Subacromial Pain Syndrome. Treatment, diagnostic imaging and predictors of outcome.

PhD Thesis

Elisabeth Kvalvaag

Faculty of Medicine, University of Oslo

Department of Physical Medicine and Rehabilitation, Oslo University Hospital, Ullevaal

November 2017
CONTENTS

1. Acknowledgements
2. List of papers
3. Abbreviations
4. Summary
5. Introduction
   5.1 Epidemiology of shoulder pain
   5.2 Anatomy of the shoulder
   5.3 Painful conditions of the shoulder
   5.4 Subacromial pain syndrome
      5.4.1 Pathogenesis
      5.4.2 Symptoms and clinical findings
      5.4.3 Diagnostic imaging of the shoulder
      5.4.4 Therapy strategies
      5.4.5 Prognostic factors
   5.5 Placebo
6. Aims of the research
7. Methods
   7.1 Study design
   7.2 Patients
   7.3 Randomization and blinding
   7.4 Patient assessment
   7.5 Outcomes
   7.6 Interventions
   7.7 Statistics and sample size
      7.7.1 Power estimation
      7.7.2 Comparing groups
      7.7.3 Associations
8. Summary of papers
   8.1 Paper I
   8.2 Paper II
   8.3 Paper III
   8.4 Paper IV
9. Discussion
   9.1 Patient sample and external validity
9.2 Patient sample and internal validity

9.3 Study Design

9.4 Sample size and statistics

9.5 Results in relation to existing knowledge
   9.5.1 Efficacy of rESWT versus sham rESWT in addition to supervised exercises
   9.5.2 Predictors of SPADI and return to work after one year
   9.5.3 MRI of the shoulder

9.6 Clinical implications

10. Conclusions

11. Future research
1. Acknowledgements

This work has been carried out during the years 2011-2017, while I was employed as a research fellow at the University of Oslo and Department of Physical Medicine and Rehabilitation at Oslo University Hospital, Ullevål. All of these years have been very exciting, educational, and from time to time challenging. But I have been so lucky to work with a large group of people that have helped me during the process, and I am deeply grateful to all of you.

I especially want to thank my main supervisor Professor Cecilie Røe, Head of the Department of Physical Medicine and Rehabilitation. She hired me and believed in me from the beginning, even though my research experience was very limited. During the whole process, she has always been available for me and patient with me, and she has provided the perfect setting for undertaking such a project. Her extensive experience, unlimited capacity, competent advice and encouraging support have been invaluable for me.

I am also extremely thankful to Professor Jens Ivar Brox, my second supervisor. His everlasting interest and patience, and vast experience in medical research in general, and shoulder research in particular, have been crucial for the completion of this work. Thank you so much for your enthusiastic, quick and constructive feedback on my innumerable questions!

Special thanks go to Dr. Helene Søberg, my third supervisor, for her constructive feedback and support during the whole process.

I am also grateful to Dr. Kaia Beck Engebretsen, for good advice and educational discussions, and for treating some of the patients in the study with supervised exercises.

I would also like to thank Dr. Niels Gunnar Juel, for his patience, keen interest and skilful advice. His experience and outstanding knowledge regarding shoulder patients have been invaluable in my years at the shoulder clinic, and in my development as a clinician.
Many thanks go to Professor Leiv Sandvik, for interesting discussions and important advice concerning the statistical methods performed.

I also want to thank Professor Erik Bautz-Holter, the project manager of this project, for always providing friendly help and constructive feedback.

All my colleagues at the Department of Physical Medicine and Rehabilitation at OUH also deserve my gratefulness for their contribution and help in recruiting patients, and for creating such a good working atmosphere. Special thanks to Kathrine Hope and Danijela Miletic for practical assistance, and the physiotherapists who performed the treatments at OUH.

Special thanks to all the study patients for their time and willingness to participate in this study, and to Egill Knag in Enimed for technical support.

I would also like to thank Sophies Minde Ortopedi AS for funding of the project.

Finally, I would like to thank my family for the most important support. My husband and best friend, Stian, for his interest in the project, encouragement and support. And our three children, Stella, Mikkel and Frida, the very best in my life.

Oslo, October 2017

Elisabeth Kvalvaag
2. List of papers


### 3. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADL</td>
<td>Activities of Daily Living</td>
</tr>
<tr>
<td>AROM</td>
<td>Active range of motion</td>
</tr>
<tr>
<td>ASD</td>
<td>Arthroscopic Subacromial Decompression</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>fESWT</td>
<td>Focused Extracorporeal Shock-Wave Therapy</td>
</tr>
<tr>
<td>GP</td>
<td>General practitioner</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention To Treat</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>OSD</td>
<td>Open Subacromial Decompression</td>
</tr>
<tr>
<td>PROM</td>
<td>Passive range of motion</td>
</tr>
<tr>
<td>RCRSP</td>
<td>Rotator Cuff Related Shoulder Pain</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized clinical trial</td>
</tr>
<tr>
<td>rESWT</td>
<td>Radial Extracorporeal Shock-Wave Therapy</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SAPS</td>
<td>Subacromial Pain Syndrome</td>
</tr>
<tr>
<td>SPADI</td>
<td>Shoulder Pain and Disability Index</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
</tr>
<tr>
<td>US</td>
<td>Ultrasound</td>
</tr>
</tbody>
</table>
4. Summary

Subacromial Pain Syndrome. Treatment, diagnostic imaging and predictors of outcome
Elisabeth Kvalvaag, Oslo University Hospital, Ullevaal, Department of Physical Medicine and Rehabilitation and University of Oslo, Medical Faculty.

Background: Shoulder pain is reported in almost half of the adult population yearly, and subacromial pain syndrome is diagnosed in about half the patients consulting. Non-surgical treatment including injection and exercises is the first choice. Radial Extracorporeal Shock Wave Therapy (rESWT) is another modality that is commonly used to treat this condition, but there is limited evidence for its effectiveness.

Aims: 1) To compare improvement in pain and disability after radial Extracorporeal Shock Wave Therapy (rESWT) versus sham rESWT in patients who also received supervised exercises (paper I, II and III), 2) To explore how calcification of the rotator cuff and treatment beliefs influence the outcome (paper II and III), 3) To examine prognostic factors of one-year outcome (paper III), 4) To evaluate the association between structural changes detected on MRI and pain and disability (paper IV).

Study Design: The main study is a randomized, controlled trial comparing supervised exercises and rESWT to supervised exercises and sham rESWT (paper I, II and III). Paper III is also a prognostic study that evaluates predictors of the Shoulder Pain and Disability Index (SPADI) and work status after one year. Paper IV is a cross-sectional and prospective observational study for identifying and evaluating imaging findings associated with SPADI baseline and the change in SPADI from baseline to one year follow up.

Patients and method: One-hundred and forty-three patients between 25 and 70 years with subacromial pain syndrome lasting at least three months were randomly allocated to one of the two treatment groups (paper I, II and III). Of these patients, 115 had a recent MRI of their painful shoulder (paper IV). The rESWT and sham were performed once a week for the first four weeks, with the highest energy the patient could tolerate. Supervised exercises were performed once per week for the first four weeks, then twice per week for the next eight weeks. The principal focus of the supervised exercises was to unload stress on the subacromial structures by relearning normal movement patterns, with focus on posture and use of manual techniques for tense muscles. Later, endurance exercises with gradually increasing resistance were performed. Follow up was at 12 and 24 weeks (paper II) and one year (paper III and IV). The primary outcome was the Shoulder Pain and Disability Index (SPADI). Secondary outcome measures were pain at rest and daily activity and shoulder function the last week, health-related quality of life and return to work. Mixed model analysis (paper II) and linear regression analysis (paper III) were used for comparing the two treatment groups. Simple and multiple regression analyses were used for the evaluation of associations in paper III and IV.

Results: At 24 weeks and one year, participants in both the sham group and the rESWT group had improved significantly in SPADI score compared with baseline, but there was no difference between the groups, except for the subgroup of patients with calcification in rotator cuff at 24 weeks. Predictors of a poor outcome at one year were marital status (single), frequent use of pain medication, sick leave at baseline, negative outcome expectations, low self-reported general health status and few supervised exercise sessions in our department. Sick leave at baseline and little or no improvement in SPADI
score from baseline to 24 weeks predicted sick leave after one year. There was a moderate, but significant association between the change in SPADI from baseline to one-year follow-up and the structural changes detected on MRI, with a poorer outcome for the patients with more structural changes.

**Conclusions:** Radial ESWT offered no additional benefit to supervised exercises, except for the subgroup of patients with calcification in the rotator cuff in the short term. Treatment beliefs influenced the outcome. Negative outcome expectations, marital status (single), frequent use of pain medication, not working at baseline, low self-reported general health status and few supervised exercise sessions predicted a poor outcome. MRI findings were statistically associated with the change in SPADI from baseline to one-year follow-up.
5 Introduction

5.1 Epidemiology of shoulder pain
Shoulder pain is very common with an annual population prevalence of up to 46.7%, and a lifetime prevalence of up to 67%. [1, 2] In primary care, shoulder pain is the third most common musculoskeletal presentation. [1, 3] The most frequent shoulder diagnosis is subacromial pain syndrome, affecting about half of all shoulder patients, both in general practice and in secondary care. [4-7] Shoulder pain may have an unfavourable outcome, with only about 50% of all new episodes of shoulder complaints presenting in medical practice showing a complete recovery within 6 months. [8] Symptoms may be disabling in terms of the patient’s ability to carry out daily activities at home and at the workplace. [9]

5.2 Anatomy of the shoulder
The bones of the shoulder consist of the humerus, the scapula and the clavicle. The clavicle is the only bony connection between the trunk and the upper extremity. There are three joints in the shoulder; the sternoclavicular, the glenohumeral and the acromioclavicular joint. The latter is at the top of the shoulder. It is the junction between the acromion (part of the scapula that forms the highest point of the shoulder) and the clavicle. The shape of the acromion is classified as flat (type 1), curved (type 2), hooked (type 3) or convex upturned (type 4). [10, 11] The glenohumeral joint is the largest and most complex joint in the shoulder region. In this joint, the head of the humerus fits into the glenoid, which is a shallow socket on the scapula. The socket is deepened by the glenoid labrum, which is a fibro-cartilaginous structure encircling the glenoid cavity. The shoulder joint is the most flexible joint of the body. This means that there is high need for support of the joint from the surrounding soft tissue structures. Some stability is provided by the joint capsule, including the glenohumeral ligaments. The static stabilizing structures are further supported by muscles, partly of long external muscles, and partly of an inner muscle layer known as the rotator cuff, providing dynamic stability. [12] The rotator cuff is composed of the muscles and tendons of the supraspinatus, infraspinatus, subscapularis and teres minor. All muscles originate at different areas of the scapula, and fuse together on their respective attachment sites. The
supraspinatus and subscapularis tendons fuse to form a sheet that surrounds the biceps tendon. Various bursae surround the joint capsule and tendons. The rotator cuff muscles and the long head of the biceps are situated in an ideal configuration to actively compress the humeral head into the glenoid cavity during shoulder movement, as they lie close to the center of rotation. Previously, the muscles and tendons of the rotator cuff were commonly considered to be recruited equally during shoulder movement, but a recent study suggests that they are activated asynchronously. [13] Shoulder abduction to about 90 degrees is possible without motion of the scapula, but the natural elevation of the upper extremity is mediated by both movement of the glenohumeral joint and the sliding of the scapula on the thoracic wall. The scapula is a dynamic contributor to shoulder/arm function. [14] Previous studies have defined normal scapular kinetics and demonstrated the relationship between decreased scapular motion and impingement. [14, 15] In addition, previous studies have indicated that fatigue and shoulder pain related to elevated arm positions may be caused by muscle ischemia in the rotator cuff induced by high intramuscular pressure present in these positions. [16, 17]
5.3 Painful conditions of the shoulder

