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Soft Tissue Aspects of the Shoulder Joint

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Abstract
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The aim of this thesis was to study different aspects of the soft tissues of the shoulder joint. The variation in the quality of the tendons and ligaments can be explained by genetic factors. To test the hypothesis that collagen 1 α1 Sp1 polymorphism is related to the occurrence of cruciate ligament ruptures and shoulder dislocations, a total of 358 patients (233 patients with cruciate ligament ruptures and 126 with shoulder dislocations) were included in the study. We found a decreased risk of these injuries associated with collagen type 1 α1 Sp1 polymorphism.

To study the mechanical properties of a better type of fixation of soft tissue to bone, 10 skeletally mature New Zealand white rabbits were operated bilaterally on the knees. The medial collateral ligaments were fixed by two types of plates one with a flat undersurface and the other with a pegged undersurface. After 4 weeks the force at failure, stiffness and energy uptake was almost double in the knees operated with the pegged plates.

The prevalence and dysfunction of rotator cuff tears was investigated in 106 subjects who had never sought for their shoulder complaints, using Constant score, ultrasound and plain x-ray. The prevalence of full-thickness cuff tears was 30% (21% of all shoulders). The Constant score was lower in subjects with full-thickness tears. Partial-thickness tears and acromioclavicular joint osteoarthritis had no impact on shoulder complaints or Constant score. The subacromial index was lower for shoulders with full-thickness tears.

Forty-eight patients with median age 56 years underwent subacromial decompression with or without acromioclavicular joint resection, investigated with MRI pre- and 3 months postoperatively. The Constant score and subjective shoulder value were measured preoperatively and at 3 and 6 months after surgery and even 2 years for subjective shoulder value. Two raters investigated the MRI. The results showed poor inter-rater reliability for MRI. However, both Constant score and subjective shoulder value improved over time. MRI is not a reliable method to study the capsular reaction after subacromial decompression due to high subjectivity of the radiologists.

Keywords: cruciate ligament, shoulder dislocation, polymorphism, collagen, biomechanical properties, rotator cuff tear, shoulder ultrasound, adhesive capsulitis, MRI

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List of Papers

I. Khoschnau S, Melhus H, Jacobson A, Rahme H, Bengtsson H, Ribom E, Grundberg E, Mallmin H, Michaëlsson K. Type I collagen alpha1 Sp1 polymorphism and the risk of cruciate ligament ruptures or shoulder dislocations. Am J Sports Med. 2008 Dec;36(12):2432-6.

II. Khoschnau S, Fahlgren A, Aspenberg P, Rahme H. Improved healing of ligament to bone with point fixation in rabbits. Acta Orthop. 2006 Dec;77(6):967-72.

III. Khoschnau S, Milosavljevic J, Sahlstedt B, Rylance R, Rahme H. High prevalence of rotator cuff tears in a population who never sought for shoulder problems: a clinical, ultrasonographic and radiographic screening study. Submitted

IV. Khoschnau S, Larsson H, Elhami H, Rylance R, Rahme H. MRI without contrast is an unreliable method for detection of capsular reaction following shoulder surgery. Submitted

Contents

Abbreviations

ACL	Anterior Cruciate Ligament
MCL	Medial Collateral Ligament
COL1A1	Collagen 1 Alpha 1
COL1A2	Collagen 1 Alpha 2
MRI	Magnetic Resonance Imaging
PCR	Polymerase Chain Reactions
OR	Odds Ratio
CI	Confidence Interval
SNP	Single-nucleotide Polymorphism
CS	Constant score
SSV	Subjective Shoulder Value

Introduction

The glenohumeral joint is unique compared to other joints in the body in that it is highly dependent on the soft tissue envelope surrounding it. There are three groups of muscles, with their tendons, acting on the joint: the muscles going from the trunk to the scapulae, the axiohumeral group and the scapulohumeral group. The joint has a loose joint capsule including the glenohumeral ligaments and the labrum. Shoulder morbidity often depends on pathological changes in the joint capsule, labrum and tendons surrounding the glenohumeral joint.

Ligaments and tendons are soft connective tissues, which transmit forces from bone to bone, and muscle to bone, respectively. These tissues serve essential roles for biomechanical function of the musculoskeletal system by stabilizing and guiding the motion of joints. Ligaments and tendons consist of highly aligned collagen in the form of fibrils, fascicles, fibers, and the associated extracellular matrix that accompanies the collagen fibers. Ligaments and tendons are one of the strongest tissues in the body. Nevertheless, these tissues are frequently injured due to repetition and overuse, eccentric activities, and quick, cutting motions that involve acceleration and deceleration. These injuries often upset the balance between mobility and stability of the joint, and the results are often pain and other morbidity, such as osteoarthritis[1-4].

The numbers on incidence of ligament and tendon injuries are huge. For example, it is estimated that tendinopathy accounts for 30% to 50% of all injuries related to sports, plus over 48% in occupational disorders[5-7]. Similarly, the incidence of knee ligament ruptures, primarily involving the anterior cruciate ligament (ACL) and the medial collateral ligament (MCL), is estimated to be 2 per 1,000 people per year in the general population[8,9]. In the shoulder, injuries to the ligaments and capsule is approximately 8 per 100,000 person-years[10], and the prevalence of rotator cuff tears is more than 30% in people over 60 years of age[11,12].

Both ligaments and tendons are collagenous bands of fibrils consisting of various collagen types, proteoglycans and glycoproteins[13]. Type I collagen is the major protein component of ligaments and constitutes 70–80% of its dry weight[14]. The type I collagen molecule is a heterotrimer consisting of two α1

and one α2 chains, which are encoded for by the *COL1A1* and *COL1A2* genes, respectively[15].

In addition to the reported association between the *COL1A1* Sp1 binding site polymorphism and cruciate ligament ruptures[16], mutations within the *COL1A1* gene have been shown to cause monogenetic connective tissue disorders such as osteogenesis imperfecta and Ehlers–Danlos syndrome[15]. The functional Sp1 binding site polymorphism has also been shown to be associated with other multifactorial disorders such as osteoporotic fractures[17], bone mineral density disorders[17,18], osteoarthritis[19], myocardial infarction[20], lumber disc disease[21] and stress urinary incontinence[22]. It was proposed that the G→T substitution within the intronic Sp1 binding site increases the affinity for the transcription factor Sp1, resulting in increased *COL1A1* gene expression[18].

The healing of ligament and tendon injuries is usually slow. In these injuries it can take up to 12 months for the pain to subside before one can return to physical and sports activity[5]. Although a ruptured MCL can generally heal spontaneously and sufficiently well such that nonsurgical management has become the treatment of choice[23-27], its remodeling process takes years, and its mechanical properties remain inferior to those for the normal MCL[23,28-32]. It is also known that a midsubstance ACL tear has limited healing capability[25,33,34] and reconstruction by replacement grafts has been regularly performed in order to regain knee function[35-38].

Little is known about the epidemiology of rotator cuff problems, since conclusions are based on patients with shoulder problems. Ultrasound imaging of the rotator cuff has been used since the mid-1980s[39-41]. Mack et al.[40] compared ultrasound evaluation with surgical and arthrographic findings; they found 95% accuracy when ultrasound was compared with surgical observations of full thickness tears and a 91% correlation when it was compared to arthrography. In an ultrasound study of an asymptomatic population Milgrom et al. found a prevalence of 50% cuff injuries in patients in their seventh decade and 80% in their ninth decade. This study indicated that rotator cuff lesions might be regarded as a natural correlate of ageing, with linear increases after the fifth decade of life[42].

Adhesive capsulitis is a syndrome defined as painful restriction of shoulder movement[43]. Inflammation combined with a fibrotic reaction is a major pathologic change leading to thickening, contraction, and subsequent adhesion of the capsule, synovium and even the surrounding ligamentous structures[44-46]. Magnetic resonance (MR) arthrography allows excellent visualization of capsulolabral and other intra-articular structures as well as the rotator cuff, which are often not visualized well in the absence of the significant

quantities of native joint fluid on conventional MR imaging[47-52]. The rotator cuff interval, known to be important in the motion of the glenohumeral joint, has been implicated in the pathogenesis of adhesive capsulitis in recent studies[53-55]. Thickening and contraction of the rotator cuff interval act as a tight check-rein that prevents external rotation of the arm[55-57]. Emig et al. found a correlation between joint capsule and synovium thickness greater than 4mm and clinical diagnosis of adhesive capsulitis[46]. MRI of the shoulder is an effective and non-invasive means of diagnosing suspected cases and also provides information that may assist the physician in differentiating between the early and late stages. Capsule and synovial thickness, as measured in the axillary pouch, demonstrates the greatest correlation with clinical stage of adhesive capsulitis. Earlier, more hypervascular stages exhibit greater combined synovial and capsular thickening, while later, more fibrotic stages demonstrate only capsular thickening[58].

Collagen

The collagen fibers

The molecular and packing structures of collagen have eluded scientists for decades; the first evidence that it possesses a regular structure at the molecular level was presented in the mid-1930s [59,60].

