle and lower trapezius, rhomboideus and serratus anterior), and a posterior shoulder stretch. Each strengthening exercise was repeated 15 times in three sets twice daily for eight weeks and then once a day for the last four weeks. The exercises were individually adjusted and progressed with increased external load by using weights and elastic rubber band at the physiotherapist visits once every other week during the whole rehabilitation period. The posterior shoulder stretch was performed for 30-60 seconds and repeated three times twice daily (Appendix 2). When deemed necessary (limited passive range of motion), the physiotherapist performed additional manual treatment by using posterior shoulder stretch.

9.5.2 Control exercise programme

The control exercise programme in *Studies IV* and *V* consisted of six non-specific motion exercises (not aiming for the rotator cuff nor the scapula stabilizers) for the neck and shoulder without any external load (shoulder abduction in the frontal plane, shoulder retraction, shoulder elevation, neck retraction, stretch of upper trapezius and pectoralis major). Each exercise was repeated ten times, and each stretching exercise three times twice daily at home and once every other week at the physiotherapist visits. There was no progress in this programme.

9.5.3 Rehabilitation after rotator cuff repair and ASD

In *Study II* an immobiliser was used for four to five weeks that could be removed during exercises and hygiene. Rehabilitation included both physiotherapist-assisted exercises and home exercises. Week zero to four included pendulum movements of the arm and passive range of motion exercises. Week five to six, active range of motion without load and continued stretching was allowed and from week seven to eight strengthening exercises including loading began and progression adapted individually. In cases with multi-tendon tears, including subscapularis, the shoulder was immobilised for five weeks whereafter similar exercises were started, but strengthening exercises were delayed until week nine to ten.

9.5.4 Rehabilitation after ASD

In *Studies I, V* rehabilitation included one week of home exercises with pendulum movements of the arm. Week two, the physiotherapist-assisted exercises started with correction of posture, retraction and depression of the shoulders. Active movement exercises started in order to restore shoulder movement. Week three isometric strengthening of the rotator cuff muscles and the scapula stabilisers began. In addition dynamic external rotation movements against gravity, lying on the side, and posterior shoulder stretching were performed. Week four to five contained progressive strengthening exercises of the rotator cuff muscles and the scapula stabilisers (eccentric as well as concentric) using a rubber band and weights. These exercises were performed in the range 0-45° of the scapula plane. Week six to eight, the strengthening exercises continued in different positions up to full range of movement. Week nine to twelve, further progression with more complex exercises and increased loading was recommended. Exercise sessions were carried out twice weekly for eight weeks and took approximately 30 min each. Between the supervised rehabilitation sessions, patients were instructed to perform daily home exercises according to the described programme.

9.6 Laboratory methods

9.6.1 Enzyme-linked Immunosorbent Assay (ELISA)

ELISA (*Study III*) is a colorimetric method to analyse the amount of a specific protein, antibody or antigen. This method uses an enzyme-labelled antibody, specific for the protein in question, which attaches to the protein and produces a signal that can be quantified. The enzymes attached to the antibodies metabolise colourless substrates, chromagens, into coloured products that are measured by absorbance at the proper wavelength. The intensity of the colour is proportional to the amount of bound protein and the absolute concentration of the protein is given by comparison with a standard curve. A variant of ELISA, the sandwich ELISA, increases the specificity by using both monoclonal and polyclonal antibodies to capture the proteins in the sample. In *Study III*, the result for TIMP-1 was further analysed using a sandwich ELISA kit (Quantikine; R&D Systems) and the samples were analysed in duplicate.

9.6.2 Luminex

Luminex (*Study III)* is another method to analyse protein concentration in various samples such as serum, plasma or cell culture medium. This method is based on flow cytometry, but the basic principle is similar to ELISA. Luminex, however, allows multiple proteins in the same sample to be quantified simultaneously.

Manufactured polystyrene particles are dyed internally with two types of red colours (red and infrared). The ratio of the intensity between red and infrared gives each batch of particles a special “tag” or “signature” which allows discrimination between particles from different batches during analysis. The particles in each batch are then coated with antibodies against the analytes in question (Figure 23). This method can analyse up to 100 different analytes in one sample at the same time. The following steps are similar to the ELISA method with washing, secondary coupled antibodies to the analytes and binding of a fluorescent marker that allows analysis in the Luminex 100™ instrument (Luminex Corp., Austin, TX, USA). This instrument analyses the particles as they pass through two laser beams, the fluorescent intensity being proportional to the concentration of the analyte in the sample.

In *Study III,* MMP-1, MMP-2, MMP-3, MMP-7 and MMP-9 were measured simultaneously using Fluorokine MultiAnalyte Profiling (F-MAP) kits from R&D Systems (Minneapolis, MN, USA). This kit can detect proforms, active forms and TIMP-complexed forms of the respective MMPs. The analyses were done in a Luminex 100™ instrument (Luminex Corp., Austin, TX, USA) according to the manufacturer’s instructions.

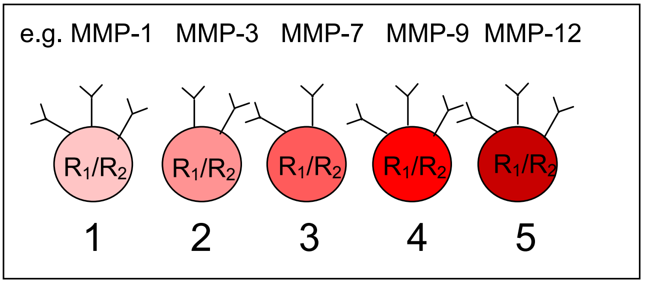


Figure 22 Particles coated with antibodies directed against the analytes. Each antibody is thereby coupled to particles that have the same red colour ratio. Figure design Pernilla Eliasson.

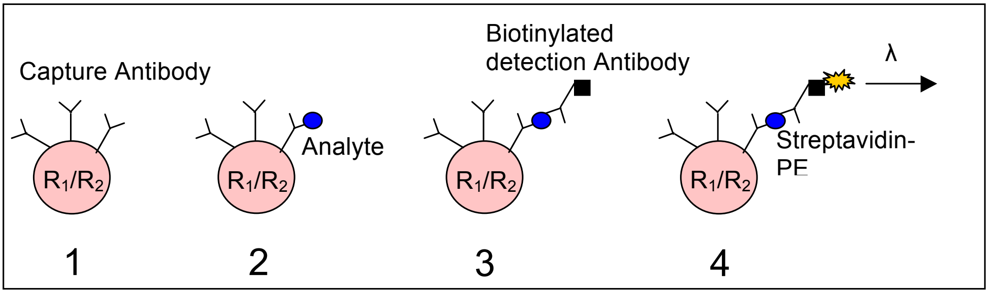


Figure 23 The analyte binds to the capture antibody (2) and a secondary biotinylated detection antibody directed against the same analyte binds to complex (3). Detection is possible when a fluorescent maker streptavidin-PE is bound to biotin and excited by a laser beam (4). Figure design Pernilla Eliasson.

10 Statistical methods

Study I) The subjects were divided into three groups according to their rotator cuff status at the 15-year follow-up; intact, PTT- and FTT-group. Descriptive statistic analysis was performed to describe the subjects in relation to the cuff status. Kruskal-Wallis variance analysis was used for comparison of the three groups' different score values. The interquartile range [IQR] was calculated to describe the distribution of the mean CM scores in the three groups.

Study II) The subjects were dichotomised into intact or defect rotator cuff (including PTT and FTT) at follow-up. Descriptive statistic analysis was used to describe the two groups according to variables of interest i.e. time to surgery and age. Student's t-test and ANCOVA, with age as a covariate, were used for comparison of means between independent groups. Proportional differences between groups were analysed using Pearson's Chi-square test or Fisher's exact test when the criteria was fulfilled.

Study III) At first all patients (including PTTs and FTTs) were compared with controls. Then FTTs were compared with PTTs and both FTTs and PTTs were compared separately with controls. The analyses were made using Mann-Whitney U test.

Study IV) The subjects were allocated to one of the two treatment groups and descriptive statistics was used to describe and compare the groups at baseline. One-way analysis of variance was used for calculating group differences at three-month follow-up in primary and secondary outcomes except for categorical data. Adjustment for gender was done but did not influence the results and was therefore not presented.

The patient's global impression of change in symptoms after treatment was dichotomised into large improvement (considered as large improvement or recovered) or unimproved (slightly recovered, unchanged, or worse). For categorical data Pearson's $\chi 2$ test was used for between-groups comparison, as well as for analysing the proportion of patients who chose surgery in each group at the three-month assessment. Logistic regression was also used to calculate the odds ratio with 95 % confidence interval (CI) for choosing surgery at three-month follow-up in the two groups.