Pain is defined the following way by the International Association for the Study of Pain (IASP): “Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”. [18]

The origin of shoulder pain is often difficult to determine with certainty. Soft-tissue around the shoulder is most frequently involved, but pain might also be referred from internal organs and the cervical spine. A thorough patient history and clinical examination help distinguish pain from local structures from other causes, and to evaluate which structures in the shoulder that may be causing the pain. However, reviews have found that few tests used to evaluate the various conditions of the shoulder provided convincing evidence of the presence or absence of disease. [19-21] Hence, the matching of symptoms and structures may be challenging for the clinician. Studies that assess the diagnostic methods for these patients are therefore warranted.

Subacromial pain syndrome is the most frequent diagnosis in patients with shoulder pain, both in general practice and in secondary care. [4, 5] The different clinical and/or radiological names, such as bursitis, tendinosis calcarea, partial tear of the rotator cuff and supraspinatus tendinopathy are all part of the same "syndrome". [22]

The other most common diagnoses of the shoulder are adhesive capsulitis (11-21%), myalgia (6-17%) and full-thickness tear of the rotator cuff (8%). [4, 7]

5.4 Subacromial pain syndrome

5.4.1 Pathogenesis

Neer proposed in 1972 that mechanical contact between the rotator cuff tendons and the overlying acromion and coracohumeral ligament leads to irritation and inflammation in the subacromial structures. He named the condition subacromial impingement syndrome. [23] This theory, proposing extrinsic mechanisms in rotator cuff pathology, has gained support, and some studies
have indicated a relationship between acromion morphology and acromiohumeral distance, and the severity of rotator cuff pathology. [24-29] Other extrinsic factors that may contribute are abnormal scapular and humeral kinematics, and postural abnormalities. [30-32]

However, other studies have found that tears in the rotator cuff most often occur within the tendon or on the articular side, which does not support the extrinsic model. [33, 34] Further, newer studies have reported a poor correlation between acromial shape and symptoms, [35, 36] and the interobserver reliability when evaluating the acromial shape has been reported as poor. [37, 38]

Current evidence suggests that the pathoetiology of rotator cuff tendinopathy is multifactorial. [39-42] Intrinsic mechanisms may play a greater role than extrinsic mechanisms in this process. [43] Intrinsic mechanisms are associated with the tendon itself and may be caused by aging, altered biology, microvascular blood supply, degeneration, tendon overload, overuse and/or trauma. [39] In addition, peripheral and central sensitization mechanisms seem to be involved in pain development and recovery. [44-46] Moreover, recent studies also suggest that there is a genetic and familial predisposition to rotator cuff disease. [47]

The terms "Subacromial Pain Syndrome" (SAPS) and "Rotator Cuff Related Shoulder Pain" (RCRSP) are suggested for all conditions affecting the structures of the subacromial space, to give a better description of the complexity of the condition. [22, 48, 49] The term "subacromial pain syndrome" will be used in this thesis.

### 5.4.2 Symptoms and clinical findings

The patients present with usually unilateral shoulder pain, often exacerbated in overhead activity. The pain is located in the lateral part of the shoulder. Night pain might be present, especially if lying on the shoulder at night. During clinical examination typical findings will be a painful arch on active abduction between 60-120 degrees and scapular dyskinesia, reduced active internal rotation, and pain on isometric abduction and/or external rotation. The Hawkins-Kennedy and Neer impingement signs narrow the subacromial space and will trigger pain.
Restricted passive range of motion (PROM) is more susceptible of other diagnosis, as adhesive capsulitis or glenohumeral osteoarthritis. The diagnosis is largely clinical, but the clinician must rule out underlying severe diseases such as neoplasms, neurological or vascular disorders. In case of progressing night pain, constant pain that is not worsened by active motion and/or neurological signs, the patient should be referred for further investigations.

The interwoven nature of the rotator cuff limits the possibility of testing individual structural units [48], and it has been demonstrated that for example during the “full” and “empty” can tests designed to evaluate the supraspinatus, eight to nine other muscles are equally active. [50] Accordingly, as individual clinical tests lack the ability to rule out specific diagnoses of shoulder pain, a combination of tests is recommended to increase the diagnostic accuracy. [51, 52]

### 5.4.3 Diagnostic imaging of the shoulder

A thorough history and physical examination are necessary, and often sufficient, to obtain the correct diagnosis for most shoulder patients. However, for some conditions of the shoulder, diagnostic imaging may increase the possibility to obtain an accurate diagnosis, and thereby the appropriate treatment. A patient with an acute rotator cuff tear may for example benefit from early surgical repair, [53] while many shoulder diagnosis should be treated conservatively. The complex anatomy of the shoulder requires choosing the appropriate imaging modality for different clinical situations.

Radiography will in many cases be the first-step imaging modality, and can reliably detect glenohumeral osteoarthritis in addition to most bone sarcomas and other neoplasms. [54]

Musculoskeletal ultrasound is increasingly used and might be a helpful supplement to the clinical examination. Ultrasound (US) can reliably detect calcification, partial- and full thickness tears of the rotator cuff, and bursitis. [55] US examination is dynamic, rapid, inexpensive and widely available, and allows immediate clinical correlation. There are no known side effects. The disadvantages to the method include user dependence and low diagnostic value for intra-articular pathology. The US examination should be performed
according to a standardised protocol in four steps assessing the following structures: (1) anterior view assessing the biceps and subscapularis tendon, (2) lateral view assessing the supraspinatus tendon and the rotator interval, (3) posterior view assessing the infraspinatus tendon, and (4) superior view assessing the acromioclavicular joint and subacromial/subdeltoid bursa. [56]

The transducer must remain perpendicular to the surface of the tissue of interest to avoid anisotrophy.

In case of suspected intraarticular pathology, such as labral tears or articular damage, the patients should be referred for an MRI instead of US. Of the available imaging modalities, MRI offers the most complete information about the shoulder, but due to high costs and limited availability it should not be used as a routine examination in patients with signs of subacromial pain syndrome. A recent review compared ultrasound, MRI and MRA and concluded that US was the best option for the characterization of rotator cuff disorders when considering cost, accuracy and safety. [57]

We did US and MRI examination of all the patients recruited to the studies in this thesis, but findings from these examinations were not used for inclusion. Examples of MRI findings from the patients included in this study are presented in figure 2A and 2B.
Figure 2A. Oblique coronal PDFS-weighted MR image demonstrating tendinosis with thickening and increased intermediate signal within the supraspinatus tendon (black arrows).

Figure 2B. Axial PDFS-weighted MR image demonstrating subacromial/subdeltoid bursitis with increased fluid and slightly thickening of the wall (white arrow)

The relationship between imaging and symptoms

Findings from previous research challenge the reliance on imaging to determine the cause of symptoms in this patient group, as the existing literature shows conflicting results for the correlation between medical imaging and symptoms. Several investigations have reported a substantial number of people without symptoms demonstrating rotator cuff structural failure. [48, 58] One study reported that shoulder abnormalities including bursal thickening, supraspinatus tendinosis and tears, and glenoid labral abnormalities, were present in 96% of men who did not have shoulder symptoms. [59] A literature review found that partial thickness tears of the rotator cuff were more common in asymptomatic volunteers than in painful shoulders. [58] And yet another study found that structural changes in the rotator cuff and subacromial bursa did not predict short-term outcome after corticosteroid injection therapy. [60] Despite this, medical imaging is frequently overused and often not requested according to guidelines or published appropriateness criteria. [61, 62] In Norway, MRI of the shoulder is often performed already in primary care in this patient group. [63] We observed that 53 (37.1%) patients had a recent MRI of the shoulder from primary care when entering this study.

5.4.4 Therapy strategies

There is limited evidence regarding the natural course of subacromial pain syndrome. Dorrestijn et al followed for 10 years 526 patients that consulted their GP for the first time for a shoulder problem. They found that 48% did not return for a follow-up consultation (they consulted their GP only once). [64] Van der Windt et al studied consultations for shoulder pain in general practice and found that approximately 40% returned at least once because of the same shoulder problem during one year follow-up. They also found that a faster recovery seemed to be related to preceding overuse, slight trauma or early presentation. [8]
**Exercise therapy**

Exercise therapy is more effective than no treatment in reducing pain and improving function of the shoulder, according to several systematic reviews. [22, 65-67] In contrast, a recent Cochrane review found that there was little or no difference in patient-important outcomes between exercise and placebo. However, this conclusion was mainly based on only one study, and the inclusion criteria for the review were very strict, which excluded among others the studies of Ketola et al. [68-70]

Exercise therapy aims to improve muscle function and range of motion by restoring shoulder mobility, proprioception and stability. [70] Isometric and isotonic exercises are designed to strengthen weakened muscles of the rotator cuff, and stretching exercises are used to improve function. [66] Exercise is recommended as the first-line treatment. [65] According to recommendations, exercise therapy should be specific and of low intensity and high frequency, especially in the first phase. Eccentric training should be combined with attention to relaxation and posture. [22] Whether most of the exercises are completed at home or within a clinic setting does possibly not matter, but an early phase supervised by a physiotherapist is recommended and there should be some level of resistance involved. [71] Treatment of myofascial trigger points (including stretching of the muscles) may be considered. [22] The addition of mobilizations to exercises may accelerate reduction of pain in the short term. [65] Exercises are reported to be equally effective as surgery for patients with subacromial pain syndrome. [68, 69, 72-75]