Collagen is considered as one of the most interesting proteins found in the body, and it is the most abundant protein in mammals. Collagen is found in many places in the body, including tendons, ligaments, bone, connective tissue, skin, blood vessels and the lens and cornea of the eye.
In each case its presence increases the tensile strength and provides support to the tissue of which it is a part.

Collagen occurs in many places throughout the body. So far, 29 types of collagen have been identified and described. Over 90% of the collagen in the body is of type I, II, III, or IV.

- Collagen I: skin, tendon, blood vessels, ligaments and bone.
- Collagen II: cartilage.
- Collagen III: reticulate (main component of reticular fibers), commonly found alongside type I in skin, tendons, vessels, ligaments and bone.
- Collagen IV: forms bases of cell basement membrane
- Collagen V: Cells surfaces, hair and placenta.

The main subunit of collagen type 1 is called tropocollagen. It consists of three polypeptide chains wrapped around one another, forming a triple helix.

This unit is 300 nm long and 1.5 nm in diameter. Each polypeptide contains about 1000 amino acids, and the three interacting chains of the helix are stabilized by hydrogen bonds between them.

The COL1A1 gene produces a component of type I collagen, called the pro-alpha1 chain. This chain combines with one other pro-alpha1 chain and also with a pro-alpha2 chain (produced by the COL1A2 gene) to make a molecule of type I procollagen. The amino group in the amino acid is important. One amino acid can react with the carboxyl group of another amino acid during a dehydration reaction, releasing a molecule of H_2O. The resulting covalent bond is known as a peptide bond. Once 10 or more amino acids are linked by peptide bonds, the chain may be referred to as a polypeptide. This will contain a free amino group at one end (N-terminus) and a carboxyl group at the other end (C-terminus).

The polypeptides are first synthesized by fibroblasts as even longer units called procollagen. These are secreted into extracellular spaces, where they are cleaved and shortened at both the N-terminus and C-terminus by specific enzymes called procollagen peptidases. Once tropocollagen has been formed these triple-helical chains associate with one another spontaneously to form dense collagen fibers. The association follows an orderly pattern, where rows of end-to-end molecules line up in a staggered fashion next to each another. In each row a gap of approximately 40 nm exists between each tropocollagen unit. This complex structural arrangement creates protein fibers that strengthen and support a variety of tissues.

The COL1A1 gene is located on the long (q) arm of chromosome 17 between positions 21.3 and 22.1, from base pair 45,616,455 to base pair 45,633,991. There are many disorders associated with defects in collagen synthesis, such as Ehlers-Danlos syndrome, osteogenesis imperfecta and Marfan syndrome. These disorders are inherited as autosomal dominant traits. It is estimated that one per 10000-20000 individuals worldwide suffer from osteogenesis imperfecta, while the classic type of Ehlers-Danlos syndrome occurs in one in 20000-40000 people.

Tendons

Tendons connect muscle to bone and allow transmission of forces generated by muscle to bone, resulting in joint movement. Tendon injuries produce considerable morbidity[1].

Healthy tendons are white in color and have a fibroelastic texture. Tendons demonstrate marked variation in form; they can be rounded cords, straplike

bands, or flattened[61]. Within the extracellular matrix network, tenoblasts and tenocytes constitute about 90%to 95% of the cellular elements of tendons[62]. Tenoblasts are immature tendon cells. The remaining 5% to 10% of the cellular elements of tendons consists of chondrocytes at the bone attachment and insertion sites, synovial cells of the tendon sheath, and vascular cells, including capillary endothelial cells and smooth muscle cells of arterioles. Tenocytes are active in energy generation using the aerobic Krebs cycle, anaerobic glycolysis, and the pentose phosphate shunt, and they synthesize collagen and all components of the extracellular matrix network[63-65].

The oxygen consumption of tendons and ligaments is 7.5 times lower than that of skeletal muscles. The low metabolic rate and well-developed anaerobic energy-generation capacity are essential to carry loads and maintain tension for long periods, reducing the risk of ischemia and subsequent necrosis. However, a low metabolic rate results in slow healing after injury[66].

The dry mass of human tendons is approximately 30% of the total tendon mass, with water accounting for the remaining 70%. Collagen type I accounts for 65% to 80%, and elastin accounts for approximately 2% of the dry mass of tendons[63,67-69].

Collagen is arranged in hierarchical levels of increasing complexity, beginning with tropocollagen, a triple-helix polypeptide chain, which unites into fibrils, fibers (primary bundles), fascicles (secondary bundles), tertiary bundles and the tendon itself (Fig. 1)[70-72]. A collagen fiber is the smallest tendon unit that can be tested mechanically and is visible under light microscopy.

The epitenon, a fine, loose connective-tissue sheath containing the vascular, lymphatic, and nerve supply to the tendon, covers the whole tendon and extends deep within it between the tertiary bundles as the endotenon[73,74]. Superficially, the epitenon is surrounded by paratenon, a loose areolar connective tissue consisting of type-I and type-III collagen fibrils, some elastic fibrils, and an inner lining of synovial cells[75]. Synovial tendon sheaths are found in areas subjected to increased mechanical stress, such as tendons of the hands and feet, where efficient lubrication is required.

The osteotendinous junction is composed of four zones: a dense tendon zone, fibrocartilage, mineralized fibrocartilage, and bone[76]. The specialized structure of the osteotendinous junction prevents collagen or fiber bending, fraying, shearing, and failure[77,78].

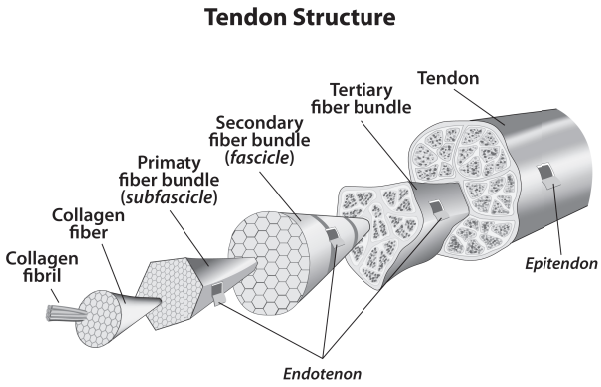

Fig. 1. Anatomy of normal tendon

Ligaments

Ligaments are short bands of flexible fibrous connective tissue that bind bones together. The ligaments are usually named by a variety of gross structural and functional features, most commonly they are named by their points of bony attachment (e.g., coracoacromial ligaments). However, other anatomic adjectives such as their shapes (the triangular deltoid), their functions (capsular ligaments), their relations to the joints (collateral ligaments), their relations to the surface (superficial or deep) or their relations to each other (cruciates) can also describe them.

The majority of ligaments are anatomically distinct; they appear to be homogeneous, dense, white structures stretched between their points of bony attachment. Next in the spectrum of the ligament forms are some less distinct sheet-like ligaments. These are still fairly discrete and well oriented for their functions. The last type is nearly impossible to distinguish, the so-called capsular ligaments.

Ligaments consist of fibers running almost parallel to each other on their course between insertions. Their insertions are usually hidden from view by the ligament itself or by the overlying tissues such as the synovium. The histological appearance of ligaments suggests multiple fibers of collagen oriented in parallel along their length. Scattered throughout these fibers are long, thin cells that produce and maintain the ligament matrix, these are called fibroblasts[79]. A regular wavy undulation of cells and matrix can be seen, a pattern that has been described as ”crimp”[80, 81]. This pattern allows a buffer by which a slight elongation is allowed to occur without damage to its fibers. It also provides a mechanism for control of ligament tension and acts as a shock absorber along the length of the ligament. When the physiological limit of this crimp is exceeded, irreversible damage occurs[82].

The perforating fibers of Sharpey are probably the only collagen fibrils that connect adjacent lamellae in the bone. However these are only a small part of the total insertional mechanism. Most skeletal ligaments insert into bone by gradual transition through layers of fibrocartilage and mineralized fibrocartilage. This transition is organized to prevent stress concentration by avoiding a sudden interface between soft tissue and bone[83].

In general ligaments consist of several biochemical parts. Most of them contain approximately two-thirds water by weight, while three quarters of their dry mass is made of collagen. Greater than 90% of this collagen is type 1, with only a little percent of type 3. Despite that this collagen is very stable chemically, it is gradually degraded and replaced. The rate of this turnover is to some extent ligament-specific and specific to a number of environmental conditions[84]. Smaller proportions of matrix are composed of elastin, glycosaminoglycan and other biochemical substances[85].

Biomechanics

Ligaments and tendons transmit force from bone to bone and from muscle to bone and act as a buffer by absorbing external forces to limit muscle damage[86]. Tendons exhibit high mechanical strength, good flexibility, and an optimal level of elasticity to perform their unique role[87-89].

The mechanical behavior of collagen depends on the number and types of intramolecular and intermolecular bonds[90]. A stress-strain curve helps to demonstrate the behavior of a ligament or tendon (Fig. 2). At rest, collagen fibers and fibrils display a crimped configuration[81]. The initial concave portion of the curve (toe region), where the ligament or the tendon is strained up to 2%, represents flattening or stretching of the crimp pattern[67, 91, 92]. Beyond this point, fibers deform in a linear fashion as a result of intramolecular sliding of collagen triple helices, and the fibers become more parallel[93, 94]. If the strain remains <4%, the ligament or tendon behaves in an elastic fashion and returns to its original length when un-loaded[71]. Microscopic failure occurs when the strain exceeds 4%. Beyond 8% to 10% strain, macroscopic failure occurs due to intrafibril damage and molecular slippage[88,91,95].