Study V) The subjects were the same as in *Study IV* but they were subdivided for regression analysis. Additional descriptive statistic analysis was done for imaging findings. For within-group comparisons paired T-test was used to calculate differences in total scores (all clinical measures used in *Study IV*) from three-month to one-year follow-up. The number of patients choosing surgery in each group was calculated and compared with Pearson's $\chi 2$ test. Mean difference in total one-year CM score with 95 % CI was calculated with T-test for patients treated only conservatively compared to patients treated with ASD in addition. Any association between radiologic and ultrasound findings was calculated using Pearson's $\chi 2$ test. The Altman kappa-value was used to grade inter-assessor agreement on radiologic and ultrasound findings as "very good", "good", "moderate", "fair" or "poor". Any associations between radiologic and ultrasound findings, baseline CM score, and the patients choice of surgery (yes/no) were analysed with logistic regression. Gender was adjusted for in the regression analyses. The baseline CM score result was divided into quartiles (25 % of the values in each quartile, 0-35, 36-44, 45-58 and 59-100 points). Statistical level of significance $p < 0.05$ was used throughout all five studies.

11 Results

11.1 Study I

11.1.1 Structural outcome

Fifteen years after ASD on patients with an intact cuff, ultrasound evaluation showed ten (14 %) PTTs and three (4 %) FTTs in the 70 study patients. The PTTs were localised on the bursal side in three patients, on the joint side in six patients, and intratendinous in one patient. There was no significant gender difference in the three groups. The patients with FTTs were older but the difference was not significant.

Table 1 Patient demographics in relation to rotator cuff status.

Rotator cuff status	No.	F	M	Mean age	Age range
Intact	57	30	27	60	38-80
PTT	10	6	4	60	41-78
FTT	3	2	1	64	58-67
Total	70	38	32	60	38-80

F: female, M: male.

11.1.2 Clinical outcome

Mean Constant-Murley score for the study population was 74 points at follow-up. Mean CM score (interquartile range [IQR], included 50 % of patients), intact group, was 77 points (IQR, 64-90 points), the PTT group had 67 points (IQR, 51-89 points) and the FTT group had 50 points (IQR, 26-66 points). Despite decreasing scores with increasing structural defect no significant differences in the CM score were found between the three groups (p = 0.274). The mean DASH score for the study population was 25 points. The mean DASH scores followed the same pattern as for CM score with poorer results in the groups with a structural defect though not reaching significant difference (p = 0.259) between the groups (Figure 24).

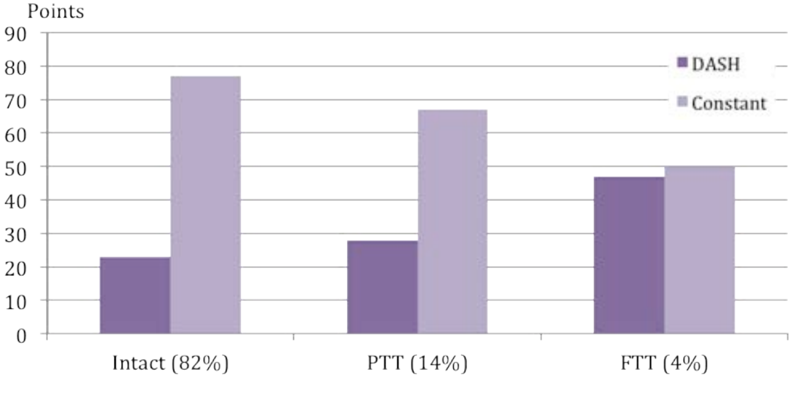


Figure 24 Mean CM score and DASH in relation to the rotator cuff status. The higher CM score the better the result (max 100 points), the lower DASH the better the result (zero points the best).

11.2 Study II

11.2.1 Structural outcome

Patients with cuff defects were significantly older than patients with an intact cuff. During the time from cuff repair until the follow-up assessment, five patients developed impingement symptoms and were reoperated with ASD. In four of these five patients, subacromial decompression had not been performed simultaneously with the cuff repair.

Table 2 The study population at follow-up.

	All patients [n=42]	Intact group [n=29]	Defect group [n=13]	Mean difference (95 % CI) [Intact–Defect]	p-value[a]
	Mean (SD)	Mean (SD)	Mean (SD)		
Days from trauma to surgical repair	38 (22)	39 (22)	38 (23)	0.6 (-14 to 15)	0.9
Months to follow-up after surgical repair	37 (23)	41 (23)	34 (24)	7.2 (-8.4 to 23)	0.4
Age at follow-up	62 (12)	60 (12)	68 (11)	-7.8 (-15 to -0.2)	0.05

a) independent Student's t-test comparing intact group with cuff defect (PTT and FTT) group

The four patients with FTT in the repaired shoulder also had FTT in the contralateral shoulder. One of the two patients with osteoarthritis had bilateral osteoarthritis. These two patients also had bilateral FTT at follow-up.

Table 3 Structural evaluation at follow-up including US and radiology.

	Repaired shoulder [n]	Contralateral shoulder [n]
Ultrasound		
Intact rotator cuff	29	29
PTT	9	2
FTT	4	11
Radiology		
Osteoarthritis	2	1
Proximal humeral migration	4	5
Signs of subacromial degeneration	2	19

11.2.2 Clinical outcome

Patients with an intact cuff had higher CM score and WORC index and lower DASH score compared to patients with a defect cuff. The difference was significant in CM and WORC score. There were however no significant differences between the groups in CM score, DASH questionnaire, or WORC index, regardless of the repair had been performed within three, six or twelve weeks. There was no significant relationship between the number of tendons involved at the primary injury and the clinical scores or the rotator cuff status and radiological findings at follow-up. There was a significant difference in Constant-Murley score between the repaired shoulder and the contralateral shoulder in the defect group, but no such difference between shoulders was found in the intact group.

Table 4 Clinical evaluation at follow-up.

	All patients [n=42]	Intact group [n=29]	Defect group [n=13]	Mean difference (95 % CI) [Intact–Defect]	Age-adjusted Mean difference (95 % CI) [Intact–Defect]	p-value[b]
	Mean (SD)	Mean (SD)	Mean (SD)			
Constant-Murley score, repaired shoulder	67 (22)	73 (21)	55 (20)	17 (3 to 31)	16 (1 to 31)	0.04
Constant-Murley score, contra-lateral shoulder	83 (18)	87 (14)	73 (22)	14 (0.2 to 28)	10 (-1 to 21)	0.07
WORC (%)[a]	75 (22)	79 (20)	65 (23)	14 (-2 to 30)	16 (1 to 32)	0.04
DASH[a]	22 (21)	17 (21)	31 (19)	-14 (-28 to 0.4)	-15 (-30 to 0.1)	0.05

[a)] 2 patients missing [b)] ANCOVA with age as a covariate, comparing intact group with defect group (PTT, FTT)

11.3 Study III

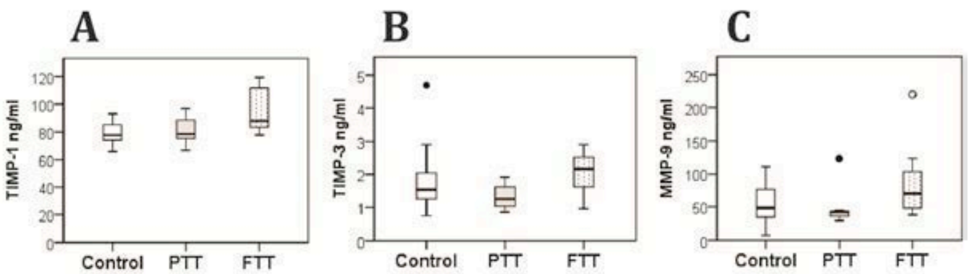
11.3.1 Analyses outcome

Patients with FTTs had elevated plasma TIMP-1 compared to controls measured by Luminex analysis (p = 0.007), this was confirmed with ELISA (p = 0.01). Plasma levels (ng/mL) of TIMP-1, TIMP-3 and MMP-9 were higher in patients with FTTs (p = 0.055, p = 0.02, p = 0.03 respectively) compared to patients with PTTs in Luminex analyses.

Table 5 Plasma levels (ng/mL) in patients with rotator cuff tears and controls. Values are expressed as median (range) within each group.