**Extracorporeal shock wave therapy (ESWT)**

Shock waves are acoustic waves, characterized by a rapid rise in positive pressure to a high peak pressure, followed by a fall in pressure to a negative pressure phase. During the low-pressure phase, cavitation is generated, characterized by the formation of gas bubbles. Today, two main types of shock waves for treating musculoskeletal disorders exist; focused (fESWT) and radial (rESWT) shock waves. There are three techniques for generating focused shock waves: electrohydraulic, electromagnetic and piezoelectric. [76] Radial shock
waves are generated pneumatically based on a ballistic principle. [77] It is well known that radial shock waves do not have the characteristics of real shock waves, as they have a lower positive peak pressure and a longer rise time. [78] However, it has been demonstrated that both focused and radial shock waves may cause cavitation. [79, 80]

Cavitation is assumed to play an important role in the working mechanisms of shock-wave therapy, through mechanical stimulation that induces biological effects (mechanotransduction). It is proposed that shock-wave therapy through this pathway may regulate inflammation, induce neoangiogenesis and stem cell activities, thus improving tissue regeneration and healing. [81]

There is some evidence for the effectiveness of fESWT and rESWT in the treatment of calcific tendinopathy of the rotator cuff, but conflicting evidence in the treatment of non-calcific rotator cuff tendinosis. [82-85]

*Corticosteroid injection*

Corticosteroid injections are reported to be more effective than placebo injections in the first 8 weeks. [22] The effect of corticosteroids in the long term is unclear. [22] Subacromial injection with corticosteroids may be indicated for persistent or recurrent symptoms. [22] Two systematic reviews have concluded that image-guided (ultrasound) injections may offer a greater clinical improvement over blind (landmark-guided) injections in patients with shoulder pain. [86, 87] In contrast, a Cochrane review including one high quality blinded, randomized, controlled trial found no differences between ultrasound guided corticosteroid injection in the subacromial bursa and systemic corticosteroid injection in the gluteal region. [88, 89] One recent systematic review and meta-analysis found that injection with corticosteroid combined with exercise therapy gained better results than exercises alone. [90]

*Surgical treatment*

The most commonly used methods are Arthroscopic Subacromial Decompression (ASD) and Open Subacromial Decompression (OSD). [90] A recent meta-analysis found that ASD together with treatments derived from it,
such as ASD combined with radiofrequency or bursectomy, showed better effects than OSD. [90] In contrast, another systematic review found no evidence that one surgical technique is superior to another, but because of the less invasive character of the procedure, ASD may be preferred. [91] However, as exercises are reported as equally effective as surgery for patients with subacromial shoulder pain, [69, 72, 73] supervised exercises are recommended as the basis in the treatment. [68] Two ongoing studies are comparing surgical treatment for subacromial pain syndrome to sham surgery, but the results are not yet published. [92, 93]

5.4.5 Prognostic factors
Prognostic studies have suggested that age, education, duration of pain, sick leave, fear avoidance beliefs and medication are predictors of sustained pain and disability after treatment for subacromial shoulder pain. [60, 94-99] In addition, some studies have proposed that patients with minor/"reversible" changes detected at MRI have a more favourable outcome after treatment, but another study found no contribution of MRI findings to their predictive model in the short term. [60, 94, 95] Ketola et al found that patients with radiological AC joint degeneration had more pain two and five years after surgery. [100]

5.5 Placebo
The word "placebo" comes from the Latin word "placere", and means to please. There are two main models of the placebo effect: Expectancy and learning (classical conditioning). [101] According to the expectancy theory, placebo effects are mediated by explicit (conciously accessible) expectancies. In contrast, according to the classical conditioning approach, they are conditioned responses. However, the two models are compatible, and expectancies may mediate conditioning. [101]

One of the placebo pioneer scientists, Fabrizio Benedetti, compared the effect of open versus hidden administration of active treatments across four different conditions (pain, anxiety, Parkinson’s disease and cardiovascular function). Across all of these treatments they found that open treatment lead to significant larger improvement than the same hidden dose. [102]
The powerful placebo effect in surgery is summarized in a systematic review. [103] Fifty-three trials were evaluated and it was reported that the effect of placebo in 51% of the identified trials did not differ from that of surgery.

Gerdesmeyer et al used a placebo shock wave device in a randomized study to evaluate its placebo effect in the treatment of chronic plantar heel pain. Both treatment arms received placebo, but one arm were told that they received real ESWT, and the other were told that they received placebo. After 6 weeks, patients that were told that they received real ESWT reported significantly less heel pain. [104]

A recent study on surgery for lesions of the glenoid labrum (type II SLAP) of the shoulder found that the results for sham surgery did not differ from surgical repair of the lesion. [105]

Due to the powerful effects of the placebo itself, the gold standard in randomized controlled trials is to include a placebo-control group. [106]

6 Aims of the research
The aims of this study were to investigate the following in a population with subacromial pain syndrome:

1. To compare improvement in pain and disability after radial Extracorporeal Shock Wave Therapy (rESWT) or sham rESWT in patients who also received supervised exercises (paper I, II and III).
2. To explore improvement in pain and disability in the patients with and without calcification in the rotator cuff, and how treatment beliefs influence the outcome (paper II and III).
3. To examine prognostic factors of one year outcome after rESWT/sham and supervised exercises (paper III).
4. To evaluate to which extent structural changes detected on MRI are associated with symptoms and predict pain and disability (paper IV).

7 Methods
7.1 Study Design
Paper I was the protocol of the study.
Paper II and III were the main study, a randomised, sham-controlled, double-blind trial with follow-up at 6, 12, and 24 weeks and one year.

Paper III was also a prognostic study with secondary analyses from the randomised trial.

Paper IV was a cross-sectional and prognostic study including data from the randomised trial, in addition to analyses of the shoulder MRI findings.

7.2 Patients
We recruited patients who were referred to the shoulder outpatient clinic at Oslo University Hospital (OUH) between January 2012 and April 2014. In order to enhance the inclusion the general practitioners in Oslo were given an information letter about the study before the study started. Patients were included if they were between 25 and 70 years old and were clinically diagnosed with subacromial pain syndrome.

The inclusion criteria were pain on one of two isometric tests (abduction or external rotation), positive Hawkins-Kennedy impingement sign [107] and normal passive glenohumeral range of motion. The exclusion criteria were previous surgery of the affected shoulder, instability, rheumatoid arthritis, full-thickness tear of the rotator cuff, cervical radiculopathy, infection, patients considered unable to fill out questionnaires or follow the treatment, contraindications for shock wave therapy (use of anticoagulant drugs, bleeding disorder, epilepsy, pregnancy or pacemaker), previous experience with shock wave therapy, injection of cortisone in the affected shoulder in the last six weeks and SPADI score below 20.

A total of 265 patients were assessed for eligibility, of these patients 60 declined to participate, and 62 patients did not meet the inclusion criteria (usually because they had tried rESWT before (N=22), could not fill out questionnaires in Norwegian (N=12), or they had SPADI score below 20 (N=12)), leaving 143 patients for the randomized trial in paper II and III (figure 3). In paper IV, we included 115 patients from the randomized trial who had a recent MRI of their painful shoulder.
Written informed consent was obtained from all patients.

Figure 3. Patient flow

7.3 Randomization and blinding

The patients were allocated to one of two treatment groups: supervised exercises and rESWT or supervised exercises and sham rESWT by computer-
generated randomization in blocks of 20 in a 1:1 ratio. A research assistant not involved in any other part of the study opened the sealed opaque envelopes and assigned the patients to their respective treatment group.

The participants, the outcome assessors, the researchers analyzing the data and the physical therapists providing the exercise regimen were all blinded to treatment allocation. The physical therapist providing the rESWT and sham rESWT was not blinded. To evaluate the success of blinding and the significance of the patients’ beliefs, the patients were asked the following question at the 24-week follow-up: "Which treatment do you believe that you have received for your shoulder pain?" The response alternatives were “exercises and regular rESWT” or “exercises and placebo/not real rESWT”.

7.4 Patient assessment
At baseline, the patients completed a comprehensive questionnaire including primary and secondary outcome measures, socio-demographic and clinical factors such as sex, age, duration of symptoms, education, drug use, sick leave and emotional distress. The patients underwent clinical examination, and were referred for an MRI of the shoulder. MRIs taken before attending the study were accepted if images were obtained within the last 3 months. Calcific deposits were detected by ultrasound examination, measured and categorized according to Bosworth [108] as small (<5 mm), medium (5-15 mm) and large (>15 mm).

At six weeks, the patients filled in a questionnaire. At 12 and 24 weeks and one year, the patients came to follow-up visits where they filled in questionnaires and went through clinical examination. All clinical examinations were undertaken by the author (EK).

7.5 Outcomes
The Shoulder Pain and Disability Index (SPADI) score was the main outcome in all papers (figure 4). This self-report questionnaire consists of 13 items grouped into pain and disability subscales. [109] Items assess various activities of daily living (ADL) that might or might not be problematic for the patient. Each item is rated on a horizontal visual analogue scale (VAS) from 0 cm (best) to 11 cm (worst) in accordance with the original scoring system. [109] First, the score for
each subscale is calculated, secondly the means of the two subscales are averaged to achieve a total score ranging from 0 to 100, with 100 being the worst possible pain and disability, figure 4. The psychometric properties of SPADI in subacromial shoulder pain are deemed to be good. [110] We used a version that is translated and adapted to the Norwegian language and culture, and previously used in other studies at the Department of Physical Medicine and Rehabilitation, Oslo University Hospital, Ullevaal. [88, 110-112]

**Pain: How severe is your pain?**
1. At its worst?
2. When lying on the involved side?
3. Reaching for something on a high shelf?
4. Touching the back of your neck?
5. Pushing with the involved arm?

**Disability: How much difficulty do you have...**
1. Washing you hair?
2. Washing your back?
3. Putting on an undershirt or pullover sweater?
4. Putting on a shirt that buttons down the front?
5. Putting on your pants?
6. Placing an object on a high shelf?
7. Carrying a heavy object of 10 pounds?
8. Removing something from your back pocket?

Figure 4. Questions contained in the SPADI score. 0 = no pain at all/no difficulty, 11 = worst pain imaginable/so difficult required help).

**7.6 Interventions**
Both interventions were performed at the outpatient clinic at the Oslo University Hospital, Ullevaal. The first four weeks the patients received supervised exercises once per week in addition to rESWT or sham rESWT once per week. The following eight weeks the patients received only supervised exercises, twice per week.
The exercise regimen was developed at Ullevaal University Hospital by Bøhmer in the 1980s. [113] Experienced physiotherapists supervised the exercises and all treatment sessions were conducted one-to-one. At the first session the physiotherapist observed the bilateral alignment, including scapula and the glenohumeral joint. The movement pattern and timing of the scapula and arm during elevation were also evaluated to obtain a functional diagnosis for individual guidance of the treatment. [114] The initial aim was relearning of normal movement patterns to unload the stress of rotator cuff and subacromial structures. [115] In this first phase, a vertically fixed sling was often used. The focus in the next phase was to increase the eccentric force when lowering the arm in standing position. Finally, endurance exercises with gradually increasing resistance were performed. [113, 116] The patients were also instructed in home exercises and exercises which could be transferred into daily activities.