The tensile strength of tendons is related to the thickness and collagen content, and a tendon with an area of 1 cm^2 is capable of bearing 500 to 1,000 kg[73, 96, 97]. Tendons are at the highest risk for rupture if tension is applied quickly and obliquely, and the highest forces are seen during eccentric muscle contraction[90, 98, 99].

Parameters obtained from the curve (Fig. 2) representing structural properties of the ligament or the tendon includes stiffness, ultimate load, ultimate elongation and energy absorbed at failure.

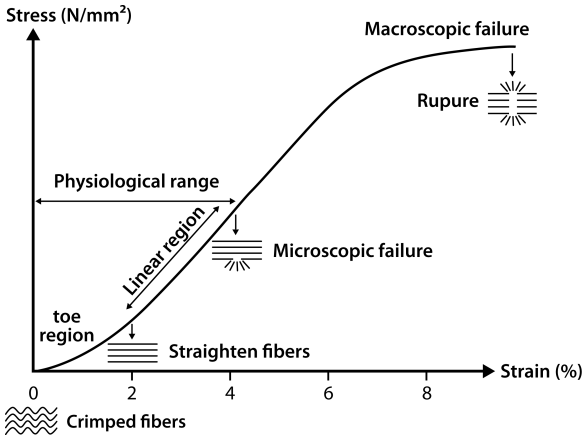

Fig 2. Stress-strain curve demonstrating the basic physical properties of a tendon.

Ligament and tendon healing process

Tendon healing can be largely divided into 3 overlapping phases: inflammation, repair and remodelling phases. During the initial **inflammatory phase**, which lasts about 24 hours, erythrocytes, platelets and inflammatory cells (eg: neutrophils, monocytes and macrophages) migrate to the wound site and clean the site of necrotic materials by phagocytosis. In the meantime, these cells release vasoactive and chemotactic factors, which recruit fibroblasts to begin collagen synthesis and deposition.

A few days after the injury, the **repairing phase** begins. In this phase, which lasts a few weeks, tendon fibroblasts synthesize abundant collagen and other extracellular matrix components such as proteoglycans. These are deposited at the wound site.

After about 6 weeks, the **remodelling phase** starts. This phase is characterized by decreased cellularity and decreased collagen and glycosaminoglycan synthesis. During this period, the repair tissue changes to fibrous tissue, and then this changes to scar-like ligament or tendon tissue after 10 weeks. During the later remodelling phase covalent bonding between the collagen fibers increases, and this results in repaired tissue with higher stiffness and tense or strength. During this phase both the metabolism of the tenocytes and tendon vascularity decline[23].

Rotator cuff tear prevalence

A rotator cuff tear is a disorder associated with pain and dysfunction in the shoulder. There are many reports regarding the prevalence of rotator cuff tears that were revealed in cadaver dissections. However, the frequency of tears varies from 5 to 39%[100-105]. This variation might be due to the differences in the subject population. In addition, the background of the patients with rotator cuff tears, such as the symptoms involving their shoulder and a history of trauma, is unknown due to the limitations of cadaveric research.

There are other reports revealing people with asymptomatic rotator cuff tears[11,42, 106-109]. Many conventional reports have focused on the patients with symptoms, which may be misleading with regard to the entire clinical picture of a rotator cuff tear. Milgrom et al.[42] reported an increased prevalence of partial- and full-thickness rotator cuff tears with increasing age in asymptomatic adults. There was a 50% rate of tears in subjects aged 70 to 79 years, and an 80% rate of tears in subjects > 80 years old. The relatively small number of subjects weakens the validity of this study. The study comprised 90 subjects between the ages of 30 and 89 years. Tempelhof et al.[108] revealed an increased prevalence of rotator cuff tears with increased age without any correlation to sex, dominant arm or level of activity. Furthermore, the epidemiology of rotator cuff tears has not been elucidated.

Ultrasound examination of the rotator cuff

Rotator cuff disease is one of the most common reasons for using ultrasound, and many authors recommend it as a primary imaging technique for soft tissue injuries of the shoulder[110]. The main advantages are the ability to perform dynamic examinations and conduct side-to-side comparisons. Many studies reveal excellent sensitivity and specificity in diagnosing rotator cuff tears[111-116]. The overall accuracy might reach up to 96%[117,118]. There are studies showing a comparable accuracy between ultrasound and magnetic resonance imaging for diagnosis and measurement of rotator cuff tears[119]. Another advantage of ultrasound examination is that the orthopedic surgeons can do it in the office[119].

Standardized technique for examination of the shoulder

The shoulder is a complicated joint to examine. Proper positioning of the patient is important for successful examination. The examination should be systematic with predetermined structures scanned step by step. Typically it begins with the long head of the biceps tendon, which is used as a reference landmark. It is examined both longitudinally and transversely with the patient's forearm resting in a supine position on the thigh.

Medially to the biceps tendon is the subscapularis, which is best examined with the arm in external rotation. Infraspinatus and teres minor are examined by putting the patient's arm across the chest with the hand on the opposite shoulder. Imaging the supraspinatus tendon is obstructed by the overlying acromion. The best way to expose it is to have the patient put his/her hand on the back pocket with the palm toward the gluteal muscle while keeping the elbow directed posteriorly. The tendon is examined in a perpendicular plane, keeping in mind that the axis of the tendon is approximately 45^{o} between the sagittal and coronal planes of the body (Fig. 3).

Because the cuff tendons inserting onto the greater tuberosity are relatively indistinct from each other, it is difficult to distinguish them. One way to separate them is by sequential measurements. The supraspinatus is approximately 1.5-2 cm from the edge of biceps tendon, and infraspinatus forms the next 1.5 cm posteriorly.

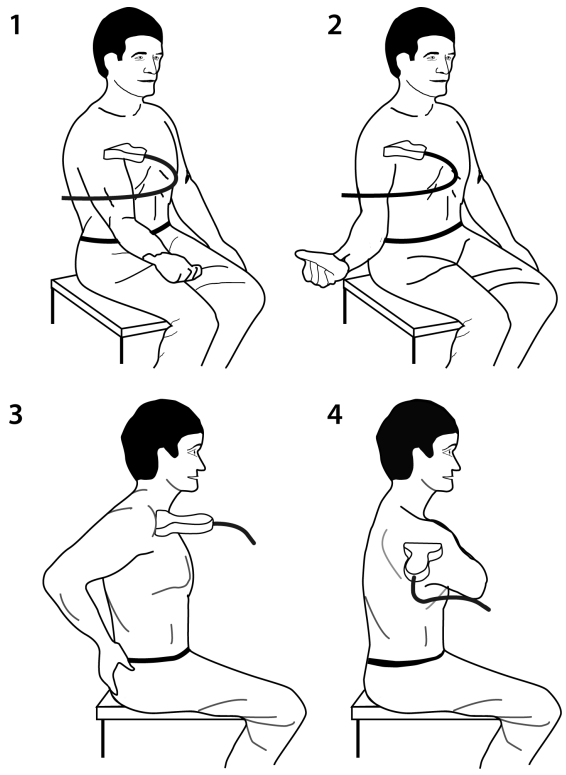

Fig.3. Sequence for rotator cuff ultrasound. 1) Ultrasound transducer placement for imaging the biceps tendon. 2) Ultrasound transducer placement for imaging the subscapularis. 3) Ultrasound transducer placement for imaging the supraspinatus. 4) Ultrasound transducer placement for imaging the infraspinatus and teres minor.

Adhesive capsulitis (frozen shoulder)

Duplay in 1872 first described adhesive capsulitis as periarthritis scapulo-humerale. In 1934 Codman[120] used the term "frozen shoulder". Neviaser[121] in 1945 was the first to use the term adhesive capsulitis. Along the years several terms have been used: frozen shoulder, adhesive capsulitis, periarthritis and pericapsulitis. Considering the pathological changes found in the joint capsule, adhesive capsulitis should preferably be used to describe this condition. This disease is characterized by a spontaneous onset of shoulder pain accompanied by progressive limitation of both active and passive glenohumeral joint movements.

The natural history of idiopathic frozen shoulder syndrome is considered benign. Codman[120] and Grey[122] concluded that the course of frozen shoulder is benign and self-limiting with complete recovery from pain and return of range of motion within a maximum of 2 years from the onset of symptoms. Shaffer et al.[123], on the other hand, reported persistence of symptoms and impaired range of movement in over 50% of their cases when followed up at 3 and 11 years. This long period of pain and disability has been the reason for many different types of intervention.

Frozen shoulder may occur as an idiopathic process or as a result of an underlying disorder that leads to disuse. Rotator cuff tendinopathy, acute subacromial bursitis, fractures about the humeral head and neck, and paralytic stroke are relatively common predisposing factors for the development of frozen shoulder. Diabetes mellitus is also considered as a frequent cause of adhesive capsulitis[124].