	All tears, partial- and full-thickness	Partial-thickness n = 7	Full-thickness n = 10	Controls n = 16
MMP-1	0.5 (0.1-1.8)	0.5 (0.2-1.8)	0.7 (0.1-1.1)	0.3 (0.1-2.0)
MMP-2	232 (155-316)	223 (155-316)	248 (183-283)	246 (138-270)
MMP-3	25 (6.6-43)	17 (14-43)	25 (6.6-35)	22 (5.3-35)
MMP-7	1.2 (0.4-2.7)	1.2 (0.6-1.5)	1.1 (0.4-2.7)	1.2 (0.3-4.2)
MMP-9	48 (30-220)	42 (30-123)	70 (38-220)[b]	48 (7-111)
TIMP-1	86 (67-119)[a]	79 (67-97)	88 (78-119)[a, c]	78 (66-93)
TIMP-2	114 (74-182)	101 (74-182)	116 (87-154)	119 (71-183)
TIMP-3	1.6 (0.9-2.9)	1.3 (0.9-1.9)	2.2 (0.9-2.9)[b]	1.5 (0.7-4.7)
TIMP-4	2.1 (1.6-4.6)	2.4 (1.6-4.7)	2.0 (1.6-2.6)	1.8 (1.2-3.3)

[a] significantly different from controls [b] significantly different from partial-thickness tears [c] p = 0.055



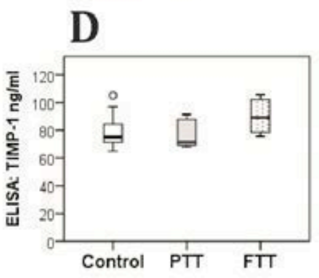


Figure 25 Plasma levels (ng/mL) of A) TIMP-1 B) TIMP-3 and C) MMP-9 in controls, patients with PTT and FTT measured by multiplex analysis and plasma levels (ng/mL) of D) TIMP-1 in controls, patients with PTT and patients with FTT measured by ELISA.
•Extreme outlier (more than three box lengths away)
○ Outlier (more than one and a half box lengths away).

11.4 Studies IV and V

11.4.1 Baseline characteristics and group comparisons

The specific exercise group and the control exercise group were comparable in baseline variables except for gender with significantly more men in the specific exercise group. HAD score was low indicating limited mental distress.

Table 6 Baseline variables for the two groups of patients with subacromial pain according to the treatment allocation. Values are numbers (percentages) unless stated otherwise.

Groups	Specific exercises (n=51)	Control exercises (n=46)
Male	37*	24
Age (years) mean (range)	52 (33-65)	52 (37-65)
Duration of pain (months), median (range)	24 (6-120)	12 (6-156)
Dominant side affected	30 (59)	22 (48)
Affected shoulder (right:left)	32:18	22:24
Occupation		
Heavy load	22 (43)	21 (46)
Light load	29 (57)	25 (55)
On sick leave at start	9 (18)	9 (20)
Rotator cuff status,		
affected shoulder		
Intact cuff	33 (65)	34 (74)
Partial-tear	15 (29)	6 (13)
Full-thickness tear	3 (6)	6 (13)
contralateral shoulder		
Intact	42 (88)	39 (87)
Partial-tear	5 (10)	3 (7)
Full-thickness tear	1 (2)	3 (7)
Radiology		
Subac. calcification	9 (18)	11 (24)
Subac. degeneration	7 (14)	9 (18)
HAD[a] (0-21)		
Anxiety, mean (range)	3.3 (0-12)	3.9 (0-13)
Depression, mean (range)	2.2 (0-9)	2.5 (0-12)

[a)] HAD, Hospital Anxiety Depression Scale * Significantly more men (p = 0.04)

11.4.2 Clinical outcomes

At three-month follow-up the patients in the specific exercise group had significantly larger improvement, in all clinical outcomes except in EQ-VAS, compared to the control exercise group (Table 7). Mean difference between groups was 15 points (95 % CI 8.5 to 20.6) in CM score. Significantly fewer patients in the specific exercise group chose surgery, ten out of 51 (20 %) compared to 29 out of 46 (63 %) resulting in odds ratio 7.7 (95 % CI 3 to 19) and $p < 0.001$.

One year after inclusion or one year after surgery all patients had improved significantly ($p < 0.0001$) in CM score (Figure 26, Table 8) as well as in all the secondary outcome measures (DASH, EQ-5D, EQ VAS, VAS at rest; night; and with activity) (at least $p < 0.05$ for all secondary outcomes) compared to three-month results.

After one-year there was still a significant difference in the number of patients choosing surgery. In the specific exercise group twelve out of 51 patients (24 %) had chosen surgery compared to 29 out of 46 patients (63 %) ($p < 0.0001$) in the control exercise group. Two patients in the specific exercise group chose surgery during the time after the three-month follow-up to one-year due to recurrent symptoms (Figure 9).

All conservatively treated patients (n=56 with 39 from the specific exercise group) had a significantly higher one-year CM score than all patients treated with ASD in addition to exercises (n=41, with 29 from the control exercise group), mean difference was 10.5 (95 % CI 4 to 17) and $p = 0.002$.

Logistic regression analysis showed that the lower quartile of the CM score at baseline had a larger risk of choosing surgery, independently of gender, treatment group and rotator cuff status compared to the highest quartile, odds ratio 7.7 (95 % CI 1.67 to 33.3) and $p = 0.007$.

Table 7 Group comparisons at baseline and three-month follow-up, values are mean (SD).

Baseline			**Baseline comparison**	**Three-month follow-up**		**Three-month comparison**
Groups	**Specific (n = 51)**	**Control (n = 46)**	**p-value**	**Specific (n = 51)**	**Control (n = 46)**	**p-value**
CM score	48 (15)	43 (15)	p = 0.10	72 (19)	52 (23)	p = 0.0001
DASH score	30 (14)	35 (19)[a]	p = 0.30	16 (15)	29 (19)[1]	p = 0.0001
EQ-5D	0.67 (0.23)	0.62 (0.23)[a]	p = 0.12	0.82 (0.14)	0.69 (0.24)[a]	p = 0.001
EQ-VAS	68 (15)	62 (20)	p = 0.12	75 (20)[c]	69 (21)[b]	p = 0.15
VAS rest	15 (19)	20 (21)	p = 0.24	10 (14)	20 (25)	p = 0.01
VAS activity	61 (22)	66 (20)	p = 0.23	25 (26)	41 (27)	p = 0.004
VAS night	46 (28)	40 (30)	p = 0.30	15 (22)	27 (27)	p = 0.01

[a)] n = 44 [b)] n = 42 [c)] n = 49

Table 8 Mean (SD) values in Constant-Murley score, the original two groups at baseline and three-month follow-up and the four groups appearing after the choice of surgery at three-month and one-year follow-up.

Groups	Baseline CM score	3-month CM score	Groups	3-month CM score	1-year CM score
Specific (n=51)	48 (15)	72 (19)	Specific Non-surgery (n=39)	78 (13)[1]	84 (14)
			Specific Surgery (n=12[a])	53 (22)[2]	79 (12)
Control (n=46)	43 (15)	52 (23)	Control Non-surgery (n=17)	75 (14)	85 (13)
			Control Surgery (n=29)	40 (16)	72 (18)

[a)] in the period from three-month to one-year follow-up two additional patients in the specific exercise group chose surgery [1)] n = 41 [2)] n = 10

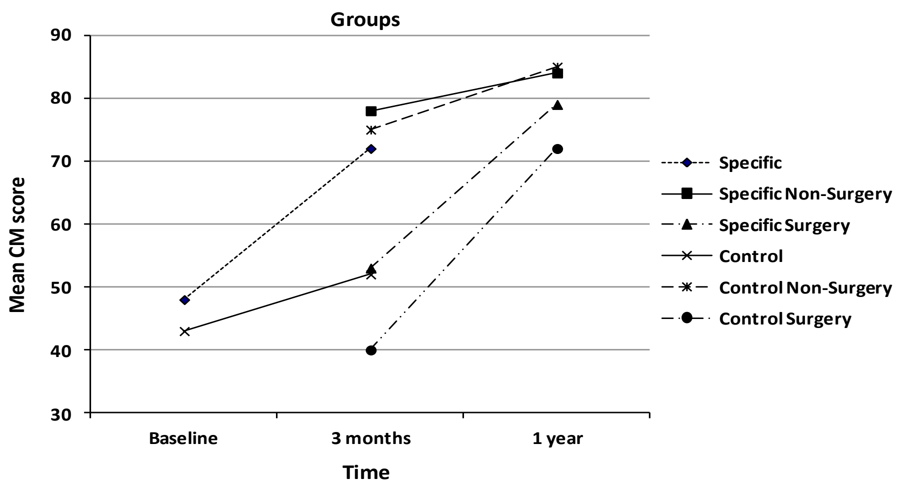


Figure 26 The mean CM score in the two original groups at baseline and three-months. The three-month and one-year mean CM score in the four groups divided by the choice of surgery. One-year follow-up was one year after inclusion (non-surgery) and one year after surgery.