Physiotherapists who went through an application course and training before the study started performed the rESWT and sham rESWT (EMS Swiss Dolor Clast/Enimed). This treatment was applied to the muscle tendons that were painful on isometric tests. For the rESWT we used 2000 impulses on each painful tendon with a pressure between 1.5 and 3 bar depending on what the patient could tolerate. The rESWT was applied with a “power” handpiece, to increase the energy delivered to the tissue, which gives a maximum of energy of 0.35 mJ/mm². [117]

7.7 Statistics and sample size
All statistical analyses were performed using IBM SPSS version 23 (SPSS Inc., Chicago, IL, USA). P values of less than 0.05 were considered statistically significant.

7.7.1 Power estimation
The estimated sample size in paper II and III was based on results from previous studies that presented a standard deviation of change in the SPADI score of approximately 20 points. [88, 112] We designed the randomized study to detect a clinically relevant group difference of 10 points [118] with a significance level (α) of 0.05 and power (β) of 80%. Using a t-test based sample-size calculator we
needed 50 patients in each group. We included 143 patients to account for dropouts and possibly some higher variance.

7.7.2 Comparing groups
In Paper II and III analyses were conducted according to the intention to treat (ITT) principle, and all patients randomly assigned to rESWT/sham rESWT were included in the analysis. [119] There were no statistically significant differences between the baseline variables and they were therefore not adjusted for in the final analyses. However, the analyses were also performed adjusting for some common baseline variables (sex, age, sick leave, emotional distress), and the results were similar. [119]

In Paper II, mixed model analysis was used to compare improvement in the SPADI score between the groups. Mixed model analysis was also performed for the secondary outcomes, pain at rest and daily activity the last week, and shoulder function the last week. Data from baseline and the 12 and 24 weeks follow-up was used. The assumptions underlying this model were checked and found to be adequately met. Missing data from the patients not attending the 12 and 24 weeks follow-up were imputed using multiple imputation. The imputation of data did not affect the results. Subgroup analyses on the treatment effect for the patients with and without calcification was also conducted by mixed model analysis in which imputed values for the missing data from the 12 and 24 weeks follow-up were used.

In Paper III linear regression analysis adjusting for baseline SPADI was applied with the SPADI score at one year as the dependent variable to evaluate the between group differences. The same analysis was performed for the subgroup analysis on patients with calcification in the rotator cuff, as well as for the secondary outcome measures pain at rest and during activity, shoulder function, and health-related quality of life. For the secondary outcome measure sick leave, logistic regression was applied.

7.7.3 Associations
In paper III, linear and logistic regression analysis was applied to analyze the associations between baseline sociodemographic and clinical variables and long-
term (one year) outcome. Outcomes were the SPADI score at one year follow up, and return to work. In the analysis on return to work, we included only patients that were working or on sick leave at baseline.

Univariate analyses were applied to assess possible predictor variables. All potential predictors with a p value below 0.2 from the univariate analyses were entered in the multivariate model. SPADI baseline, age, gender, education and work status at baseline were kept in the model regardless of significance level. Manual backwards selection was applied until all remaining variables had a p value below 0.05. Variance inflation factor (VIF) was calculated to check for collinearity in the model.

For the analysis of return to work, predictors were assessed by multivariate binary logistic regression using manual forwards selection starting with the variable with the lowest p value from the univariate analysis. A maximum of three variables were entered at the same time.

In paper IV multiple linear regression analyses were applied with the SPADI baseline score and the change in SPADI score from baseline up to one year follow-up as dependent variables and with the MRI total score and the individual MRI findings as covariates. Age, gender, education, work status and emotional distress were adjusted for in analyses.

8. Summary of papers
8.1 Paper I
Background
Subacromial pain syndrome is a common complaint. Radial Extracorporeal Shock Wave Therapy (rESWT) is being increasingly used to treat calcific and non-calcific tendinosis, although there is no evidence of the effectiveness of rESWT in non-calcific tendinosis of the rotator cuff. A randomized single blind study showed that the short-term effect of supervised exercises (SE) was significantly better than rESWT on subacromial pain syndrome, but both groups improved. In a clinical trial on achilles tendinopathy rESWT improved the effectiveness of treatment with eccentric loading. The objective of this present study is to evaluate if rESWT in addition to SE is more effective in improving
shoulder pain and function compared with sham rESWT and SE in patients with subacromial shoulder pain.

**Methods/Design**
This is a double blind, randomized sham-controlled trial which is performed at the shoulder clinic at the Department of Physical Medicine and Rehabilitation in Oslo University Hospital, Norway. One-hundred and forty-three patients with subacromial pain syndrome lasting at least 3 months, age from 25-70 years old are included in the trial. Patients are randomly allocated in a 1:1 ratio to receive either rESWT or sham rESWT once a week in addition to SE once a week for the initial four weeks. Subsequently SE are provided twice a week for eight weeks. The primary outcome measure is a change in the Shoulder Pain and Disability Index (SPADI) at 24 weeks follow-up. Secondary outcomes include return to work, pain at rest and on activity, function, and health related quality of life. The patients, the physiotherapist providing the exercise regimen and the outcome assessor are blinded to group assignment. The physiotherapist providing the rESWT is not blinded.

**Discussion**
Because of the extensive use of rESWT in the treatment of subacromial shoulder pain the results of this trial will be of importance and have impact on clinical practice.

**8.2 Paper II**
**Background**
Subacromial pain syndrome is a common complaint and radial Extracorporeal Shock Wave Therapy (rESWT) is increasingly used to treat this condition. Although many therapists use rESWT in combination with supervised exercises, no studies have evaluated the additional effect of rESWT to supervised exercises for subacromial pain syndrome.

**Purpose**
To assess whether radial Extracorporeal Shock Wave Therapy (rESWT) is more effective than sham rESWT when combined with supervised exercises for improving pain and function in patients with subacromial pain syndrome.

**Methods**

Patients between 25 and 70 years, with subacromial pain syndrome with and without calcification in the rotator cuff, lasting at least three months, were assessed for eligibility. One-hundred and forty-three patients were recruited. Participants were allocated (1:1) by computer-generated randomization in blocks of 20 to receive either rESWT or sham rESWT in addition to supervised exercises. The rESWT/sham were performed once a week with additional supervised exercises once a week for the first four weeks. The following eight weeks, the patients received supervised exercises twice a week. The primary outcome was change in the Shoulder Pain and Disability Index (SPADI) after 24 weeks. Patients and outcome assessors were masked to group assignment.

**Results**

At 24 weeks, participants in both the sham group and the rESWT group had improved (p < 0.001) in SPADI score compared with baseline (-23.9 points (23.8) and -23.3 points (25.0), respectively), but there were no differences between the groups (mean difference 0.7, 95% CI -6.9 to 8.3, p=0.76), figure 5. Pre-specified subgroup analysis of patients with calcification in rotator cuff showed that the rESWT group had a greater improvement in SPADI score after 24 weeks (mean difference -12.8, 95% CI -24.8 to -0.8, p=0.018), figure 6.

**Conclusions**

Radial ESWT offered no additional benefit to supervised exercises in the treatment of subacromial pain syndrome after 24 weeks, except for the subgroup of patients with calcification in the rotator cuff.
Figure 5. All patients. SPADI score at baseline, 12 and 24 weeks for the two treatment arms.

Figure 6. Patients with calcification in rotator cuff (n=23 patients in each group). SPADI score at baseline, 12 and 24 weeks.
8.3 Paper III

Background
Radial extracorporeal Shock Wave Therapy (rESWT) is increasingly used to treat patients with subacromial pain syndrome despite conflicting evidence of its effectiveness. Better knowledge regarding prognostic factors may contribute to the improvement in treatment and prognosis for the patients.

Aim
The first aim of this study was to evaluate the effect of rESWT in addition to supervised exercises in patients with subacromial pain syndrome after one year. The second aim was to identify predictors of pain and disability and work status after one year in this patient group.

Methods
Patients aged 25 to 70 years, with subacromial pain syndrome lasting at least three months were included and randomly assigned to receive either rESWT and supervised exercises or sham rESWT and supervised exercises. The Shoulder Pain and Disability Index (SPADI) and work status were assessed after one year.

Results
We screened 265 patients and enrolled 143; 74 were allocated to receive sham rESWT and exercises, and 69 were allocated to receive rESWT and exercises. After one year, no differences were found for the SPADI score (mean difference -1.6, 95% confidence interval (CI) -10.2 to 7.0, p=0.71). Subgroup analysis of patients with calcification in the rotator cuff demonstrated no significant additional effect of rESWT to supervised exercises (mean difference -6.3, 95% CI -22.4 to 9.8, p= 0.44). Marital status (single), frequent use of pain medication, not working at baseline, negative outcome expectations, low self-reported general health and few supervised exercise sessions predicted a poor outcome on SPADI after one year. The included prognostic factors explained 28% of the variance in SPADI score after one year.

Conclusions
Radial ESWT was not superior to sham rESWT in addition to supervised exercises in the long term for patients with subacromial pain syndrome. The identified predictors for pain, disability and sick leave should be assessed in future studies and addressed by clinicians in order to improve the effectiveness of supervised exercises.

7.4 Paper IV

Background

Previous studies on shoulder patients have suggested that the prevalence of rotator cuff or bursa abnormalities are weakly related to symptoms and that similar findings are often found in asymptomatic persons. In addition, it is largely unknown whether structural changes identified by magnetic resonance imaging (MRI) affect outcome after treatment for shoulder pain. The purpose of this study was therefore to evaluate the presence of structural changes on MRI in patients with subacromial pain syndrome and to determine to what extent these changes are associated with symptoms and predict outcome after treatment (evaluated by the Shoulder Pain and Disability Index (SPADI)).

Methods

A prospective, observational assessment of a subset of shoulder patients who were included in a randomized study was performed. All participants had an MRI of the shoulder. An MRI total score for findings at the AC joint, subacromial bursa and rotator cuff was calculated. Multiple linear regression analysis was applied to examine the relationship between the MRI total score and the outcome measure at baseline and to examine to what extent the MRI total score was associated with the change in the SPADI score from baseline to the one year follow-up.