The prevalence of adhesive capsulitis is 2–5% in a normal population[125,126]. It is most frequent in females and in patients over 40 years[121]. A genetic[127] component is reported even if the direct mechanisms by which genes might influence soft tissue disorders are still unknown. Contra-lateral shoulder involvement occurs in up to 20–30% of the patients. Recurrence in the ipsilateral shoulder is rare[126].

Pathogenesis

The etiology of adhesive capsulitis is still unknown. Bulgen in 1976[128] found HLA B27 more common in patients with adhesive capsulitis, but this has not been confirmed in subsequent studies[129]. Rodeo et al.[130] in 1997 demonstrated increased deposition of cytokines as transforming growth factor, platelet derived growth factor and tumor necrosis factor-alpha in the synovium and in the capsule of the adhesive capsulitis group compared to a control group. They postulated that cytokines might be involved in the fibrotic and inflammatory process. Especially the matrix-bound transforming growth factor-beta may act as a persistent stimulus, resulting in a capsular fibrosis. Lundberg[131] documented periarticular inflammatory changes and thickening of the joint capsule without intra-articular adhesions. Rizk et al.[132] discovered thickening and constriction of the capsule. Ozaki[133] found a contracted and hypertrophied coracohumeral ligament. Neviaser[134] described the hypothesis that the underlying pathological changes are synovial inflammation with subsequent reactive capsular fibrosis.

Diagnosis

The most used criteria are the following:

- Painful stiff shoulder for at least 4 weeks
- Severe shoulder pain that interferes with activities of daily living
- Night pain
- Painful restriction of both active and passive range of motion
- Normal plain x-ray
- Arthrography was the investigation of choice for years. Joint volume less than 10 ml and a marked loss of the normal axillary fold[122]

MRI and capsulitis

The imaging findings of adhesive capsulitis have been previously limited to conventional arthrography. The arthrographic criteria of adhesive capsulitis include the following: limited injectable fluid capacity of the glenohumeral joint (7–10 ml), a small dependent axillary fold, and irregularity of the anterior capsular insertion at the anatomic neck of the humerus[135,145].

Recently, MRI features have been helpful in the diagnosis of adhesive capsulitis. The overall specificity has been relatively disappointing for the disease[46, 137-139]. Most of the reports have included MRI images obtained with either indirect (intravenous) or direct (intraarticular) arthrography[140-142]. Emig et al.[46] reported a thickening of the joint capsule and synovial membrane in the axillary recess in a T1 oblique coronal plane of adhesive capsulitis

shoulders without intravenous Gd-chelate injection. Tamai and Yamato[139], using dynamic MRI, showed that the synovium in adhesive capsulitis differed from that in normal shoulders.

Thickening of the joint capsule and synovial membrane:
– In the axillary recess: measured by the widest portion of the capsule and synovial membrane at its insertion at the humeral head perpendicular to the adjacent cortical bone, according to Emig[46], on a coronal T1-weighted spin-echo and a coronal T1-weighted spin-echo Gd-chelate-enhanced sequence (Fig. 4a). Normal reference ranges, however, for asymptomatic joint capsule and synovial thickness, have been previously determined to be 2.9mm or less[46].

– In the rotator interval: measured by the widest portion of the capsule and synovium at the central part of the rotator interval perpendicular to the adjacent humeral head cortex, according to Emig, Vahlensieck, Tetro and Merila[46,143-145], on a sagittal T1-weighted spin-echo Gd-chelate-enhanced sequence (Fig. 4b). The rotator interval is located in the concavity of the coracoid process. Its contents include the coracohumeral and superior glenohumeral ligaments, which are distinct structures surrounded by fatty tissue[143].

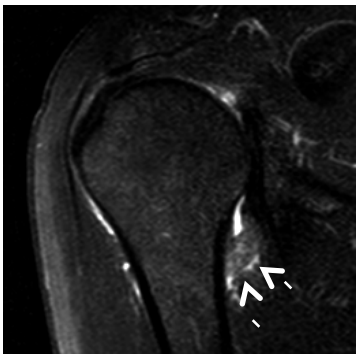

Fig 4a
Coronal oblique MR image taken posteriorly shows thickened axillary pouch (arrows).

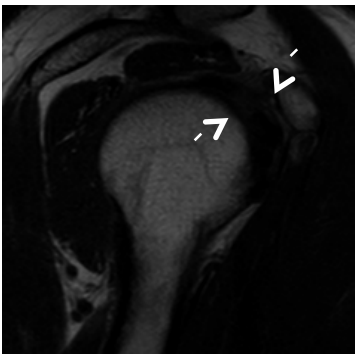

Fig 4b
MR image shows enhancement of the rotator interval lesion (arrow) which sits above the subscapularis tendon

Treatment

Several treatment modalities have been tried over the years. The use of corticosteroids did not make any difference in long-term outcome as compared to physiotherapy even if they could provide some pain-relief[146]. Arslan et al.[147] reported that local steroid injection therapy was as effective as physical therapy for the treatment of adhesive capsulitis. The improvement in range of motion at the end of the study was similar in both groups. Physiotherapy alone is an effective treatment, but it is also a complement to other therapies, especially to improve the range of motion in external rotation[148-150]. There are many controlled studies describing the effectiveness of physiotherapy in patients with adhesive capsulitis of the shoulder. However, methodological flaws, such as small number of subjects, high dropout rates and a short follow-up, limit the interpretation of the results of all of these studies[148,151-153].

Distension arthrography described by Andren[154] in 1965, appears to be another good therapeutic intervention for achieving rapid symptomatic relief from adhesive capsulitis[154,155]. It consists of an injection of a saline solution causing the rupture or dilatation of the capsule by hydrostatic pressure. This might be combined with corticosteroid injections in some cases.

Manipulation under anesthesia is normally used in patients resistant to physiotherapy, and it can reduce the period of pain and disability[156,157]. However, this might be associated with some risks such as dislocation, fracture, nerve palsy and rotator cuff tear.

Reichmister and Friedman[158] performed a retrospective study of 38 shoulder manipulations in 32 patients. These patients were followed for an average of 58 months. The patients were examined in a follow-up for combined shoulder range of motion, external and internal rotation strength and status of the long head of the biceps. In this series, 97% of patients had relief of pain and recovery of near complete range of motion.

Hill and Bogumill[159] studied 17 patients who were followed up for a mean of 22 months, and they found that 70% had returned to work in less than 6 months and had improved motion and no complications. A recent study Farrell et al.[156] showed that manipulation under anesthesia leads to sustained improvement in shoulder motion and function at a mean of 15 years after the procedure.

Arthroscopic capsular release has become a reliable method for restoring range of motion in patients for which physical therapy and manipulation have failed[160]. Arthroscopy has been considered useful to confirm the diagnosis, to exclude other significant pathologies, to classify the stage of the

condition, and to treat the stiff shoulder in combination with or without manipulation[161]. It might also be recommended in diabetics or in patients with post-operative or post-fracture frozen shoulder[162].

Segmuller et al.[163] treated 24 patients with 26 shoulders by arthroscopic capsular release. At 3.5-month follow-up 76% demonstrated return to normal or near normal function, 50% had residual loss of internal rotation and 87% achieved a good/excellent result using the Constant scoring system.

Other treatments, such as the suprascapular nerve block, might also be useful in some patients in combination with steroids, especially when pain control is particularly difficult[164,165]. Dahan et al.[166] stated that the use of bupivacaine suprascapular nerve blocks was effective in reducing the pain at 1-month follow-up.

Aims of the studies

Study I

Since collagen type I is a major protein constituent of cruciate ligaments, joint capsules and tendons, we hypothesized that a polymorphism in COLIA1, might be associated with soft tissue injuries such as cruciate ligament ruptures and shoulder dislocations.

Study II

To test the hypothesis that point fixation, as with suture anchors, might result in better healing and better biomechanical properties than when the soft tissue is compressed against the bone with a flat surface, e.g. with a screws with washers or tags.

Study III

To assess the prevalence of rotator cuff tears in a population aged 50-75 years, who had not previously sought for complaints from their shoulders. To determine if there is any relationship between dysfunction measured by Constant score and the presence of cuff tears detected by ultrasound, and to identify any characteristic changes on plain radiology that might correlate to rotator cuff tears.

Study IV

To study if MRI can demonstrate reactions of the shoulder joint capsule and the cause of persistent suffering of some patients following arthroscopic subacromial decompression with or without concomitant resection of the acromioclavicular joint. To correlate the MRI findings with the clinical assessments over time.

Materials

Study I

All patients treated between 1999 and through 2003, at the Orthopedic Department of Uppsala University Hospital due to an established cruciate ligament rupture or confirmed shoulder dislocation, were invited to participate in our study. A total of 358 patients (age 15-60 years) accepted, whereas only three declined participation. Of the 358 cases, 233 suffered from damage of the cruciate ligament and 126 had had a shoulder dislocation, i.e., one had both diagnoses. As a control group for the present investigation we used a previously described cohort randomly selected from the population register[167], 325 females, aged 19-39 years with whole blood samples.