11.4.3 Structural outcomes, Study V

Logistic regression analysis showed that having a FTT significantly increased the risk for choosing surgery, odds ratio 5.5, 95 % CI 1.1 to 29, p = 0.04, but having a PTT did not differ significantly from having an intact cuff (Table 9).

A significant association between radiological subacromial degeneration and a FTT (p = 0.03) was found but the presence of subacromial degeneration or calcification did not independently influence the choice of surgery or not.

A total of 30 patients in the study had cuff tears, both groups included (Table 6). Twenty-six patients had isolated supraspinatus tears and four had a combination of lesions involving supraspinatus, subscapularis and the long head of biceps. None of the supraspinatus tears extended into the infraspinatus.

When analysing the influence of treatment group in addition to rotator cuff status the logistic regression showed a significant association between treatment group, rotator cuff status and the patient's choice of surgery or not. Patients in the control exercise group with FTT had the highest odds ratio for choosing surgery (Table 10). The results from this analysis should be interpreted with caution due to a wide CI but the analyse indicates that some patients with cuff tears may respond positively to specific exercises.

Table 9 Influence of the rotator cuff status in relation to the patient's choice of surgery (yes/no) during the follow-up period analysed with logistic regression. Reference group was patients with intact rotator cuff.

n	Rotator cuff status	Odds Ratio	95 % Confidence interval	p-value
67	Intact	1	–	–
21	PTT	1	0.4 to 2.7	0.95
9	FTT	5.5	1.1 to 28.6	0.04

Table 10 Influence of the rotator cuff status analysed with logistic regression in relation to the patients' choice of surgery or not. Gender was adjusted for. The variables; treatment group and rotator cuff status interacted. Reference group was patients in the specific exercise group with intact rotator cuff.

n	Group	Rotator cuff status	Odds Ratio	95 % CI	p-value
33	Specific (reference)	Intact	1	–	–
15	Specific	PTT	1.6	0.4 to 6.9	0.52
3	Specific	FTT	7.8	0.6 to 102.2	0.12
34	Control	Intact	7.8	2.3 to 26	0.001
6	Control	PTT	8.6	1.3 to 58.7	0.03
6	Control	FTT	19.5	1.9 to 202	0.01

12 General discussion

12.1 What do we know about the effects of ASD on subacromial structures?

The subacromial pain syndrome includes a spectrum of disorders ranging from reversible inflammation to massive rotator cuff tears (Arnoczky et al. 2007). The degree of pain and shoulder dysfunction varies in patients with subacromial pain (Gotoh et al. 1998). This spectrum of symptoms may be related to different structural lesions but does not necessarily reflect the extent of tissue damage. Patients with bursitis and PTTs, for example, may report more pain than patients with FTTs (Gotoh et al. 1998). Individual factors such as genetics, coping and psychosocial factors may influence symptoms and results of treatment. Because of the diversity in subacromial structural engagement and its multifactorial aetiology, the result of an ASD procedure may vary between different patients. The success rate after ASD has been reported to range between 48-90 % (Henkus et al. 2009) but is frequently reported to be 75-85 % (Koh et al. 2012, Norlin and Adolfsson 2008). In *Study V* the patients not satisfied with their outcome after one of the two exercise programmes (specific and control) were operated with ASD, and their mean CM score one-year after surgery was 74 (SD 17) points, which is in line with the literature (Koh et al. 2012, Norlin and Adolfsson 2008).

The ASD procedure has been extensively investigated regarding outcome, but the mechanisms of action are still not fully understood. According to the extrinsic theory as described by Neer (1972) the ASD procedure reduces mechanical wear by removal of spur formations at the AC-joint and under the coracoacromial arch (Figure 4). Several studies support the extrinsic theory and suggest a correlation between morphology of the acromial arch and the incidence and severity of symptoms (Bigliani et al. 1991, Epstein et al. 1993, Henkus et al. 2009, Ogawa et al. 2005). This part of the procedure is thought to protect the rotator cuff from bursal-sided tearing as discussed in *Study I* (Blaine et al. 2005, Burkhart 1991). Decompression is also associated with improved shoulder function and decreased pain, probably due to relief of impingement of the subacromial bursa and the rotator cuff against the coracoacromial arch resulting in inhibited range of movement and recruitment of nerve fibres (Gotoh et al. 1998).

The subacromial bursa is believed to be a source of pain and bursal resection is believed to be an important part of the ASD procedure, contributing to the positive effects (Blaine et al. 2005, Hoe-Hansen et al. 1999, Santavirta et al. 1992). Not only mechanical but also chemical factors such as substance P may generate shoulder pain and possibly induce degeneration (Del Buono et al. 2012, Gotoh et al. 1998). Bursal resection alone and debridement of partial cuff tears without bone resection have been reported to result in 79 % good to excellent results, and a randomised study could not find any clinically relevant difference between a bursal resection alone and a combination with bone resection (Henkus et al. 2009). The importance of bursal resection is probably due to bursal engagement in the intrinsic degenerative process (Codman and Akerson 1931, Rathbun and Macnab 1970, Sano et al. 1999, Shindle et al. 2011), but still the question is whether the degenerative process starts in the bursa, on the under surface of the acromion or in the rotator cuff (Henkus et al. 2009, Lo et al. 2004). Extrinsic and intrinsic factors may both influence subacromial pathology, independently of each other or together. In the literature bursal resection is usually described as bursectomy, an incorrect term since there is still quite some bursal tissue left and a new bursa will develop. Despite this, bursal resection in symptomatic patients greatly reduces the degree of tissue inflammation, which may result in a reduction of pain mediators and degrading enzymes such as substance P and MMPs (Gotoh et al. 1998, Gwilym et al. 2009, Henkus et al. 2009). It may well be that removal of bursal tissue also protects the rotator cuff from bursal-sided tearing as indicated in *Study I.*

Another aspect is that the reduction in pain after ASD, enables the patient to perform postoperative exercises, which in turn probably leads to better biomechanical and better shoulder function.

The main finding in *Study I* is that there were fewer rotator cuff tears than expected compared to the literature, 15 years after ASD. This is a result that may have several different explanations. This was a selected group of impingement patients with intact tendons at surgery at a mean age of 45 years, which may reflect that they had a favourable genetic and biomechanical profile. Other possible explanations are that the literature has overestimated the prevalence of tears or that the result was due to chance because of a too small sample size (type II error). The result may however also reflect that the extrinsic theory is true and/or that the bursal resection reduces or halter the intrinsic degenerative process in the tendons.

In *Studies IV and V,* 31 % patients of the whole study sample had a cuff tear but none of the tears were surgically repaired, only treated with exercises and/or ASD. Nevertheless these patients reached an acceptable one-year outcome. This questions the need for suture of a degenerative rotator cuff tear.

As things stand today one can only speculate on the mechanisms of action of ASD but nevertheless it is a method that reduces pain and improves shoulder function in subacromial pain patients with or without tears.

12.2 Acute rotator cuff tears, what factors influence the treatment outcome?

Recommendations from the Swedish National Centre of Competence in Orthopaedics (NKO) state that acute tears of the rotator cuff should be repaired within three weeks to achieve the best outcome (Swedish National Musculoskeletal Competence Centre 2006). This recommendation is based on a study from 1983 by Bassett and Cofield, showing that early repair within three weeks resulted in better shoulder function. More recently Petersen and Murphy (2010) stated that clinical outcome is not affected by a surgical delay of four months. *Study II,* showed that there was no significant difference in the frequency of cuff defects and no significant difference in the clinical scores between the patients repaired within three, six or twelve weeks at follow-up after a mean of 39 (12-108) months. Repair as soon as possible in patients with pseudoparalysis is desirable, but in every day clinical life a delay is common for several reasons. Our study of acute traumatic rotator cuff tears in previously healthy shoulders shows that the tear may be repaired with an open technique, up to at least three months after the injury with successful results.

There are no specific guidelines in the literature about repair of acute tears in relation to age. At follow-up in *Study II,* those patients with a rotator cuff defect were significantly older. It seems as though age affects the integrity of the cuff repair, and similar findings have been presented in mid- to long-term follow-up studies involving both acute and chronic tears (Harryman et al. 1991, Oh et al. 2010, Zingg et al. 2007).