Results

There was a weak, but significant, inverse association between the SPADI score at baseline and the MRI total score ($\beta=-3.1$, with 95% CI -5.9 to -0.34; $p=0.03$), i.e the SPADI score was higher for patients with a lower MRI total score. There was a clear association between the change in the SPADI score from baseline to the
one-year follow-up and the MRI total score ($\beta=8.1$, 95% CI -12.3 to -3.8; $p < 0.001$), with a poorer outcome for patients with a higher MRI total score, figure 7. Both tendinosis ($p=0.01$) and bursitis ($p=0.04$) were associated with a poorer outcome after one year.

**Limitations**

As there was no previously validated score for findings at MRI of the shoulder available, we calculated a total score that is not previously used in other studies. This might be considered a major limitation. In addition, the patients were not blinded to the results of their MRI scans, which may have influenced the final results.

**Conclusion**

In this study, MRI findings were significantly associated with the change in the SPADI score from baseline and to one year follow-up, with a poorer outcome after treatment for the patients with higher MRI total score, tendinosis and bursitis on MRI.

![Figure 7. Change in SPADI score from baseline to 1-year follow-up for the patients with 0, 1, 2, 3 and 4 points on the MRI total score.](image)
9. Discussion

9.1 Patient sample and external validity

External validity refers to the extent to which the results may be generalized to subjects outside the study sample.

Patients were recruited from the outpatient shoulder clinic at Oslo University Hospital. Due to the extended invitations sent to the GPs, our study population also included some patients more typical for general practice, in addition to the patients typical for specialist care. Patients in primary care have a better prognosis because of lower baseline pain level and shorter duration of pain. [120, 121] The patient population in specialist-care consists of patients with more severe pain and more chronic pain patients. [4] However, in the present study, about one third of the patients had had symptoms for more than two years, and the characteristics of the patients were more comparable to patients from a previous study published by our department, than a study from general practice. [88, 122] This suggests that many of the patients in the present study were typical specialist-care patients, and that the letter to the GPs was of minor importance. The findings of this study therefore need to be replicated in a primary care setting. [123]

The present study was designed as a randomized controlled trial (RCT), which is considered to be the superior study design for assessment of treatment efficacy. [124-126] However, one limitation within the RCT is that the external validity may be poor. [125] In the present study, the clinical inclusion criteria were strict, to allow for comparison between sham and rESWT, to avoid including patients with other shoulder conditions, and to make reproduction of the study possible for other researchers. Of the total of 265 patients screened for for eligibility, only 143 were included in the study. Among the 62 patients that were excluded, 28% had tried rESWT before, 20% could not participate because of poor Norwegian skills, and 20% had SPADI score below 20. This is clearly a limitation to the population and a possible selection bias. [127, 128] Moreover, 60 patients declined to participate, mainly because of long distance to the hospital or not willingness to follow regular visits to the clinic.
We included patients based on only clinical inclusion criteria (as opposed to inclusion based on imaging findings). This may actually increase the external validity as most caregivers diagnose these patients based on the history and clinical examination only.

9.2 Patient sample and internal validity

Internal validity is the extent to which the results of the study are true, i.e. to which extent the design and conduct of the study keep the possibility of bias to a minimum. [119, 125]

We performed a double-blind, randomized, controlled trial. Randomization is the best method to achieve similarity between two groups and to prevent confounding and systematic bias. [119, 129] Blinding of participants and researchers is the best way to avoid information and selection bias, [129, 130] and increases the internal validity of the present study.

Few patients dropped out, which is a strength of the conduct of the study.

Subacromial pain syndrome is a clinical diagnosis and we used a recommended set of clinical tests for inclusion. [131, 132] All patients had ultrasound examination at baseline, and most patients had a recent MRI or performed an MRI at the hospital shortly after inclusion in the study. However, the results from the imaging were not used for inclusion. Previous studies have suggested that the prevalence of rotator cuff or bursa abnormalities is weakly related to symptoms and that similar findings are often found in asymptomatic persons. [58, 133-136] The addition of imaging findings to the inclusion criteria would probably not have improved the validity of the results in this study.

Pain reduction after a local anaesthetic subacromial injection has been suggested as a diagnostic test for subacromial pain syndrome. [23, 137, 138] Having identified a primary subacromial pain source by adding this to the inclusion criteria could have increased the diagnostic accuracy and increased the internal validity of the study. However, this test has so far not been previously thoroughly validated. [139]

To avoid including patients not in need of an extensive supervised exercise program and also to avoid floor-effects in the SPADI score, patients with a SPADI score below 20 were excluded. This could have resulted in a more
homogenous population with regard to the primary outcome. However, the population turned out quite heterogenous, reflected by the high standard deviations of the study population, but this is in accordance with other studies of this patient group. [88, 112, 140]

When comparing the present study with other trials from secondary care, we find that the gender, age, education and emotional distress in our study population were in accordance with these trials. However, our study included more patients with long-standing symptoms. [60, 74, 112, 141]

The intervention regarding the rESWT was mainly delivered as intended. Most patients (136 of 143, 95.1%) attended 4 sessions of rESWT or sham rESWT. However, most patients attended less than the planned 18 to 20 supervised exercise sessions. Only 21 of 143, 14.7%, attended 18 or more supervised exercise sessions. Some patients attended less sessions in agreement with the physiotherapist as they were more or less completely recovered. But most patients that attended few sessions dropped out of the sessions because of daytime working hours, misunderstandings or unwillingness to attend, even though their shoulder was not recovered. This is clearly a limitation to the study.

9.3 Design
The study design was a double blind RCT, which is widely regarded as the gold standard for assessment of treatment efficacy, and a major strength of the present study. [119, 142] Even though double blind randomization is the best way to avoid bias, the risk of bias is still present for example if the caregiver or patient manage to predict or suspect which treatment they will receive. To avoid this we used sealed envelopes, a data program to generate random block sizes and an independent statistician not involved in any other part of the study. These are also strengths of the study.

Another strength in the design is that we performed the rESWT very similar to the recommendations by Schmitz, except that we had four (not three) weekly treatment sessions. [117] We applied the maximum energy tolerated by the patient, had weekly intervals, and used 2000 impulses on each tendon. [117] In addition, the combination of exercises and rESWT for patients with
subacromial pain syndrome was recently recommended in the narrative review by Moya et al. [143]

The main limitation of the design was the lack of a group that received nothing else than sham/placebo, or a group that received no treatment (to follow the natural course of the condition). The reason for not including another group was that the time frame was too short to include a sufficient number of patients for a three-arm trial.

The success of blinding is an important issue in many clinical trials, but is not always assessed. [144, 145] Previous studies comparing blinded and non-blinded trials have found that non-blinded patients and assessors exaggerated the effect size and that this resulted in pronounced bias. [146, 147] In the present study we assessed the blinding, in which all patients were asked the following question at the 24-week follow-up: “Which treatment do you believe that you have received for your shoulder pain?”. The response alternatives were: “Exercises and regular rESWT” or “Exercises and placebo/not real rESWT”. However, the option to answer “I don’t know” was not available in our questionnaire, and it was therefore not possible to calculate a blinding index, which is a limitation to the study design. [144] In addition, we asked the participants only one time, where ideally they should have been asked about their beliefs several times. This is because blinding assessment in an early stage tends to reflect a person’s wish, while a later assessment may be confounded with treatment effect. [148]

In the present study, the blinding was not entirely successful (see paper II), as a high number of patients in the subgroup with calcification in the rotator cuff guessed correctly which treatment they had received. However, the reason for correct guesses might be due to a clear therapeutic effect. [148]

We used data from the RCT when we developed a prognostic model, which also represents a limitation, as the prognostic study could have restricted generalizability because of strict eligibility criteria for the randomized trial. [149] The best design to answer prognostic questions is a cohort study. In addition, in paper IV, we studied imaging test results, which require subjective interpretation from a radiologist. These types of predictors are of particular
concern because there is a risk of studying the predictive ability of the radiologist rather than that of the predictors. [149]

In paper IV we applied an MRI total score that is not previously validated or used in other studies. This is a clear limitation to that paper.

9.4 Sample size and statistics

Previous studies were used to plan the sample size in paper II and III. [88, 112]

The study was designed to detect a clinically relevant difference of 10 points (SD 20) between the groups with significance level (α) of 0.05 and power (β) of 80%. [118] When allowing for 10% drop out we calculated a necessary sample size of 50 patients per group using a sample size calculator. However, to allow for a higher variation in patient outcome than previously reported, we included 143 patients.

We did not do a formal sample size calculation for the study in paper IV as this was secondary analyses of the results from the randomized trial. Based on the results from paper IV, new hypotheses and sound calculations of sample sizes for future studies can be elaborated. In addition, we did not do a sample size calculation for the subgroup analysis on patients with calcification in the rotator cuff.

SPADI is a composite score, but considered a continuous variable. [118, 150] For paper II we chose to apply mixed model analysis as this is recommended for continuous outcomes measured over time. Mixed model analysis may be seen as an extended linear regression analysis. However, adjustment is made for the correlation between repeated observations within the subject by modeling the variability among the subjects. [151]

Missing data can lead to less precision and potential bias, as missing rarely occur at random. [152] In the present study there were few missing data, still missing data was imputed using multiple imputation. However, there is a current debate regarding whether it is necessary to perform imputation when using mixed model analysis. [153] One study found that the mixed model analysis with multiple imputation for missing data actually was quite unstable when repeated 100 times. [153]
In paper III we used linear regression analysis to estimate differences in outcome between the groups, adjusted for the baseline value. This was done because we already had evaluated the trajectory over time in paper II.

In paper II and III we evaluated the proportion of patients in our sample exceeding the true change, i.e. surpassing the change that could be expected due to measurement error alone on the SPADI score. [154] As the Smallest Detectable Change (SDC) we used the value 19.7 that was calculated in a previous study on a similar population as ours. [110] Other studies have found similar values for SDD. [154-156] However, some studies have evaluated the proportion of patients making a Minimally Clinically Important Change (MCIC) in total SPADI score instead of the SDD. [157] The value for MCIC is calculated as close to 10 in several previous studies. [118, 132]

The candidate variables chosen in paper III for the predictor analysis were chosen after a literature review. As the treatment was ineffective, the sham and rESWT group was combined in the prognostic models, without adding the treatment group as a separate predictor. [149] Manual backwards selection is the recommended approach and was applied for the main analysis, [158] however forwards selection was applied for the work status analysis as this was a logistic regression analysis with categorical outcome, and we only could have three possible predictors in this analysis at the same time.

In paper IV we adjusted for possible confounders. As degenerative changes increase with increasing age, it was important to adjust for age. In addition, we adjusted for gender, education, work status and emotional distress. However, the analysis gave mainly the same results as the analysis performed without these adjustments.