Study II

10 skeletally mature New Zealand White rabbits (5 male) weighing 4.4 (4.0–4.8) kg were used. Special plates were designed and made by an instrument maker. The plates were made of stainless steel and shaped to conform to the proximal part of the rabbit tibia, where the medial collateral ligament inserts. The plates were identical in shape, except that half of the plates had 5 pegs of 1 mm height and diameter on the undersurface, resembling point fixation (Fig.5a). The other half had a smooth flat undersurface, resembling fixation with a compression device (Fig.5b). The plates were fixed to the tibia with two 1.5-mm AO cortical screws.

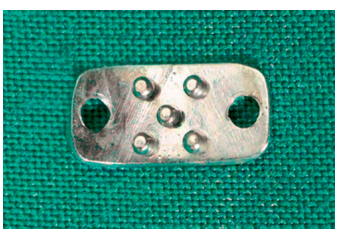

Fig. 5a. Plate with pegged undersurface

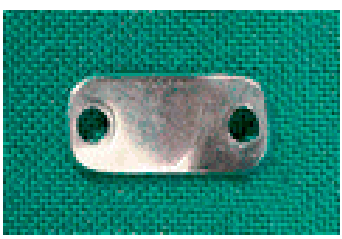

Fig 5b. Plate with flat undersurface

Study III

Between September 2007 and December 2009, subjects for this study were recruited through a questionnaire that was given to patients and the relatives who accompanied them when they sought our hospital outpatient clinics for specialities other than orthopedics. A written questionnaire was specifically directed to elicit any history of pain from their shoulders. All subjects aged 50-75 (median 66) years, were contacted and asked to participate in this research project. The participation was voluntary. Those who had previously received medical care or any kind of treatment for their shoulder pain were excluded. 106 (54 female and 52 male) subjects met the criteria to be enrolled in the study.

Study IV

Forty-eight consecutive patients aged 33-77 (median 56) years that had subacromial impingement with or without concomitant acromioclavicular joint arthritis, were included in this study. Patients with clinical signs of rotator cuff tear or adhesive capsulitis were excluded. Twenty-two patients had a painful acromioclavicular joint with positive compression sign. The dominant side was affected in 26 patients.

Methods

Study I

Blood samples were collected from the participants to determine the genotype at the collagen 1α1 Sp1 polymorphism. Joint laxity according to Carter-Wilkinson was determined[168]. Leisure physical activity (none, < 1 hour per week, 1-2 hours per week or >2 hours per week) in recent years and during the teenage was determined by a questionnaire. The gene for the collagen 1 type 1α is located on the autosomal chromosome 17, and not on the sex chromosomes. Therefore, the collagen gene is inherited in a similar way in both men and women. Therefore, we did not feel that it would pose a problem to compare the results of the (all female) control group with those from the (both male and female) participants. Weight and height were measured for all participants.

Genotyping for the collagen Iα1 Sp1 polymorphism

Genomic DNA from each individual was extracted from 3 ml of whole blood using a Wizard Genomic DNA purification kit (Promega Corporation, Madison, WI, USA). The genotype of each individual was determined using solid phase minisequencing 169-171. Polymerase chain reactions (PCR) were run on a Gene Amp PCR system-9700 robot using Ampli-Taq Gold® kits and standard reagents (Perkin Elmer Co, Norwalk CT, USA.). The polymorphic nucleotide was detected in the captured DNA strand by single-base extension of the primer GTCCAGCCCTCATCCCGCCC with ^{3}H-labeled nucleotides, the primer anneals immediately adjacent to the polymorphic site. The genotype of the individual is defined by the ratio between incorporated ^{3}H-labelled nucleotides.

Study II

Types of fixations

A good healing of ligaments and tendons to bone is best achieved by close fixation to the bone. This might be done either by pressing the tissue against the bone or suturing the tissue to the bone.

Suture Anchors

Suture anchors are very useful fixation devices for fixing tendons and ligaments to bone. They are made up of:

1. **The Anchor** - which is inserted into the bone. This may be a screw mechanism or interference fit. They may be made of metal, plastic or biodegradable material (which dissolves in the body over time).
2. **The Eyelet** - is a hole or a loop in the anchor through which the suture passes. This links the anchor to the suture.
3. **The Suture** - is attached to the anchor by passing through the eyelet of the anchor. It also may be a non-absorbable material or absorbable material (Fig.6).

Suture tags

Suture tags achieve fixation by pressing the soft tissue to the bone. They can be made of either nonabsorbable or biodegradable materials (Fig.7).

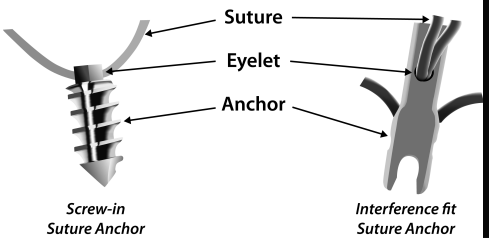

Fig 6. Suture anchors

Fig 7. Suture tags

Surgical procedure and treatment

The rabbits were sedated with fentanyl fluanisone (Hypnorm Janssen Pharmaceutica, Beerse, Belgium; 0.1–0.2 mg/kg body weight) subcutaneously. Under general anesthesia using isoflurane gas (Forene; Abbot Scandinavia, Solna, Sweden) and oxygen, the rabbits were operated on both the right and left knee. Surgery was performed under standard aseptic conditions. The skin was shaved, and prophylactic antibiotics (dicloxacillin) and analgesics in the form of 0.015 mg buprenorphine (Temgesic; Schering-Plough, Brussels, Belgium) were given preoperatively by subcutaneous injection. A 3-cm skin incision was made midway between the medial collateral ligament (MCL) and the patellar tendon insertion. The MCL was exposed, the synovial bursa under the ligament removed and the cortical bone roughened with a rasp proximal to the distal insertion of the ligament. A 3-0 nonabsorbable suture was passed under the ligament and pulled distally as far as possible to mark the insertion on the tibia without compromising it. The plate then fixed the ligament portion proximal to the suture and beneath the joint line. The plate was fixed to the bone with two 1.5-mm AO screws, one on each side of the ligament. The plate with pegs was used on the right side, and on the left side the plate with a flat undersurface was used. The skin was closed with a 4-0 etylon suture intracutanously. Minimal bleeding was observed during the operations. After the operation, the rabbits were housed 1 per cage (0.5 m^2) and activity was allowed only in the cages. They received analgesia with Temgesic, 0.03 mg/kg twice daily for 3 days postoperatively. The condition of each rabbit was documented in an individual rabbit journal on a daily basis.

Evaluation

The rabbits were sacrificed 28 days after the operation using an overdose of pentabarbitural injected intravenously. Each knee joint was harvested by transecting the femur just below the trochanteric region and the tibia above the ankle. The MCL attached to the femur and the tibia was isolated, while the remaining soft tissue was removed. Before removing the plate, a transverse cut was made through the MCL adjacent to the distal border of the plate, proximal to the original insertion of the MCL (marked with the nonabsorbable suture) (Fig. 8a). This enabled us to test the mechanical properties of the ligament fixation in the area under the plate. The knee was fixed to a material testing machine (100R, DDL Inc., Eden Praire, Mn, USA) using 1.6 mm Kirschner wires inserted into drill-holes made in the femur and tibia (Fig. 8b). Testing was performed within a few hours after the rabbit had been killed. In that time interval it was kept cool and wet. A constant distension in the direction of the MCL with a speed of 1 mm/sec was applied until failure. We recorded the peak force at failure, stiffness and energy uptake until the force dropped to 90% of maximum (Fig. 9).

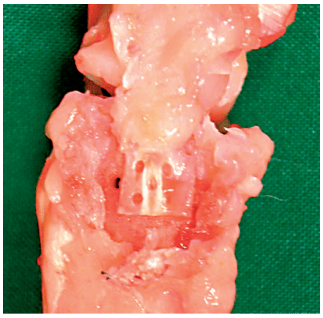

Fig 8a. MCL after preparation, before mechanical testing

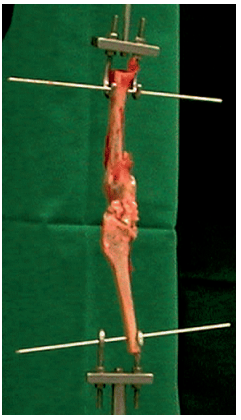

Fig 8b. Mechanical testing

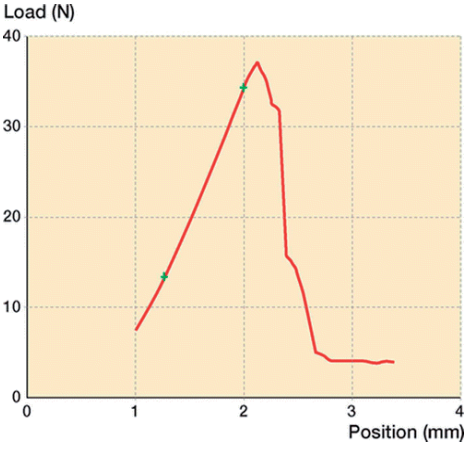

Fig 9. Load-displacement curve for a specimen with pegged plate

Study III

Clinical examination was performed and consisted of measurement of Constant score on each shoulder. Bilateral ultrasound examination was performed according to a standard protocol using a Philips HDI 5000 (Bothell, WA, USA), with a 12 MHz linear-array transducer. All tendons were examined, both in longitudinal and transverse plane. Then a conventional x-ray examination of each shoulder was done. It included a standard anterioposterior view with the glenoid in its absolute profile and the head of the humerus in neutral position. We listed different areas to be examined, including the presence of osteoarthritis of the glenohumeral and acromioclavicular joints, the acromion index (AI) according to Nyffler et al.172 (Fig. 10) and the subacromial index (SAI) (Fig. 11).