There is evidence of decreased protein synthesis in the tenocytes of older patients with a shift toward s anaerobic metabolism with increasing age, which may be part of the explanation (Chaudhury and Carr 2012).

When several chronic tears are repaired in the same patient, a worse clinical and structural outcome has been reported, but this has not been described for acute traumatic tears (Jost et al. 2006, Oh et al. 2009, Zingg et al. 2007). In *Study II,* we could not find any evidence for such a relationship, since patients with acute multiple tendon tears did not have an inferior clinical or structural outcome at follow-up compared to patients with only one tendon affected.

There are diverging results regarding clinical outcome, recurrent structural defect, or never healed defect, in tendons after repair (chronic tears) (Harryman et al. 1991, Zingg et al. 2007). More recent publications, however, describe better functional outcome with intact repair at follow-up (Djahangiri et al. 2012, Perry et al. 2009). No such correlation has been investigated for acute tears. *In Study II,* patients with a structural defect at follow-up had significantly lower CM score and WORC index. Despite the acute appearance of tears at surgery, degenerative changes might already have been present in the tendons. The findings of contralateral FTTs in patients with cuff defects at follow-up support this.

Subacromial decompression was performed in 35 of the 42 patients in *Study II***,** to protect the repair from mechanical wear as suggested by results from *Study I* and others (Adolfsson and Lysholm 1993, Chin et al. 2007). Four out of seven patients in *Study II* who did not have a subacromial decompression as a part of the cuff repair procedure, had to be decompressed at a later stage. In contrast, only one of the 35 patients who underwent simultaneous cuff suture and decompression developed impingement symptoms during the follow-up period. This suggests that decompression should be an integrated part of a cuff repair.

12.3 Why are MMPs and TIMPs interesting when considering rotator cuff disease?

MMPs and their endogenous inhibitors TIMPs, are responsible for maintaining balance between degradation and regeneration of normal rotator cuff tissue. The different proteases are subdivided according to their substrate preference and have somewhat different actions. Since they have a critical role in maintaining the integrity of the extracellular matrix, several studies have investigated the levels of MMPs and TIMPs in synovial fluid, torn supraspinatus tissue and the subacromial bursa. Elevated levels of MMPs and TIMPs in these samples have been reported (Lo et al. 2005, Lo et al. 2004, Shindle et al. 2011, Voloshin et al. 2005) but the MMPs responsible have yet to be identified, and it is unknown whether the elevated levels are causative, or secondary to tendon tearing. It has been speculated that MMPs and TIMPs may be used in the future as indicators of rotator cuff disease, and even possible therapeutic targets (Jacob et al. 2012). In an animal model, local delivery of a universal MMP inhibitor improved tendon-to-bone healing after acute cuff repair (Bedi et al. 2010b).

Elevated TIMP-1 concentrations in serum has been observed in patients with active fibroproliferative Dupuytren's contracture (Ulrich et al. 2003) but *Study III* is, to our knowledge, the first study that investigates the possibility to measure systemic levels of MMPs and TIMPs in patients with rotator cuff disease. Our results should be considered descriptive and explorative, but are still very interesting and it seems possible that changes in plasma concentrations of both MMPs and TIMPs may be used to detect patients with rotator cuff disease. We identified significantly increased levels of TIMP-1 and a tendency towards increased MMP-9 in patients with a tear compared to controls. We also found increased levels of TIMP-1, TIMP-3 and MMP-9 in patients with FTT compared to those with PTT and patients with FTT had significant increased level of TIMP-1 compared with controls. The association between these specific proteinases and tendon disease is supported in the literature (Garofalo et al. 2011, Jacob et al. 2012, Jones et al. 2006, Robertson et al. 2012). The low levels of the other MMPs and TIMPs tested could be due to the fact that their specified substrates were not available in the plasma sample. MMP-13 (collagenase-3) was unfortunately not tested in our study because the multiplex method could not analyse MMP-13, and in previous unpublished research we failed to detect MMP-13 using ELISA. The fibroblast collagenase, MMP-13, has, however, been shown to be increased locally in the subacromial space, especially in patients with FTT (Bedi et al. 2010b, Garofalo et al. 2011, Jacob et al. 2012, Shindle et al. 2011).

Regulation of the MMP and TIMP system is highly complex since many influencing factors exist such as age, gender, hormones, metabolic status, vascularisation, mechanical load, inflammatory response and genetics (Arnoczky et al. 2007, Garofalo et al. 2011, Jones et al. 2006, Millar et al. 2009, Shindle et al. 2011). In *Study III* we used strict inclusion and exclusion criteria and a control group to increase the specificity when measuring MMPs and TIMPs related to cuff disease, but there may still be other factors involved that we do not know of. It is not likely that MMP and TIMP testing in plasma will be used in clinical practice in the near future, but our findings provide interesting information about the relationship between MMPs, TIMPs and rotator cuff disease.

12.4 Is there a genetical explanation to subacromial pain and rotator cuff tearing?

A long list of alterations in gene expression have so far been identified as being associated with rotator cuff tendinopathy and tearing. There is also growing evidence that a subset of patients have an increased genetic susceptibility to early tearing, as well as subsequent progression of symptoms and tear size (Chaudhury and Carr 2012). Siblings to patients with known rotator cuff tears have an increased incidence of symptomatic tears and progress of tear size compared to the normal population (Harvie et al. 2004). Second- and third-degree relatives to patients with a tear developing before the age of 40 are reported to have a significantly increased relative risk for developing a tear (Tashjian et al. 2009).

The altered gene expressions so far identified are related to cellular, vascular, and extracellular matrix (ECM) composition of the torn tendon edge, as well as its metabolism and viability (Chaudhury and Carr 2012) but uncertainty exists as to whether altered gene expressions associated with rotator cuff tears actually predispose to tears or occur in response to tears. The contribution of altered gene expressions to the aetiology of subacromial pain and rotator cuff tearing is difficult to quantify and compare with the contribution of other factors such as the biomechanical environment (Chaudhury and Carr 2012).

In Study I, a low prevalence of cuff tears was seen in our study group compared to that reported in literature in asymptomatic persons of the same age (Milgrom et al. 1995, Yamaguchi et al. 2001). Perhaps the low prevalence of tears in our group is explained by the fact that patients in the group had been operated with ASD, but perhaps the fact that these patients had a favourable genetic profile protecting them from altered gene expression might contribute.

In Study III, the difference in plasma levels of MMP-9, TIMP-3 and TIMP-1 between patients with PTTs and FTTs may reflect a susceptibility to progression of tearing, but may also reflect inherently different or altered gene expression as a response to altered mechanical load.

The question remains: is it possible to reverse altered gene expressions associated with rotator cuff tendinopathy or tears, and can surgery or rehabilitation modify gene expression. The future treatment of cuff tendinopathy might include drugs that modify gene expressions in addition to other intervention.

12.5 How do we evaluate shoulder function and pain?

In this thesis we used the CM score to evaluate shoulder function and pain as a primary outcome measure in *Studies I, II, IV* and *V*. This was combined with the WORC index (*Study II*) and the DASH questionnaire (*Studies I, II, IV* and *V*) as secondary outcome measures. A visual analogue scale was used in *Studies IV* and *V* for situation-based pain assessment.

The CM score is one of the most commonly used assessment tools for evaluation of shoulder function and pain in shoulder research and is recommended by the European Society for Surgery of the Shoulder and Elbow (Coghlan et al. 2008, Constant et al. 2008). Because of it's wide usage in the literature, results from different studies can be compared with each other. Such comparison, however, should be made with caution especially if scores are not adjusted for age, gender, and performed in a standardised way. When the score is used to analyse idividual difference, e.g. the patients score before and after an intervention, and using the same assessor the score is not affected by factors such as age and gender, or psychometerically. This is the preferable way to use the score when evaluating shoulder function and pain. Intra-reliability is high but inter-reliability is lower (Rocourt et al. 2008, Roy et al. 2010). In *Studies I* and ***II*****,** the CM score was used to assess post -treatment results in a retrospective design, and also to compare groups with defect and intact rotator cuffs. In *Studies IV* and *V*, the CM score was used to evaluate the mean change in shoulder function and pain between baseline (before exercises) and three-month and one-year follow-ups. It was also used in the regression analysis. The same assessor was used in all studies, which limited observer variation and enhanced reliability.