9.5 Results in relation to existing knowledge

9.5.1 Efficacy of rESWT versus sham rESWT in addition to supervised exercises

In Paper II and III, we found no additional effect of rESWT to supervised exercises regarding shoulder pain and function, self-reported general health (EQ-5D) or return to work, neither at 24 weeks nor after one year, except for the patients with calcification in rotator cuff after 24 weeks.
No previous study has evaluated the additional effect of rESWT to supervised exercises in shoulder patients. However, the results are in accordance with other studies of rESWT and fESWT on patients with subacromial pain syndrome without calcification, who found no effect when compared to placebo. [140, 159-161] In contrast, Galasso et al found a beneficial effect of ESWT in non-calcific tendinopathy of the supraspinatus, but the sample size was small. [162]

The subgroup analysis on patients with calcification suggests that rESWT is superior to sham treatment in the short- and medium term, but not in the long term. This is in concordance with most of the previous studies that have reported effectiveness of rESWT and ESWT on pain and function in patients with calcifying tendonitis of the shoulder. [82, 84, 163-167] However, most studies have typically had a short- or medium time follow-up of 3-6 months. The studies that previously have evaluated the long term (one year or longer) effect of rESWT and ESWT in calcific subacromial pain syndrome have been of variable quality and with methodological weaknesses, such as small sample size, lack of a placebo group and/or blinding and considerable loss to follow up. [165, 168-172] Their results should be used to create hypotheses rather than influence treatment practice. There is a need for well-designed studies that evaluates the long-term results of rESWT and fESWT in patients with calcification in rotator cuff.

The placebo effect seems considerable of sham rESWT in patients with subacromial pain syndrome, as the patients believing to have received real rESWT had a significantly more favourable result than the patients believing to have received sham. Previous studies on ESWT have also demonstrated large placebo effects of the sham treatment in patients with shoulder and heel pain. [104, 140]

9.5.2 Predictors of SPADI and return to work after one year

In paper III we found that the following variables predicted a negative outcome on the SPADI score after one year: negative outcome expectations, marital status (single), frequent use of pain medication, sick leave at baseline, low self-reported general health (EQ-5D) and few supervised exercise sessions in our department.
The model explained 28% of the variance in SPADI score after one year. The amount of variance is in line with the study by Engebretsen et al, however, their model included other variables than ours: low education and previous shoulder pain. [96]

Sick leave and use of pain medication have been recognized as negative prognostic factors for patients with subacromial pain syndrome in two previous studies. [60, 98] These variables are influenced by the clinician prescribing sick leave and medication and may apparently cause more harm than gain. Accordingly, the clinician should take precaution when considering using sick leave and pain medication as treatment strategies.

Regarding prognostic factors for sick leave and return to work, we found that sick leave at baseline and little or no improvement in SPADI from 0 to 24 weeks predicted sick leave at one year. A recent review has evaluated determinants and predictors of absenteeism and return to work in workers with shoulder disorders. The only determinants that were found significant in more than one study were atraumatic history, disease severity and previous sickness absence. They concluded that there is currently inconsistent evidence on the role of any determinants or predictors of work absence or delayed return to work for workers with shoulder disorders, and that more methodologically sound studies are needed. [173] However, their population was different from the present study as they included all studies on shoulder pain, including studies evaluating only patients with full-thickness tear of the rotator cuff.

The sick leave process is complex, demonstrated by a non-systematic review on the sick leave process in low back pain that concluded that the doctor usually followed the patient’s demand. [174]

9.5.3 MRI of the shoulder

In paper IV we found a weak, but significant, association between the patient’s pain and disability (as evaluated by the SPADI score) and structural changes detected on MRI. The association was inverse, i.e the patients with more pain and disability had less structural changes on MRI. Previous studies reporting the association between MRI findings and pain and disability in patients with shoulder pain have found no association. [58, 134, 135, 175] Only one study
found that subacromial bursal effusion was correlated to reported severity of shoulder disability in patients with subacromial impingement syndrome. [176] In addition, it is well documented that a number of symptomatic shoulders reveal no MRI findings, and that structural changes also may be present in asymptomatic shoulders. [177, 178] However, no previous study has reported an inverse association, and one possible explanation may be that the general practitioners refer patients with several structural changes on MRI also when they do not have a high symptom burden, i.e. we have a selection bias in the present study.

In addition, we found a significant association between the improvement after treatment and the structural changes on MRI, with a poorer outcome for the patients with many structural changes. Two previous studies have also evaluated the association between structural changes on MRI and improvement after conservative treatment in this patient group, and our results were in accordance with the results in these studies. [94, 95]

When we analyzed only the patients with tendinosis on MRI (N=85), we found that for these patients a high number of physiotherapy sessions in our department was even more significantly correlated with a good outcome after one year than in the group as a whole, with a p-value of 0.009 (not published data). This may suggest that tendinopathy in the shoulder, in concordance with tendinopathy in other body regions, [179, 180] responds well to training.

9.6 Clinical implications
Finally, the implication of our findings for clinical practice must be discussed. The recommendations refer to patients with shoulder pain who satisfy the clinical criteria for subacromial pain syndrome and are treated in a hospital setting.

The patients without calcification in the rotator cuff should be referred for exercise therapy without the addition of rESWT, which is the best documented treatment. [22, 65, 67] However, it should be noted that not all patients will be cured by this treatment. The mean SPADI score in our study at 12-months follow-up was 27.6, which is a significant reduction from their mean baseline score of 51.8, but still indicates some pain and reduced function. In addition, the score at one year ranged from 0 to 90, and as many as 23% had a
SPADI score of 50 or above at the one-year follow-up. This is in accordance with previous studies. [72, 181]

For the patients with calcification in the rotator cuff the clinician may explain that rESWT may increase the effect of the exercises, at least in the short- and medium term. [82, 163]

Attention should be paid to the prognostic factors as most factors may be addressed by the clinician in order to improve the effectiveness of supervised exercises.

10 Conclusions
The conclusions apply for patients with subacromial pain syndrome who are treated in a hospital setting (secondary care).

1. Radial ESWT was not more effective than sham rESWT when applied in addition to supervised exercises to improve pain and disability in patients with subacromial pain syndrome.

2. A) For patients with calcification in the rotator cuff there was a significant difference after 12 and 24 weeks, but not at 1-year, in favour of real rESWT.
   
   B) The patients believing to have received real rESWT achieved a better result than the patients that believed to have received sham which is in keeping with a placebo effect.

3. The included prognostic factors explained 28% of the variance in the SPADI score after one year. Negative outcome expectations was the most significant predictor of a poor result. In addition, frequent use of pain medication, not working at baseline, marital status (single), low self-reported general health status and attending few supervised exercise sessions in our department predicted a poor result on the SPADI score after one year.

4. The combined findings on MRI of the shoulder (the MRI total score) explained 10% of the change in the SPADI score from baseline to the one-year follow-up, with a poorer outcome for the patients with several findings on MRI.
11 Future research

Few high-quality studies have been conducted on rESWT in this patient group. Future research on rESWT should differentiate between calcific and non-calcific subacromial pain syndrome, and include long-term follow-up, large enough sample size, double-blind design and a placebo group.

Prognostic factors have been evaluated in previous studies, but most of these studies have used data from RCTs. Future prognostic studies should follow a larger cohort of patients with subacromial pain syndrome to increase the generalizability of the findings, and provide insight into the natural course of the condition.

For the association between imaging findings and symptoms, and imaging findings and treatment results, previous research is sparse. Future studies are warranted to evaluate the association between degenerative and clinical findings. In particular tendon morphology should be assessed before and after treatment and related to load, intensity, type and duration of exercise treatment.
References


113. Bøhmer AS SP, Brox JI: Supervised exercises in relation to rotator cuff disease (impingement syndrome stages II and III): A treatment


154. Schmitt JS, Di Fabio RP: Reliable change and minimum important difference (MID) proportions facilitated group responsiveness comparisons using individual threshold criteria. Journal of Clinical Epidemiology, 57(10):1008-1018.


Is radial Extracorporeal Shock Wave Therapy (rEWST) combined with supervised exercises (SE) more effective than sham rESWT and SE in patients with subacromial shoulder pain? Study protocol for a double-blind randomised, sham-controlled trial

Elisabeth Kvalvaag*, Jens Ivar Brox, Kaia Beck Engebretsen, Helene Lundgaard Søberg, Erik Bautz-Holter and Cecilie Røe

Abstract

Background: Subacromial shoulder pain is a common complaint. Radial Extracorporeal Shock Wave Therapy (rESWT) has being increasingly used to treat calcific and non-calcific tendinosis, although there is no evidence of the effectiveness of rESWT in non-calcific tendinosis of the rotator cuff. A randomised single blind study showed that the short-term effect of supervised exercises (SE) was significantly better than rESWT on subacromial shoulder pain, but both groups improved. In a clinical trial on achilles tendinopathy rESWT improved the effectiveness of treatment with eccentric loading. The objective of this present study is to evaluate if rESWT in addition to SE is more effective in improving shoulder pain and function compared with sham rESWT and SE in patients with subacromial shoulder pain.

Methods/Design: This is a double blind, randomised sham-controlled trial which is performed at the shoulder clinic at the Department of Physical Medicine and Rehabilitation in Oslo University Hospital, Norway. One-hundred-forty-four patients with subacromial shoulder pain lasting at least 3 months, age from 25 to 70 years old are included in the trial. Patients are randomly allocated in 1:1 ratio to receive either rESWT or sham rESWT once a week in addition to SE once a week for the initial 4 weeks. Subsequently SE are provided twice a week for 8 weeks. The primary outcome measure is a change in the Shoulder Pain and Disability Index (SPADI) at 24 weeks follow-up. Secondary outcomes include return to work, pain at rest and on activity, function, and health related quality of life. The patients, the physiotherapist providing the exercise regimen and the outcome assessor are blinded to group assignment. The physiotherapist providing the rESWT is not blinded.

Discussion: Because of the extensive use of rESWT in the treatment of subacromial shoulder pain the results of this trial will be of importance and have impact on clinical practice.

Trial registration: ClinicalTrials.gov NCT01441830

* Correspondence: ekvalv@ous-hf.no
Department of Physical Medicine and Rehabilitation, Oslo University Hospital
HF, Ullevål, Postboks 4956, Nydalen 0424, Oslo, Norway

© 2015 Kvalvaag et al. Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
Background
Shoulder pain is a common complaint, and in Norway about half of the population reports to have at least one episode of shoulder pain annually [1]. The most frequent diagnosis is subacromial pain (impingement syndrome or rotator cuff tendinosis are used synonymously) [2, 3]. The exact structures involved in the development of the pain condition are not clear, but the rotator cuff and the subacromial bursa are possible pain generators [4]. Current studies suggest that central mechanisms are involved [5]. In accordance with the complexity of this pain condition, a Cochrane review that has evaluated the physical tests used to identify subacromial pain have concluded that there is extreme diversity in the performance and interpretation of tests, which hinders synthesis of the evidence and/or clinical applicability [6].