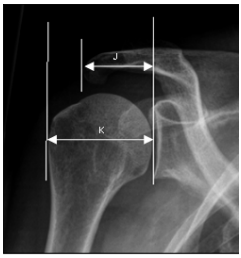

Fig. 10
Measurement of acromion index
AI=J/K

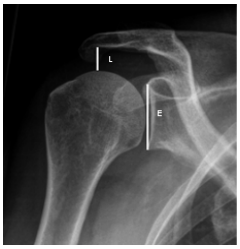

Fig. 11
Measurement of subacromial index
SAI=L/E

Study IV

An MRI of the affected shoulder was done preoperatively and at 3 months after surgery. Preoperatively, patients with cuff tears, osteoarthritis of the glenohumeral joint, labrum injuries due to instability, diabetes mellitus or rheumatoid arthritis were excluded from the study.

A scoring system for the MRI was obtained, giving two points for edema of the axillary capsule, two points for thickening of the axillary capsule, two points for the pericapsular edema and one point for the rotator interval edema. A total score of seven points indicated a maximum value for adhesive capsulitis.

Surgical technique

The operative procedure was a modification of the technique described by Ellman[173]. All procedures were performed in the beach chair position, under general anaesthesia or long acting scalene block, with the arm in forward traction. The passive range of motion was first assessed without any attempt for manipulation. The arthroscope was introduced through the posterior portal and the subacromial space inspected. An anterior acromioplasty was performed with a motorized resector. The adequacy of the decompression was judged by introducing a straight blunt probe through the posterior portal. This determined whether the undersurface of the acromion was flat and the anterior hook of the acromion had been eliminated. For those patients who had symptomatic arthritic changes in the acromioclavicular joint, an arthroscopic resection of the lateral end of the clavicle was done through an anterior portal.

Follow-up assessments

The clinical assessments by measuring the Constant score and Subjective Shoulder Value were done before surgery, at 3 months and at 6 months after surgery. A follow-up interview of the Subjective Shoulder Value was done by an independent secretary two years after surgery.

Two musculoskeletal radiologists independently evaluated the MR images. The images were evaluated in the same manor regardless if they were pre- or postoperative.

Statistics

Study I

The injury risk, associated with the three genotypes of the collagen 1α1 gene, was analyzed with the SS genotype as the reference. For these associations, we used age-adjusted unconditional logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CIs). We also considered including body weight and height, or body mass index, in the age-adjusted model, but that gave only marginal influences on our estimates. Consequently, we only present results from the age-adjusted model, with age in continuous form. Statistical analyses were carried out using SAS software (version 9.1, SAS institute Inc., Cary, NC, USA).

Study II

We used Wilcoxon's signed-rank sum test to compare the flat and pegged sides. Confidence intervals for the median difference between the sides are based on the observations with rank 2 and 9, which yields approximately 90% confidence[174].

Study III

Each subject contributed with both shoulders in the study. A mixed model approach was used to address the issue of the correlated shoulders and adjust for the variance of the bilateral observations. Mixed effects logistic regression was implemented to model the relationship between the variables. Many of the analysis dealt with the Constant score as the dependent variable with one other factor as an independent variable. Unpaired t-test was used for the correlation between the presence of full-thickness cuff tear and osteoarthritis. The significant level was set to $p<0.05$.

Study IV

The data were set up as longitudinal data with each visit corresponding to a visit on a timeline. A biased corrected weighted kappa score using bootstrapping was used to assess the correlation between the MRI scores of the two raters pre- and post surgery. Spearman's test was used for the correlation between the MRI scores and Constant score at baseline and three months after surgery. Standard ANOVA was used to evaluate a possible difference in the mean values for the three Constant scores. The same analysis was done for the mean values for the Subjective Shoulder Values at each time point. For the relationship between the change in external rotation and the change in MRI score from the baseline to three months, simple linear regression was used.

Results

Study I

The control group consisted only of females whereas the case group is presented according to sex. The genotype distribution among the controls was 71% SS, 25% heterozygotes Ss and only 4% ss. The polymorphism genotype in the study cohorts was in Hardy-Weinberg equilibrium. This equilibrium is a common test in genetic epidemiology. It measures the chance of a skewed genotype distribution. If the genotype distribution is not in Hardy-Weinberg equilibrium, there is a risk of selection bias in the study. Cases and controls had a similar age distribution. Female and male cases had a similar genotype distribution, and only one female and one male case had the ss genotype.

There was an 85% reduced odds ratio (95% CI 34-97%) of an injury for those with the rare ss genotype as compared to those with the genotype SS (Table 1). We observed a similar reduction in risk for cruciate ligament ruptures and shoulder dislocations. No significant difference in injury risk was observed among those with the Ss genotype as compared with the homozygotes with the SS genotype.

Table 1. Age-adjusted odds ratios with 95% confidence intervals (95% CI) of having a cruciate ligament injury or a shoulder dislocation according to procollagen Ia1 Sp1 genotype.

Injury	Genotype	Cases	Controls	Odd ratio (95% CI)
All	SS	257	230	1.0
	Ss	99	83	1.06 (0.76-1.49)
	ss	2	12	0.15 (0.03-0.68)
Cruciate ligament rupture	SS	162	230	1.0
	Ss	70	83	1.19 (0.82-1.75)
	ss	1	12	0.12 (0.02-0.92)
Shoulder dislocation	SS	95	230	1.0
	Ss	30	83	0.88 (0.54-1.41)
	ss	1	12	0.20 (0.03-1.56)

Study II

No animals were excluded. All the wounds healed uneventfully, and the rabbits loaded their hind limbs immediately postoperatively. Gross inspection of the knee joints at the harvest showed that the plates were covered by fibrous material similar to tendon callus (Table 2). Rabbit no. 7 was an outlier, probably due to malplacement of one screw through the ligament on the pegged plate side. In the other 9 animals, the force at failure, stiffness and energy uptake were always higher on the side with the pegged plate. Analyzing all 10 animals, the force was 133% higher on the pegged side (range –24 to 342; 90% CI for median 51–322%). Stiffness and energy were increased by 75% and 210%, respectively. (Stiffness: range –22% to 426%; 90% CI for median 8–260%. Energy uptake: range 79% to 659%; 90% CI for median 90–515%).

Table 2. Mechanical results of flat or pegged plates in all rabbits

Animal	**Force at failure (N)**			**Energy uptake (Nmm)**			**Stiffness (N/mm)**		
Attachment plate	**flat**	**pegged**	**diff**	**flat**	**pegged**	**diff**	**flat**	**pegged**	**diff**
1	**16**	**39**	**23**	**9**	**57**	**48**	**16**	**17**	**1**
2	**9**	**39**	**30**	**7**	**29**	**22**	**8**	**29**	**21**
3	**19**	**29**	**10**	**21**	**19**	**-2**	**15**	**26**	**11**
4	**7**	**24**	**17**	**12**	**21**	**9**	**3**	**18**	**15**
5	**18**	**38**	**20**	**16**	**28**	**12**	**16**	**28**	**12**
6	**19**	**37**	**18**	**21**	**29**	**8**	**21**	**29**	**8**
7	**69**	**51**	**-18**	**79**	**62**	**-17**	**35**	**27**	**-8**
8	**17**	**77**	**60**	**18**	**91**	**73**	**15**	**38**	**23**
9	**11**	**33**	**22**	**14**	**34**	**20**	**10**	**23**	**13**
10	**36**	**69**	**33**	**30**	**93**	**63**	**26**	**31**	**5**
Min	**7**	**24**	**-18**	**7**	**21**	**-17**	**3**	**17**	**-8**
Med	**18**	**39**	**21**	**16**	**32**	**29**	**15**	**28**	**16**
Max	**69**	**77**	**60**	**79**	**93**	**73**	**35**	**38**	**23**

Study III

Among 106 subjects, 64 (60%) had complaints from their shoulders. 19 had bilateral symptoms, 32 on the right and 13 on the left side. There were 25 men and 39 women. The prevalence of a full-thickness cuff tear was 30% (32/106) and a partial-thickness tear, 20% (22/106). All shoulders with full-thickness tears had tears on the supraspinatus tendon. When the prevalence was calculated on the bases of each shoulder, we found a prevalence of 21% (44/212) for full-thickness tears and 14% (29/212) for partial-thickness tears. A significant result was found between complaints and full-thickness tears. Those who had full-thickness tears had 3.7 times higher odds of having complaints than those without cuff tears (CI 1.4-10.0). No relationship was found between shoulder complaints and partial tears (Table 3).