A standardised procedure should be used to obtain reliable CM scores, as Constant et al. (2008) outlined in their guidelines from 2008. We assessed all patients according to the original version of the CM score using the same protocol, the same assessor and with the same equipment to secure reliability. A Swedish translation of the original score protocol (Constant and Murley 1987) (Appendix 1) was used.

The CM score is a combination of assessor- and patient-administrated items which makes the objectivity of the score questionable. The trend in research today is to use subjective scores only because objective scores may be influenced by the assessor. Nevertheless the objective part of CM scoring makes it useful in quantifying improvements in range of motion and strength after intervention in subacromial pain patients.

The CM score is based on measurements in young, healthy men (Constant and Murley 1987) and it is known that age and gender influence the score, especially the strength part which acounts for 25 % of the total score (Katolik et al. 2005). Age- and gender-normalisation have been made on an American population and the calculated score may now be age- and gender-adjusted (Katolik et al. 2005). When the CM score is used to compare two groups with different gender or age distribution an adjustment of the statistical methods can reduce the impact of these differences. In *Study II***,** age was used as a covariate in analyses since the group with a cuff defect at follow-up was significantly older, and in *Studies IV* and *V* gender adjustments were made since there were significantly more men in the specific exercise group. In *Studies IV* and *V* there was no difference between men and women in the change from baseline to three-month and one-year follow-up, but women had lower baseline values and their one-year absolute score was therfore inferior. This was mainly due to a relative inferiority in strength, for example, middle-aged women may not reach a maximum score. This could affect the score's validity when comparing absolute scores. Because of these issues, other outcome measures were used as complements when evaluating pain and shoulder function. In *Studies I, II, IV* and *V* DASH and in *Study II* the WORC index followed the same trends as the CM score (Figure 24, Table 4). These results are supported in the literature where a strong correlation between CM score and WORC (>0.70) but weaker with DASH (0.30-0.70) have been reported (Roy et al. 2010).

Conboy et al. (1996) concluded that the CM score was easy to use and responsive to changes in patients with rotator cuff disease and osteoarthirits, but not as sensitive in patients with shoulder instability. We have also found the CM score easy to use, furthermore it is quick to work out and does not require expensive sophisticated equipment. It is also an advantage that the score captures both the clinical change percieved by the assessor and the change experienced by the patient after treatment of subacromial pain as we have experienced the score.

In *Study IV* the patient PGIC values correlated well with CM score, this result was analysed but not included in the manuscript. Once again, however, it must be kept in mind that the only truly objective part of the CM score is the strenght part, the other parts may be influenced by the assessor.

The DASH questionnaire used in *Studies I, II, IV***,** and *V* is entirely self-assessed, extensively validated and tested reliable, even the Swedish version (Atroshi et al. 2000). DASH can be used for patients with any condition of the upper extremity making it attractive as an evaluation tool in the clinical setting for non-diagnosed patients but the wide scope of the questions in this tool may make it less specific and sensitive in clinical trials. Our experience is that it is very important to instruct the patient that the questions concern their ability to perform tasks with both upper extremities and not just the injured one, otherwise there is a risk that the patient misinterprets the questions.

In *Studies IV* and *V,* pain was recorded at rest, during activity and at night using a VAS to enable a more detailed and situation-based pain assessment as apposed to the momentarily perceived pain assessed by the CM score. A statistically significant mean difference was found between the specific and non-specific exercise groups in all three variables at three-month follow-up (Table 7). Mean change between groups, however, was only significantly higher in VAS at night. The non-significant mean change in VAS at rest in *Study IV*, is interpreted as a floor effect since the patients rated very low mean values at baseline indicating no or minor pain. The non-significant mean change in VAS activity between groups is considered to be explained by large variations. Perhaps one should specify a standard activity when rating VAS at follow-up in order to avoid reference to more challenging activities due to improved shoulder function.

The clinical tests used in this thesis are commonly used in day-to-day clinical practice. Their ability to reproduce pain by tension and compression of the subacromial structures has been validated in several studies (Holtby and Razmjou 2004, Kelly et al. 2010, Leroux et al. 1995, Valadie et al. 2000). Appropriate sensitivity is reported, but less specificity for the exact structure at fault (Kelly et al. 2010). The Neer impingement sign, Hawkins-Kennedy impingement sign, Patte's test and Jobe supraspinatus test have been reported reproducible and valid in clinical practice when identifying patients with subacromial pain, including cuff tears (Iannotti et al. 2005). The accuracy of the tests however, has been questioned, especially when used one by one (Hegedus et al. 2012). To enhance the accuracy of our diagnostic procedure in *Study IV*, three out of four tests had to be positive. Furthermore a thorough overall patient assessment, with clinical characteristics, radiology and ultrasound was used to verify the diagnosis. The low specificity of the tests reflects the heterogeneity of the condition with several subacromial structures as possible cause of pain. Ultrasound is a helpful instrument to increase the specificity of the structural diagnosis.

In *Studies IV* and *V,* Neer's impingment test (1977) was performed with a blind subacromial injection technique, which may be a source of error. Rutten et al. (2007) reported equal accuracy with blind injection as with ultrasound guided. A recent systemic review by Sho et al. (2011) suggests, however, that ultrasound-guided corticosteroid injections are more beneficial than blind ones. These results should be interpreted with some caution since only two studies were included and the sample sizes were small.

12.6 Ultrasound evaluation of the shoulder, how and why?

In all five studies in this thesis US was chosen as the tool to examine the integrity of the rotator cuff. US was preferred to MRI for several reasons; In several studies US has been reported to have the same accuracy as MRI for both detecting and measuring PTTs and FTTs, especially when an experienced investigator uses the latest US-techniques (Harryman et al. 1991, Nho et al. 2009, Oh et al. 2009, Sorensen et al. 2007). Teefey et al. (2004) concluded that when an investigator has comparable experience in both these imaging modalities, the decision regarding technique for rotator cuff assessment does not need to be based on accuracy concerns. The choice, instead, can be based on other factors, such as the presence of an implanted device, patient tolerance, availability and cost. Furthermore, suture anchors that interfere with MRI do not distort US images. US is not a problem for patients with claustrophobia and the investigation is cheap, rapid, harmless, dynamic and bilateral comparisons can easily be made.

The use of US imaging as well as clinical scores at follow-up in *Study II* made it possible to study associations between clinical findings and cuff pathology, which is a strength of that study compared to previous studies using clinical follow-up only (Bassett and Cofield 1983, Lahteenmaki et al. 2006). An interesting finding in *Study II* on acute tears is the number of patients with subacromial degeneration radiologically and FTTs in the asymptomatic contralateral shoulder indicating that these patients have an on-going degenerative process in both shoulders. This speculation is supported by a study, which reported a high prevalence of bilateral lesions two years after surgical repair of a chronic tear (Harryman et al. 1991). Bilateral tears were found also in *Study V* supporting the notion that subacromial pain has an intrinsic degenerative component and altered gene expression leading, for example, to a disturbance in the MMP balance.

In *Study V*, a significant association between radiological subacromial degeneration and a cuff tear was found, which further indicates that these findings are related.

Since US and radiological findings in *Study V* are associated with the choice of treatment the findings of these examinations are recommended to consider when deciding treatment and studying subacromial pain patients.

In *Studies II* and *V*, two or three independent investigators assessed the radiological images and patients were examined with US by two different assessors (HBH one of them). All assessors were in agreement with their findings, which validates our results. During the process of this thesis the author (HBH) examined 129 patients using US. Validation of the results was performed and HBH reached an accuracy of 93 % when compared with an experienced radiologist specialised in ultrasound. This finding supports the statement by Iannotti et al. (2005) that an experienced orthopaedic surgeon can effectively perform US, in conjunction with clinical examination and shoulder radiology, to accurately diagnose the extent of rotator cuff tears.

12.7 The rationale of eccentric exercises

We believe that the entire management with the structured specific exercise programme and the corticosteroid injection contributed to the positive results in *Studies IV and V*. The specific exercise programme focused on eccentric exercises (EE) for strengthening of the rotator cuff and concentric/eccentric exercises for the scapula stabilisers, in combination with manual mobilisation.

Eccentric contraction occurs with muscle-tendon unit lengthening as a load is applied to it, producing so-called negative work. This is in contrast to concentric contraction where the muscle-tendon unit shortens in length resulting in positive work. With isometric contractions the same unit does not shorten despite resisting a force and no work is produced (Rees et al. 2009).

Eccentric strength training was first introduced in 1984 by Stanish and Curwin (1986) and has been reported beneficial in the treatment of chronic tendinosis especially in Achilles, patellar and extensor carpi radialis brevis (ECRB)-tendinopathy. The histological changes found in the tendons at these locations are similar to those found in the supraspinatus tendon (Jonsson et al. 2006, Khan et al. 1999, Nirschl 1992).