The patients with subacromial shoulder pain are treated by physicians with different specialities, including general practitioners, rheumatologists, doctors in physical medicine and rehabilitation, orthopedic surgeons, and physiotherapists. Many patients with subacromial shoulder pain undergo surgery, even though supervised exercises (SE) have been shown to be as effective as surgery in both short and long term, and better than placebo [7, 8]. The main principles of SE are relearning of “normal” movement patterns which can then be transferred into daily activities. Optimal scapular positioning and centralisation of caput humeri are of importance when
performing the exercises before muscle-strengthening program begins [9, 10]. Several studies using similar supervised exercise programs have shown effect on pain and function [11].

Extracorporeal Shock Wave Therapy (ESWT) is another treatment option for patients with subacromial shoulder pain. The proposed mechanisms for the effect of ESWT include pain relief, tissue regeneration and destruction of calcification [12]. A systematic review found level 1 evidence of midterm effectiveness of ESWT in reducing pain and improving shoulder function for patients with chronic calcific tendinopathy of the rotator cuff, but no evidence in favour of ESWT in non-calcific rotator cuff tendinosis [13].

In recent years, a new method of shock wave treatment has been developed: radial Extracorporeal Shock Wave Therapy (rESWT), also called radial pulse therapy (RPT). In contrast to regular focused shock wave therapy (ESWT), rESWT creates a diverging pressure field, which reaches a maximal pressure already at the source, and therefore has a more superficial, but broader, effect than ESWT [12]. This treatment is increasingly used for calcific and non-calcific tendinopathy, probably because it is easier to apply and more affordable than ESWT. For calcific tendinopathy of the shoulder, a systematic review found limited evidence for the benefit of rESWT [13]. However, there is no evidence of the effectiveness of rESWT in non-calcific rotator cuff tendinosis [13, 14].

Musculoskeletal ultrasound might be an important supplement to the clinical examination [4]. Ultrasound can reliably detect calcification, partial and full-thickness tears, bursitis and tendinopathy [15]. Ultrasound examination may be particularly valuable when considering rESWT because rESWT would be expected to be most useful in case of calcification. With respect to routine radiological examination (MRI and ultrasound), a recent study found that structural changes in the rotator cuff and subacromial bursa did not predict short-term outcome after corticosteroid injection therapy [16].

Physiotherapy treatment for subacromial shoulder pain often is a combination of rESWT and exercise therapy. In a recent randomised single blind study the short-term effect of supervised exercises was significantly better than the effect of rESWT on subacromial shoulder pain, but both groups improved [17]. A clinical trial on achilles tendinopathy showed that rESWT significantly improved the effectiveness of eccentric training [18]. However, these studies did not comprise a sham rESWT study arm.

Additionally, previous studies have reported that the prognosis of subacromial shoulder pain is affected by education, work status, polymedication and high baseline pain and disability [16, 19, 20].

Aims
1. To evaluate whether rESWT in addition to supervised exercises is more effective in improving pain and function (SPADI) compared with supervised exercises and sham rESWT in patients with subacromial shoulder pain at 24 weeks follow-up.
2. To evaluate the influence of demographic and clinical factors on the clinical course of SPADI and sick leave in patients with subacromial shoulder pain during 1-year follow-up.

Methods
Study design
This study is a double blind, randomised, sham-controlled trial. All the patients are recruited from the shoulder clinic at the Department of Physical Medicine and Rehabilitation at Oslo University Hospital, Norway.

Ethics
This study has received approval from the Regional Committee for Medical and Health Research Ethics (2011/255).

Participants
Patients aged 25–70 years, with subacromial shoulder pain lasting at least 3 months, are eligible for inclusion.

The inclusion criteria are: dysfunction or pain on abduction, normal passive glenohumeral range of motion, pain on at least one of two isometric tests (abduction and/or external rotation) and a positive Hawkins impingement sign [21]. Patients with bilateral shoulder pain are included if both shoulders fulfil the inclusion criteria.

The exclusion criteria are: previous surgery on the affected shoulder, instability, rheumatoid arthritis, full thickness tear of the rotator cuff, cervical radiculopathy, infection, patients considered not being able to fill out questionnaires or follow the treatment, contraindications for shock waves therapy (use of anticoagulant drugs, bleeding disorder, epilepsy, pregnancy or pacemaker), previous experience with shock wave therapy, injection of cortisone in the affected shoulder in the last 6 weeks and SPADI score below 20.

Randomisation and blinding
The patients who fulfil the inclusion criteria and give their informed consent after having received oral and written information are randomised to one of the two treatment groups: supervised exercises and rESWT, or supervised exercises and sham rESWT. Computer-based block-randomisation with 20 in each block in a 1:1 ratio will be performed. A research assistant not involved in
the further management of the patients opens the sealed envelopes and assigns the patients to their respective treatment group. The rESWT and the sham rESWT are subsequently performed by a physiotherapist not involved in any further management of the patients.

The patients, the researchers collecting and analysing the data, the authors and the physiotherapists providing the exercise regimen are all blinded for rESWT/sham rESWT. The blinding will not be revealed until the results are analysed and the interpretation is discussed and written down in two versions, one assuming that treatment A is rESWT, and one assuming that treatment A is sham rESWT.

To evaluate the blinding, all the patients are asked at the 24-week follow up whether they think they have received real rESWT or sham rESWT.

**Interventions**

Patients from both intervention groups receive a supervised exercise regimen by experienced physiotherapists. During the initial 4 weeks, they conduct supervised exercises once a week. The last 8 weeks, they perform supervised exercises twice a week. Each supervised exercise session lasts 40 min. In addition, the patients are instructed to conduct home exercises daily.

The patient’s history and functional diagnosis are used as individual guidelines for treatment in the first phase. The main goals of the supervised exercise regimen used in this study are to unload mechanical stress and to normalise dysfunctional neuromuscular movement patterns. Postural exercises, optimal scapular positioning and centralisation of caput humeri are of importance when performing the exercises. The physiotherapist supervises and ensures that the patients perform the movements correctly. Then eccentric training, exercises with gradually increasing resistance, and plyometric exercises to improve muscle strength and endurance are performed [9]. Newer research also emphasises a specific and non-generalised treatment approach to this disorder [22]. It is essential to achieve a normal scapulothoracic motion before a muscle-strengthening program can begin, and different studies emphasise the importance of correcting scapular dyskinesis [22–24]. Review articles conclude that the exercise regimen for patients with subacromial shoulder pain are poorly described, but should include postural exercises (posture, shoulder retraction), pendulum exercises for the glenohumeral motion, active assisted AROM, exercises for the rotator cuff, scapular stability training, and stretching/flexibility exercises [11, 25, 26].

The first 4 weeks, the patients receive rESWT or sham once a week in addition to the exercises. The rESWT or sham treatment (SwissDolorClast/EMS) is given by one of two physiotherapists who both went through an application course and training before the study started. The rESWT/sham is given on one to three tendons (supraspinatus, infraspinatus and/or subscapularis), depending on which tendons are painful at isometric tests. Two thousand impulses of shock waves are applied to each painful tendon, with a pressure between 1.5 and 3 bar (depending on what the patient tolerates). We use a power handpiece, which provides an energy of 0.01 – 0.35 ml/mm2. This handpiece was chosen after advice from the producer (Enimed/SwissDolorClast). Physiotherapists with experience in rESWT, and a previous systematic review concluding that future research on rotator cuff tendinosis should focus on high-energy shock wave [27].

The sham rESWT is administered in the exact same way as the rESWT. The sham handpiece is similar to the real handpiece in design, shape and sound, and vibrates exactly like the real handpiece, but no real shock waves are conducted.

Compliance to the treatment is recorded.

**Outcome measurements and assessment**

The patients eligible for inclusion are referred to a physician (EK), who examines all the patients at baseline according to a structured protocol including active and passive range of motion, isometric tests, Hawkins sign, examination of the AC joint and biceps tendon. Ultrasound examination of the affected shoulder is performed the same day. The patients also complete a comprehensive standardised questionnaire including primary and secondary outcome measures, the prognostic demographic and clinical factors including sex, age, duration of symptoms, education, drug use, sick leave status and emotional distress. If an MRI has not been performed within the last 3 months, the patients are also referred for an MRI of the affected shoulder.

Self-reported primary and secondary outcome measures are filled in at each follow-up. At 6 weeks after starting the treatment, the patients fill in a short questionnaire. At 12- and 24 weeks and at 1 year they come to follow-up visits where they have an additional clinical examination, all done by the same blinded physician (EK) Fig 1. At 1 year we also perform ultrasound examination.

The primary outcome measure is the Shoulder Pain and Disability Index (SPADI). The SPADI is a self-assessed, validated shoulder score that consists of 13 questions in two subscales, five about pain and eight about function. We use the original version, with each question scoring previous week’s symptoms on a visual analogue scale (VAS). The total SPADI is calculated from averaging the two subscales, and the total score ranges from 0 to 100 with higher score indicating worse pain and disability [28].

Secondary outcomes are return to work, pain at rest and activity measured on an 11-point Likert type scale, function (ability to take something down from a shelf or
to carry a 5-kg shopping bag) measured on an 11-point Likert type scale, and health related quality of life on EuroQol.

EuroQol (EQ-5D and EQ-VAS) is a standardised generic instrument for describing and valuing health related quality of life. The EQ-5D comprises five domains that define health in terms of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each domain has three response categories; no problem, some or moderate problems, extreme problems. The resulting health state can therefore be defined as a five-digit number by using the response (1–3) from each dimension. Potentially 243 health states can be defined. The five-digit number is then transformed into a number between -0.56 and 1 with 1 representing the best imaginable health state. The EQ-VAS is a self rating of health status on a vertical VAS from 100 (best imaginable health state) at the top to 0 (worst imaginable health state) at the bottom [29].

The patients are instructed not to attend to any other treatment in the study period. We will register on each follow-up visit if they have received any other treatment since the last visit. The use of analgesics is recorded on follow-up visit if they have received any other treatment since the last visit. The use of analgesics is recorded on baseline and on each follow-up visit.

Sample size
A previous study indicates an expected standard deviation (SD) of 20 points [17]. To detect a difference in SPADI on 10 points between the groups with a statistical power of 80% and a significance level of 0.05 we need 50 persons in each group. We have planned to include 144 persons to account for drop out and possibly higher variance.

Statistical analysis
Descriptive statistics will be used to describe baseline characteristics of the treatment groups. The comparison of between group difference in both primary and secondary outcome variables will be performed according to the intention to treat principle.