Constant score was higher in shoulders without complaints than in shoulders with complaints. Those who had complaints had a Constant score that was 7.3 (CI 4.0-10.6) points lower than those without complaints. The difference was significant between the full-thickness tear group and the other two groups (Table 4). The average Constant score for subjects with full-thickness cuff tears was 7.9 (CI 3.7-12.1) points lower.

No correlation was found for the acromion index among the subjects with full-thickness supraspinatus tears, subjects with partial-thickness tears, and those without tears. However, the subacromial index was correlated with full thickness supraspinatus tears (Table 5). The ratio was 0.025 (CI 0.002-0.048) lower for full-thickness tears. The acromion index was lower for the group with primary osteoarthritis than the group with full-thickness tears ($p<0.01$), but the subacromial index did not differ significantly ($p=0.6$) (Table 5).

Table 3. Numbers of subjects with/without symptoms in relation to cuff tears and arthritis.

	Symptomatic (n.)	Asymptomatic (n.)	Total (n.)
Normal cuff	47	92	139
Partial tears	9	20	29
Full-thickness tears	27	17	44
GH osteroarthritis	9 + 2 tear arthropathy	8	19
AC joint arthritis	28	40	68

GH = glenohumeral. n = number of patients.

Table 4. Constant score in relation to symptom complaints and rotator cuff tears.

	Number of shoulders (n.)	Constanta score
No complaints	129	82 (CI 80-84)
Complaints	83	68 (CI 64-71)
No cuff tears	139	78 (CI 76-81)
Partial-thickness tears	29	80 (CI 80-84)
Full-thickness tears	44	69 (CI 63-74)

CI = Confidence Interval.

Table 5. Acromion and subacromial indices in relation to rotator cuff tears and glenohumeral arthritis.

	Acromion Index (AI)	Subacromial index (SAI)
No tears or partial tears	0.65 (CI 0.63-0.66)	0.28 (CI 0.27-0.29)
Full-thickness tears	0.66 (CI 0.64-0.68)	0.26 (CI 0.24-0.28)
Glenohumeral arthritis	0.60 (CI 0.56-0.64)	0.27 (CI 0.24-0.30)

CI = Confidence Interval.

Study IV

Although there were significant differences between the MRI scores pre and post surgery for both raters, this was not clinically important since the Kappa scores for the two MRI raters were 0.498 (CI 0.305-0.690) before surgery and 0.295 (CI -0.006-0.490), which shows a poor reliability between the raters. The relationship for the Constant score and MRI scores after surgery was not significant. The differences between the average Constant scores preoperatively, at 3 months, and at 6 months after surgery were significant, 46 (CI 41-51), 70 (CI 66-74) and 77 (CI 73-81), respectively. In addition, the differences in average Subjective Shoulder Values were significant for all visits and even for the two-year follow-up, 50 (CI 45-55), 69 (CI 63-75), 76 (CI 70-82) and 97 (CI 96-99), respectively. No relationship was found between the changes in external rotation and MRI scores over the time period studied (Fig. 12, 13).

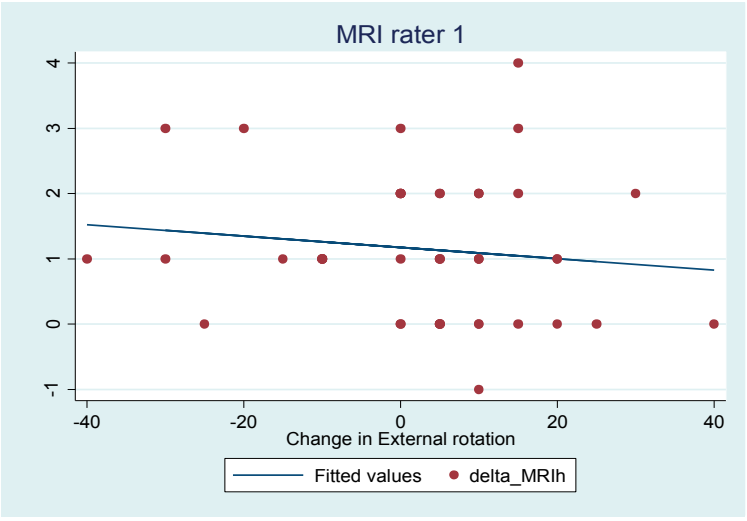

Fig12. Correlation between the change in external rotation and MRI score pre- and at three months postoperatively for rater one

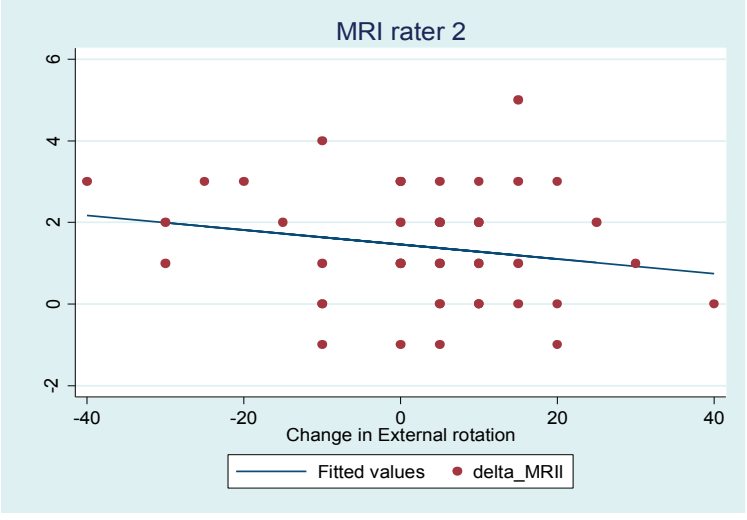

Figure 13. Correlation between the change in external rotation and MRI score pre- and at three months postoperatively for rater two.

General discussion

The shoulder is one of the largest and most complex joints in the body. It is a multi-axial ball-and-socket type of synovial joint with a large range of movement, and this is due to the limited interface between the head of humerus and the shallow glenoidal fossa. The joint is protected against displacement by numbers of tendons and ligaments, which surround it. The behavior of the soft tissues plays an important role in the overall function of the shoulder joint. The available information on the soft tissue structural and biomechanical properties is mainly based on animal models, which may be of limited value. However, with newly developed techniques it is possible to study the genetics of soft tissue injuries and the characteristics of the healing properties of both tendons and ligaments.

This thesis presents new information regarding the structural and mechanical properties of tendinous injuries, based on understanding the genetic properties of the collagen, which is the main protein constituent of the tendon and ligament structures. Besides this, this thesis improves understanding of the mechanical properties of different types of repair methods and the post-repair reactions of these structures.

Understanding the biology of tendon-to-bone healing may offer novel therapeutic options to improve the rate of long-term structural healing. Rotator cuff healing occurs by reactive scar formation rather than by regeneration of a histologically normal enthesis. The poor healing response is multifactorial but could be related to insufficient and disorganized expression of cytokines to direct formation of a complex healing structure. Other factors may include the presence of inflammatory cells at the tendon-bone interface that precipitates scar formation. The inflammatory response that occurs in adult healing leads to a gene expression program that results in scar-based healing rather than the formation of the native insertion site, unlike the complex signaling that occurs during embryologic development[175]. During the healing process, the activation of fibroblasts results in the expression of many cytokines, which enhances healing in different biological processes. These cytokines have the potential to improve tendon-to-bone healing through their role in cell proliferation, matrix synthesis and cell differentiation[176].

Remarkable advances have been made in understanding the human gene contribution to health and disease. Large scale genetic studies have made it possible to measure associations between single-nucleotide polymorphisms and the occurrence of genetically complex diseases. Type 1 collagen is the most abundant protein in the body, and it is synthesized by fibroblasts, osteoblasts and odontoblasts[177]. Although bones, ligaments and joint cartilage contain this common collagen type, various reports have described different locations for the regulation of the promoter region that control transcription of COLIA1[177]. One such location is the Sp1 transcription factor-binding site of the COLIA1 gene. One of the most widely studied polymorphisms in relation to bone quality is the Sp1 polymorphism in the COLIA1 gene[178], which has been associated with low bone mass[179-181], osteoporotic fracture risk in postmenopausal women[182] and female children[183] and osteoarthritis[19]. Functional analysis has shown that the osteoarthritis- and osteoporosis-related s allele of the Sp1 polymorphism is associated with increased DNA–protein binding, increased transcription from the s allele, and increased production of the collagen type I α1 mRNA and protein[18].

Even though the s allele of the Sp1 polymorphism is associated with an increased production of collagen type 1 α1 chains, it is still unclear how the ss genotype would reduce the odds of having a soft tissue injury. Nevertheless, the results from our study on Sp1 polymorphism in the COLIA1 gene are in accordance with studies done in South Africa on anterior cruciate ligament and achilles tendon ruptures[16,183].