The specific exercises in *Studies IV* and *V* focused on EE and prior to completion of *Study IV* there had been no other randomised study focusing on the effectiveness of EE. There are, however, two non-controlled studies, which have shown promising results with painful EE on patients with chronic shoulder pain (Bernhardsson et al. 2011, Jonsson et al. 2006).

The mechanism of the effects of eccentric training is still not fully understood, but there is a growing body of evidence regarding the effect on tendons. These findings include the effects on structure and capillary blood flow, collagen synthesis and biomechanics (Rees et al. 2009).

One theory is that EE reduces the formation of new vessels and nerve endings around the affected tendon. Studies on painful Achilles tendinosis have demonstrated vasculo-neural ingrowths as being the most likely source of pain, and good clinical results after treatment with eccentric calf-muscle exercises were associated with regress of neovasculature (Alfredson 2003, Ohberg and Alfredson 2003). Neovascularisation has also been suggested to be associated with subacromial pain (Chansky and Iannotti 1991). Alfredson et al. (2006) treated neovascularisation in the supraspinatus tendon and bursa wall with injections of the sclerosing substance polidocanol. This treatment significantly reduced the shoulder pain during horizontal shoulder movement in ten of 15 patients. These studies indicate that areas with increased vascularity and sensory nerve endings may be the source of pain and perhaps, also, the site of action for EE (Alfredson 2003, Alfredson et al. 2006, Chansky and Iannotti 1991).

Other theories are based on remodelling stimuli and biomechanics. Stanish and Curwin (1986) showed that with EE the tendon is subjected to greater forces than with concentric exercises (CE), and thereby a greater anabolic remodelling stimulus takes place. This may stimulate tenocytes and restart the healing process that is haltered in tendinosis (Rees et al. 2009, Stanish et al. 1986). Physical training in general is shown to increase both synthesis and degradation of collagen. Langberg et al. (2007) showed that EE increased collagen synthesis without corresponding collagen degradation in patients with chronic Achilles tendinosis. EE has also been reported to induce sarcomereogenesis and this is speculated to change the muscle architecture by increasing fascicle length. A lengthening of the fascicle changes the force–length relationship with less strain on the tendon during motion and less tendon pain (Brughelli and Cronin 2008, Fahlstrom et al. 2003, Stanish et al. 1986). Another theory is that fluctuations in force while performing EE, due to the difficulty in controlling a movement with a lengthening muscle, may constitute a remodelling stimulus (Rees et al. 2009).

The EE used in *Study IV* was sometimes painful, as recommended by Mafi et al. (2001), but it is unclear why EE causing pain is more effective than pain-free training as originally described by Stanish et al. (1986) since the pain mechanisms in tendinosis are still unclear.

As described in this text, there are several theories but the precise mechanisms of EE action still remain unclear. Despite the extensive use of EE for various tendinosis, the knowledge of EE for subacromial pain are scarce (Bernhardsson et al. 2011, Jonsson et al. 2006, Virta 2009). *Studies IV* and *V* fill this gap by presenting positive results after three months exercise intervention, including EE, with instructions and progression for patients with subacromial pain. Due to the design of *Study IV* where EE was part of a multifaceted exercise programme, conclusions on the specific effect of the EE-component cannot be drawn.

12.8 Factors influencing conservative or surgical management of subacromial pain patients?

It is not easy to predict which patients with subacromial pain will be successfully treated using a specific exercise programme, and who will ultimately need surgery, and research into predictive factors has been limited. *Studies IV* and *V* aimed to approach this and we found that there was a significant association between having a low initial CM score and choosing surgery after the three months of exercises independently of gender, rotator cuff status and treatment group. This is supported by the literature where baseline scores, duration of disability and pain are reported to be one of the most powerful predictors of outcome regardless of treatment (Rahme et al. 1998, Thomas et al. 2004, Thomas et al. 2005). We also found a significant association between having a FTT and choosing surgery compared to having an intact rotator cuff, but patients with a PTT did not more often choose surgery (Table 9). When adding treatment group in the same logistic regression analysis we found that some patients, despite having a cuff tear may benefit from the specific exercises but there is an increased risk for not responding satisfactorily with a FTT (Table 10). The subgroup analyses can only be considered indicative because of the limited number of patients with a tear in some groups.

The knowledge concerning the influence of rotator cuff status on treatment outcome is limited, but less satisfactory results after both ASD (Benson et al. 2009) and physiotherapy (Tanaka et al. 2010) in patients with a FTT have been described. In *Study I*, patients with a tear had an inferior CM score and DASH compared to patients with intact tendons, but the difference was not significant, possibly due to the limited number of patients in the tear group. *Study II* showed a significantly better outcome in CM score and WORC index at follow-up for patients with intact tendons compared to those with a cuff defect. In patients with a FTT, a history of trauma or night pain is reported not to influence the outcome of exercises or surgical treatment (Itoi and Tabata 1992a, Tanaka et al. 2010). Restricted external rotation, tear extension from supraspinatus to infraspinatus and muscle atrophy are, however, factors reported to negatively influence the results of exercise treatment in patients with FTTs (Itoi and Tabata 1992a, Tanaka et al. 2010). None of the ruptured supraspinatus tendons reported in *Study V* extended into the infraspinatus and this might be part of the reason why some patients with a FTT responded well to specific exercises.

Guided treatment is one factor that has been reported to influence exercise treatment positively, especially early in the rehabilitation or in postsurgical rehabilitation period when the patient is still dealing with pain and disability (Holmgren et al. 2011, Thorstensson et al. 2006). Other factors such as motivation and adherence influence failure or success, especially when exercise at home is recommended (Deutscher et al. 2009). To account for these factors, our exercise programmes included only a few exercises that were designed to be as easy as possible to follow, and could be performed in a reasonable time. Patients were also guided and supervised by the same physiotherapist throughout the three-month training period. This probably explains why there was no difference in compliance between the two groups in *Study IV,* which otherwise could have influenced the results.

Subacromial corticosteroid injection is one of the most commonly used treatments for subacromial pain. The combination of subacromial corticosteroid injection and exercise has been reported to lead to earlier improvement in pain and dysfunction than with exercise alone (Buchbinder et al. 2003, Crawshaw et al. 2010, Paavola et al. 2002). Corticosteroid injections are believed to diminish inflammation and thereby reduce pain and adhesions by inhibiting production of inflammatory mediators, collagen production and the release of noxious chemicals. Even so, the biological effect of corticosteroid injection is largely unknown and evidence of its long-term beneficial effect is scarce (Paavola et al. 2002). There are, however, studies reporting reduced pain and increased range of movement, primarily in the short-term, thus allowing patients to start adequate rehabilitation sooner (Buchbinder et al. 2003, Green et al. 2000, Paavola et al. 2002). This supports the strategy in *Studies IV* and *V,* where all patients received an injection prior to starting the exercises.

Complete tendon rupture with loading is an adverse effect reported after corticosteroid injection, but this comes from case reports and animal studies only. No reliable evidence for this exists and the question whether these ruptures are an effect of the corticosteroid injections or a manifestation of the tendon disease remains (Paavola et al. 2002). Corticosteroids, however, are shown to have detrimental effects on the extracellular matrix through increased MMP production, decreased collagen production and enhanced bone resorption both *in vitro* and *in vivo* studies. The extent of these effects is unknown, but may be involved in tendon rupture and other adverse events such as skin atrophy and fat necrosis after local steroid injection (Scutt et al. 2006, Tempfer et al. 2009, Tillander et al. 1999, Van den Steen et al. 2002, Wong et al. 2004). Corticosteroid injection may also contribute to infection by suppressing the immune response with altered protein expression (Paavola et al. 2002). In *Studies IV* and *V* this risk was minimised by sterile injections.

Sick leave and prolonged intake of pain medications has been shown to be a poor strategy for patients with subacromial pain (Brox et al. 1999, Haahr et al. 2005, Rahme et al. 1998). The patient's work situation and the use of analgesia or anti-inflammatory drugs were registered at baseline in *Study IV* and these did not differ between the treatment groups. About 20 % of the patients were on sick leave and 24-33 % used pain medication. Psychological factors have also been incriminated as a cause of failed treatment, and are thus important to document. Our two treatment groups (*Studies IV* and *V*) had low mean scores on the HAD scale with no difference between groups at baseline, indicating limited mental stress.