This type of polymorphism is not only associated with musculo-skeletal diseases. Over one fourth of women with cervical insufficiency have a family history of cervical insufficiency, and the COLIA1 Sp1 binding site polymorphism has been associated with the condition[184]. Furthermore, otosclerosis, the single most common cause of hearing impairment in white adults, has also been associated with polymorphisms in the COLIA1 gene[185].
Soft tissue injuries might be polygenic with different types of polymorphisms in nature.
Nowadays, it is possible to perform whole-genome association studies and not just the candidate SNP approach used in our preliminary report. Therefore, attempts to identify several possible genes and genetic pathways by whole genome sequencing associated with these soft tissue injuries are feasible in order to define genetic mechanisms behind the predisposition to soft-tissue injuries. Secondarily, there might also be an interest to find out the genetic susceptibility of healing impairment of these injuries. These types of investigations will increase the understanding of possible intrinsic risk factors for these injuries and may influence prevention, treatment and rehabilitation programs for these injuries.

The rotator cuff is a composite of tendons around the shoulder joint. Rotator cuff insufficiency has been defined as a condition in which interference with the cuff's function prevents it from fulfilling its physiological role. There are many reports regarding the prevalence of cuff tears that were revealed by cadaveric dissections, but most of these were deficient from data about the history and level of activity before death. Recently MRI or ultrasound imaging has enabled in-vivo assessment of the rotator cuff tear prevalence.

Tempelhof[108] conducted an ultrasound prevalence study of asymptomatic shoulders, and he found prevalences from 23 to 51%, increasing over the age from 50-80 years of age. Milgorm[42] demonstrated that the prevalence of partial- or full-thickness tears increases significantly after the age of 50 years. The prevalence in our study was based on a population who had not sought any medical advice for their shoulders. The prevalence was comparable with previous reports[42,108]. We believe that this prevalence would be even higher if we include a real true population regardless if they hade sought before or not for shoulder complaints. This means that the adage "grey hair equals cuff tear" could be true, and that the cuff tears are to be regarded as a normal part of the aging process.

We also found that shoulders with full-thickness cuff tears had lower functional outcome measured by Constant score. This can be supported by the facts reported in the literature[107,108]. They noted that the Constant score was lower for patients who had tears in rotator cuff despite that they were asymptomatic in their shoulders. These findings may raise the question of whether the symptoms may develop over time in patients who previously did not have symptoms. Yamaguchi[186] studied this fact and found that 51% of these patients developed symptoms and had a significant decrease in activity of daily living over a mean of 2.8 years.

Regarding partial-thickness cuff tears, however, there were no differences in Constant score when compared with shoulders without any cuff tears. We often notice in our practice these types of tears on MRI, but these tears have no relevance for the shoulder dysfunction, and they do not need to be repaired. Partial-thickness cuff tears could be compared to degenerative meniscal tears in the knee, which are considered part of the degenerative osteoarthritic changes associated with aging[187].

Plain x-ray is a simple investigation, and it is often the first modality employed to investigate patients seeking for shoulder complaints. A lot of information could be gained from this investigation such as changes associated with rotator cuff tears. Neer[103] established a correlation between subacromial impingement and changes on x-ray. Morrison and Bigliani[188] reported increased hooked acromions in cadavers with cuff tears. They stated that the

acromion types were innate anatomical variations and remained unchanged during life. These morphological classifications are often criticized as being subjective and showing poor interobsever reliability. Zuckerman[189] reported only a fair level of agreement between three orthopaedic surgeons when they assessed the acromion types. Bright[190] found only 18% agreement between six observers.

Recently some authors have concentrated on both the morphology of the acromion in relation to the humeral head and the biomechanical effect, which is expected from this morphology. Nyffler et al[172] described the ratio between lateral extension of acromion and humeral head width as a predictor of rotator cuff tears. They predicted that it is not the frictional effect that is considered to be the primary cause of the changes in the rotator cuff but rather a biomechanical one. The lateral extension of the acromion influences the orientation of the deltoid muscle force vector. The larger the lateral extension the higher the ascending force component of the force vector. Small lateral extension leads to larger compressive force, which could be a predisposing factor for the development of glenohumeral osteoarthritis. The ascending force can cause upward migration of the humeral head. Depending on this theory and the fact that one of the outcomes after rotator cuff tear is that the humeral head migrates upward, which leads to a narrowing of the subacromial space, we tried to find a predictive factor on x-ray depending on the measurement of the space between the under surface of the acromion and the top of humeral head. To avoid the bias, which can occur by different magnifications of x-rays, we calculated a ratio between the subacromial space and the length of the glenoid (subacromial index). We found a lower index for full-thickness cuff tears than for partial-thickness tears or shoulders without tears. We took into consideration that partial tears will not affect the wideness of the subacromial space. We also found a significant difference between shoulders with full-thickness tears and those, which had osteoarthritic changes. More research is needed to evaluate these two indices, especially to find a breakpoint along the range of indices that can predict the presence and absence of rotator cuff tears.

The healing property of tendons and ligaments to bone is an important issue for the orthopaedic surgeons in order to obtain an optimal result. A controversy exists regarding the most favorable fixation technique. Regarding the rotator cuff, some studies have reported that suture anchors are weaker than interosseous tunnels[191], while others have reported higher fixation strength with suture anchors[192]. Previously the repair of the rotator cuff was achieved by osteosutures. After the development of arthroscopic technique many kinds of fixation materials have been developed, such as suture anchors. The arthroscopic technique is more difficult than open repairs because all surgical steps have to be performed through cannulae and holes through the mus-

cle layers. Therefore, the repaired tissue will usually be attached to the bone surface rather than to a trough in the bone. The healing might be expected to be more difficult to achieve, because the bone surface appears less vascularized, and, if the periosteum is scraped off, there are probably fewer progenitor cells. However, in a goat model, no difference was found in the healing process or in the mechanical properties between tendon healing to cortical and cancellous bone[193].

There are several key biomechanical factors that may influence the results of soft tissue repair. The repair should be strong enough to resist the early structural failure and high footprint contact pressure to assist biological healing. This will be achieved by creating multiple contact points between the soft tissue and the bone surface. A literature review found significantly lower re-tear rates for double-row repairs of the rotator cuff tears as compared with single-row for all tears greater than 1 cm[194].

As mentioned before, there seems to be a genetic predisposition for the susceptibility of soft tissue injuries. We know that the mechanical properties after repair will remain inferior to the original, despite intensive remodelling. Complete regeneration of tendons and ligaments is never achieved. The character of the collagen fibrils will alter. There will be reduction in the proportion of type 1 collagen and increase in the amount of type 3 collagen. Type 3 collagen is responsible for the reduced tensile strength of the tissue due to reduced number of cross links compared with type 1 collagen[195].

Additional studies are necessary to confirm SNPs, to identify genetic pathways that predispose to soft tissue injuries, and to identify genetic and lifestyle components that affect the healing process and the mechanical properties of soft tissue repair. The goal is to gain a personalized medicine approach to the healing of soft tissue injuries.

The inflammatory processes that occur in and on the soft tissues after surgical procedures cause excessive suffering for patients. In the shoulder joint this presents like a type of capsulitis, causing pain and stiffness. It is known that capsulitis has a genetic predisposition. Bulgen in 1976[128] found HLA B27 more common in patients with adhesive capsulitis. There is also a relation between capsulitis and both diabetes and Dupuytren disease. In paper IV we tried to find a diagnostic modality through MRI in order to visualize the changes that occur in the shoulder capsule after a common surgical procedure, subacromial decompression with or without concomitant acromioclavicular joint resection. We investigated different parts of the joint capsule with MRI, and we found significant differences in MRI scores before and after surgery. However, the reliability between results of the radiologists was poor. This indicates that it is difficult to achieve an exact measurement of the

edema and thickness of the joint capsule. There were relations between the MRI scores and the functional outcome of the patients measured by Constant score and Subjective Shoulder Value. Previous studies have discussed the role of MRI in the diagnosis of adhesive capsulits, but there is still discrepancy about the areas that should be included in the diagnosis of capsulitis[46,53,142].

Conclusions

Study I

In conclusion, we found that the COLIA1 Sp1 ss genotype was associated with a substantially reduced odds ratio of cruciate ligament ruptures and shoulder dislocations. Since our influential genotype is rare, the absolute risk of cruciate ligament injuries and shoulder dislocations seems to be only marginally affected by COLIA1 Sp1 polymorphism. Accordingly, this particular SNP polymorphism has limited clinical relevance as a predictor for these injuries.

Study II

Using the pegged plate roughly doubled the mechanical variables. One possible explanation might be that the flat plate compromises the blood supply, leading to tissue necrosis and thereby impairing the healing process. Therefore our recommendation is to use suture anchors or devices with a pegged undersurface for fixation of soft tissue to a flat bone surface.

Study III

The prevalence of rotator cuff tears was high in our study population who had never sought for their shoulder problems. The presence of a full-thickness cuff tear affects shoulder function. Both degenerative changes in the acromioclavicular joint and the existence of partial-thickness cuff tears are considered to be part of the natural aging process. The subacromial index can be used as a predictor for full-thickness cuff tears.

Study IV

MRI had a low reliability for assessment of capsular reactions after surgery. Subacromial decompression with or without acromioclavicular joint resection is a good surgical procedure with high patient satisfaction.

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