In *Study V* subacromial calcification was not found to influence the patient's choice of surgery. This is in line with previous research where subacromial calcification in most cases is reported to be self-limiting, resorbed spontaneously and does not influence outcome after treatment (Hurt and Baker 2003, Tillander and Norlin 1998).

To gain long lasting successful result after ASD, selection of patients is important as stated by previous studies (Coghlan et al. 2008, Lunsjo et al. 2011, Magaji et al. 2012). However, there is no consensus on the selection criteria. Our specific exercise strategy including corticosteroid injection and specific exercises may be looked upon as a selection process in addition to treatment, whereafter the majority of subacromial pain patients are improved to the extent that they do not need surgery. This reasoning may be justified with the result that patients in the specific exercise group without surgery gained the highest one-year CM score and the fact that all patients improved significantly after treatment even the ones going through surgery (Figure 26, Table 8).

Despite the association between having a full-thickness tear and choosing surgery we still know very little about factors influencing both exercise treatment and surgery. The responsiveness to exercises is probably multifactorial including; physiological and biomechanical properties, structural tissue changes, capability of developing compensatory mechanisms and psychological factors such as anxiety (Lentz et al. 2009, Vlaeyen et al. 1995).

We showed however in *Study V* that patients treated only conservatively are different from patients choosing surgical treatment in addition to exercises, in the sense that they reached a higher one-year CM score. The level of improvement was however about the same in all groups, patients with a low baseline scores had an inferior one-year score, and surgery did not change this, still the one-year score was acceptable even in this group (Figure 26, Table 8).

"Life is the art of drawing sufficient conclusions from insufficient premises."

- Samuel Butler

13 Conclusions

The prevalence of rotator cuff tears in patients with subacromial pain was lower than expected 15 years after arthroscopic subacromial decompression in patients with intact rotator cuff at surgery. This low prevalence of tears suggests that bursal and bone resection has a protective effect on the rotator cuff. There was a tendency towards inferior clinical results in patients with a structural cuff defect at follow-up.

Acute traumatic rotator cuff tears in patients with a previously healthy shoulder can be treated with cuff repair and subacromial decompression up to three months after the injury and still achieve a successful clinical and structural outcome. The number of tendons injured at repair does not affect the outcome but a higher age at repair significantly influences the outcome with lower Constant-Murley score and WORC index and increased risk for late structural cuff defect.

Alterations in plasma levels of MMPs and TIMPs can be measured in patients with a rotator cuff tears, patients with a full-thickness tear in particular have increased levels of TIMP-1 compared to healthy shoulder controls. This might reflect a local pathological process in or around the rotator cuff, or a genetic predisposition in these patients. The difference in TIMP-1 and certain MMPs between patients with partial- and full-thickness tears may reflect the extent of the lesion or different aetiology and pathomechanisms between partial- and full-thickness tears.

A specific exercise programme, focusing on eccentric exercises for the rotator cuff and scapula was in short-term significantly more effective than control exercises in reducing pain, improving shoulder function and thereby reducing the need for arthroscopic subacromial decompression in patients with subacromial pain.

The positive short-term outcome after a specific exercise programme was maintained after one-year, and there was still a significantly reduced need for arthroscopic subacromial decompression in the specific exercise group compared to the control exercise group.

A low baseline Constant-Murley score but also the presence of a full-thickness tear were associated with choosing surgery and influenced the one-year Constant-Murley score negatively, still a three-month period of specific exercises can be recommended as first line of treatment for all subacromial pain patients.

The rotator cuff protective effect of ASD found in *Study I***,** the finding of MMP and TIMP alterations in plasma in *Study III* and the positive one-year outcome after specific exercises suggest that different mechanisms such as extrinsic, intrinsic and biomechanical factors are involved in the pathogenesis of subacromial pain.

Patients in *Studies I, II,* and *V* with a FTT at follow-up had an inferior clinical outcome compared to patients with an intact cuff. This finding underlines the importance of the rotator cuff status and the need to consider this when treating and studying subacromial pain patients in the future.

14 Future research

The study and understanding of patients with subacromial pain raises new questions and ideas for future research;

The results in *Study III* are interesting findings but there are methodological limitations such as the difficulty to verify that the altered MMP and TIMP plasma levels are due to pathology in the shoulder and not another still asymptomatic pathological process elsewhere in the body. In future studies, MMP and TIMP levels in tissue samples, arthroscopic or needle biopsy, from the shoulder could be analysed and compared with plasma levels to verify that these represent the cuff tear. Furthermore, MMP-13 should be analysed since there are several studies showing increased levels of this MMP in tissue samples from shoulders with rotator cuff tears (Jacob et al. 2012, Lo et al. 2004, Shindle et al. 2011). Another interesting approach is to collect plasma and, where possible, local tissue samples from the subacromial bursa in patients without a tear. Later on, after some years, the plasma analyses and US of the rotator cuff may be repeated to see if patients who develop a cuff defect also have alterations in plasma MMPs and TIMPs.

A longer follow-up of the patients in *Studies IV and V* would show if the positive effects after the specific exercise programme are maintained, and if there is a difference between the patients with tears and subacromial degeneration compared to the others.

An already on-going study is further evaluating the specific exercise programme in a primary care setting. In a population with less prominent symptoms the exercises may have an even greater effect. The natural course of subacromial pain in patients with intact cuff is unknown and the efficacy of all treatments should be examined in relation.

A larger study population with the possibility of sub-grouping would enable analysis of several predictive factors at the same time, such as gender, age, work, smoking, rotator cuff status and baseline clinical score.

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- Sam Levenson

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17 Appendixes

Appendix 1 The CM score (Constant and Murley 1987), Swedish version used in *Studies I, II, III, IV* and *V*. Translation into Swedish and design, Rolf Norlin.

			hö	vä				hö	vä
smärta	svår	0			**Utåtrot**	nacke/ armb fram	2+		
	måttl	5				nacke/ armb ut	2+		
	lindrig	10				huvud/ armb fram	2+		
	ingen	15				huvud/ armb ut	2+		
ADL	opåv sömn	2+				full elev	2		
	opåv arb	4+			**Flex**	0-30	0		
	opåv fritid	4				31-60	2		
	midjan	2				61-90	4		
	xiphoid	4				91-120	6		
	nacke	6				121-150	8		
	på huv.	8				151-180	10		
	över huv	10			**Abd**	0-30	0		
Inåtrot	låret	0				31-60	2		
	glutealt	2				61-90	4		
	lumbo-s	4				91-120	6		
	L3	6				121-150	8		
	Th12	8				151-180	10		
	Th7	10			**Kraft**	0,5kg/p	max 25		
					SUMMA	max 100p			

Appendix 2 Specific exercise programme used in *Study IV* and *V*

Specific exercise programme

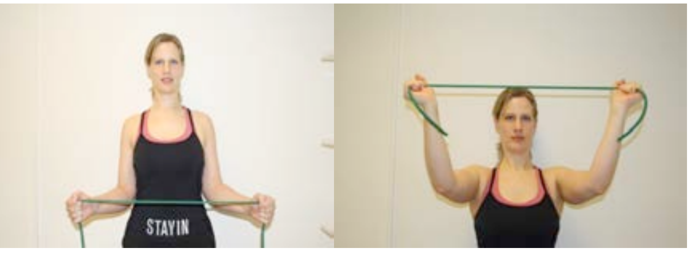
- To perform twice a day for the first 8 weeks then once a day for the last 4 weeks

Exercise 1: Week 1-12, shoulder retraction, exercise for the scapula stabilisers, 15 repetitions x 3.

Exercise 2: Week 1-8, full can eccentric exercise in the scapular plane for m. supraspinatus, 15 repetitions x 3. Week 9-12, full can concentric/eccentric exercise for m. supraspinatus, 10 repetitions x 3, 15 repetitions x 3.

Exercise 3: Week 1-8, eccentric exercise for m. infraspinatus and m. teres minor, 15 repetitions x 3. Week 9-12, concentric/eccentric exercise 10 repetitions x 3, 15 repetitions x 3.

Exercise 4: Week 1-8, concentric/eccentric exercise for m. serratus anterior, 15 repetitions x 3. Week 9-12, push up plus exercise, 10 repetitions x 3, 15 repetitions x 3.



Exercise 5: Week 5-8, bilateral external rotation, a combined exercise for the rotator cuff and the scapula stabilisers, 10 repetitions x 3, 15 repetitions x 3. Week 9-12, elevation with bilateral external rotation, 10 repetitions x 3.

Exercise 6: Week 1-12, posterior shoulder stretch, 30-45 seconds x 3.