Analysis of variance will be applied to evaluate the difference between groups in the change of primary outcome measure (SPADI) between the baseline and 24 weeks follow-up, adjusting for demographic and medical factors such as age, sex, education, sick leave, duration of symptoms, calcification in the rotator cuff, dominant arm affected, bilateral shoulder pain, drug use, emotional distress and compliance to the rESWT treatment. Secondary outcome measures will be assessed with the same approach in separate models. Cox regression will be used to analyse the secondary outcome of return to work at 1 year follow-up.

Finally, mixed model will be applied to explore the variations of the mean SPADI from baseline through the 1-year follow-up within and between patients (between the intervention groups) simultaneously. The effects of demographic and clinical factors on the change of SPADI will also be explored. Number needed to treat will be calculated according to Guyatt et al [30]. Bonferroni correction will be used to correct for multiple testing of secondary outcome.

To deal with missing values of the important analytic variables multiple imputation will be carried out. Estimations from the imputed data will be compared with the estimation from the data with complete values.

Discussion
Placebo means to please (from latin placere). It is proposed that placebo and opioid analgesics share a neuronal network [31]. The powerful placebo effect is summarized in a recent systematic review [32]. The vertebroplasty trials [33, 34] and the knee arthroscopy trial have demonstrated the effectiveness of sham surgery [35]. One early trial in patients with subacromial shoulder pain reported that sham ESWT was superior to ESWT [36].

Radial ESWT is being increasingly used for musculoskeletal complaints including subacromial shoulder pain, with and without calcification. Current evidence suggests that rESWT may have an effect on calcific tendinopathy of the shoulder, but there is no evidence so far to support the use of rESWT in subacromial shoulder pain without calcification [13, 14, 17, 27]. Most therapists use rESWT on shoulder pain without the use of imaging, and thus do not know whether they are treating a calcific shoulder or not. In this present study we treat patients with subacromial shoulder pain (with and without calcification) with supervised exercises and rESWT. We perform ultrasound examination before treatment and may therefore do subgroup analysis to evaluate if the results are different in the patients with calcific tendinopathy compared to the patients with non-calcific tendinopathy.

In the present study we have included sham treatment to make sure that any difference in results between the groups is due to the rESWT treatment, and not the placebo effect. All the patients get supervised exercises in addition to rESWT or sham, because this is the way most therapists use rESWT today. Exercise therapy is an evidence based treatment option for subacromial shoulder pain, both in short- and long term [11, 37].

Because of the abundant use of rESWT, the results of this study will be of major interest. A positive result will support current practice, while no difference between the groups indicates that the use of rESWT for subacromial shoulder pain should not be recommended.

Competing interests
The authors declare that they have no competing interests.
Authors’ contributions

EK participated in the design of the study, drafted the manuscript, and evaluated the patients for inclusion and follow-up visits. JB participated in the design the study and drafted the manuscript. KBE participated in the design of the study, did some of the supervised exercise treatment of the patients, and helped to draft the manuscript. HLS participated in the design of the study and helped draft the manuscript. EBR participated in the design of the study and helped draft the manuscript. CR participated in the design the study and drafted the manuscript. All authors read and approved the final manuscript.

Acknowledgements

We would like to thank Sophies Minde Ortopedi AS for financial support. We would also like to thank Niels Gunnar Juell for clinical advice and contribution to recruit shoulder patients.

Received: 25 November 2014 Accepted: 7 September 2015

Published online: 11 September 2015

References

Shoulder MRI features with clinical correlations in subacromial pain syndrome: A cross-sectional and prognostic study.


E Kvalvaag1,2 MD
Corresponding author
1Department of Physical Medicine and Rehabilitation, Oslo University Hospital HF, Ullevaal, Postboks 4956 Nydalen, 0424 Oslo, Norway
2University of Oslo, Medical Faculty, Boks 1072 Blindern, 0316 Oslo, Norway
E-mail: e.m.kvalvaag@medisin.uio.no
Telephone: +47 911 007 33/ +47 230 274 44

M Anvar, MD, PhD
Department of Radiology, Oslo University Hospital HF, Ullevaal, Postboks 4956 Nydalen, 0424 Oslo, Norway
E-mail: masoud.anvar@gmail.com

AC Karlberg, MD
Department of Radiology, Oslo University Hospital HF, Ullevaal, Postboks 4956 Nydalen, 0424 Oslo, Norway
E-mail: anceka@ous-hf.no

JI Brox MD, Professor
Department of Physical Medicine and Rehabilitation, Oslo University Hospital HF, Ullevaal, Postboks 4956 Nydalen, 0424 Oslo, Norway
E-mail: j.i.brox@medisin.uio.no

KB Engebretsen PT, PhD
Department of Physical Medicine and Rehabilitation, Oslo University Hospital HF, Ullevaal, Postboks 4956 Nydalen, 0424 Oslo, Norway
E-mail: k.b.engebretsen@medisin.uio.no

HL Søberg PT, PhD
Department of Physical Medicine and Rehabilitation, Oslo University Hospital HF, Ullevaal, Postboks 4956 Nydalen, 0424 Oslo, Norway
E-mail: h.l.soberg@medisin.uio.no

NG Juel MD
Department of Physical Medicine and Rehabilitation, Oslo University Hospital HF, Ullevaal, Postboks 4956 Nydalen, 0424 Oslo, Norway
E-mail: ungxju@ous-hf.no

E Bautz-Holter MD, Professor
Department of Physical Medicine and Rehabilitation, Oslo University Hospital HF, Ullevaal, Postboks 4956 Nydalen, 0424 Oslo, Norway
E-mail: erik.bautz-holter@medisin.uio.no

L Sandvik Professor
University of Oslo, Faculty of Dentistry, Boks 1072 Blindern, 0316 Oslo, Norway
E-mail: leiv.sandvik@odont.uio.no

C Røe MD, Professor1,2
1Department of Physical Medicine and Rehabilitation, Oslo University Hospital HF, Ullevaal, Postboks 4956 Nydalen, 0424 Oslo, Norway
2University of Oslo, Medical Faculty, Boks 1072 Blindern, 0316 Oslo, Norway
E-mail: e.c.t.roe@medisin.uio.no
ABSTRACT

Background:
Previous studies on shoulder patients have suggested that the prevalence of rotator cuff or bursa abnormalities are weakly related to symptoms and that similar findings are often found in asymptomatic persons. In addition, it is largely unknown whether structural changes identified by magnetic resonance imaging (MRI) affect outcome after treatment for shoulder pain. The purpose of this study was therefore to evaluate the presence of structural changes on MRI in patients with subacromial pain syndrome and to determine to what extent these changes are associated with symptoms and predict outcome after treatment (evaluated by the Shoulder Pain and Disability Index (SPADI)).

Methods:
A prospective, observational assessment of a subset of shoulder patients who were included in a randomized study was performed. All participants had an MRI of the shoulder. An MRI total score for findings at the AC joint, subacromial bursa and rotator cuff was calculated. Multiple linear regression analysis was applied to examine the relationship between the MRI total score and the outcome measure at baseline and to examine to what extent the MRI total score was associated with the change in the SPADI score from baseline to the one year follow-up.

Results:
There was a weak, inverse association between the SPADI score at baseline and the MRI total score ($\beta=-3.1$, with 95% CI -5.9 to -0.34; p=0.03), i.e. the SPADI score was higher for patients with a lower MRI total score. There was an association between the change in the SPADI score from baseline to the one year follow-up and the MRI total score ($\beta=8.1$, 95% CI -12.3 to -3.8; p < 0.001), with a poorer outcome for patients with a higher MRI total score. Both tendinosis (p=0.01) and bursitis (p=0.04) were associated with a poorer outcome after one year.

Limitations:
As there was no previously validated score for findings at MRI of the shoulder available, we calculated a total score that is not used in previous studies. In addition, the patients were
not blinded to the results of their MRI scans, which may have influenced the observed associations.

**Conclusion:**
In this study, MRI findings were significantly associated with the change in the SPADI score from baseline and to one year follow-up, with a poorer outcome after treatment for the patients with higher MRI total score, tendinosis and bursitis on MRI.

**Trial registration**
Clinicaltrials.gov no NCT01441830

**KEYWORDS**
MRI, shoulder pain, subacromial pain syndrome, patient outcome, prognosis
BACKGROUND

Shoulder pain is a common musculoskeletal problem that causes disability and pain for the patient, and sick leave expenses for the patient as well as for the society. [1, 2] The most frequent shoulder diagnosis is subacromial pain syndrome (also called shoulder impingement syndrome). [3] It is important to establish valid diagnostic methods for these patients to potentially improve management and treatment of this syndrome.

Magnetic resonance imaging (MRI) has become a frequently used diagnostic tool for the evaluation of structural abnormalities in the shoulder. This includes the rotator cuff and the subdeltoid/subacromial bursa, and other structural abnormalities. [4]

Previous studies have suggested that the prevalence of rotator cuff or bursa abnormalities is weakly related to symptoms and that similar findings are often found in asymptomatic persons. One study found changes (grade 1) in 80% of the supraspinatus tendons of asymptomatic baseball pitchers with no significant difference between the throwing and the non-throwing arm. [5] Another study found no significant differences for the prevalence of partial tears, AC joint degeneration or tendinopathy in symptomatic vs asymptomatic Ironman Triathletes. [6] One review reported that partial thickness tears of the rotator cuff were more common in asymptomatic volunteers than in individuals with painful shoulders. [7] Enhancement of the subacromial/subdeltoid bursa was not found to have any relationship to shoulder symptoms in symptomatic and asymptomatic rotator cuff tears in two studies. [8, 9] In contrast, another study found that subacromial bursal effusion was correlated to the reported severity of the shoulder disability in patients with subacromial impingement syndrome. [10]

It is largely unknown whether structural changes identified by MRI affect the outcome of non-operative treatment for shoulder pain. One previous study reported no predictive value of rotator cuff tendon pathology or bursal exudation as detected via sonography or MRI on short term outcome after corticosteroid injection in patients with subacromial pain. [11] However, two other studies reported that patients with minor-grade (possibly reversible) MRI findings presented a more favorable course after conservative treatment compared to patients with more severe findings on MRI. [12, 13]

Despite the weak correlation between clinical and radiologic findings, many patients with symptoms of subacromial pain syndrome are referred for an MRI, in Norway often
already in primary health care. In addition, MRI findings (together with clinical examination) are often used as indications for surgery in this patient group.

The objective of this study was therefore to evaluate the presence of structural changes on MRI in patients with subacromial pain syndrome and to determine to what extent these changes are associated with symptoms and predict outcome after treatment (evaluated by the Shoulder Pain and Disability Index (SPADI)). We hypothesized that degenerative findings like tendinosis, bursitis, partial tears, AC joint osteoarthritis, calcification and acromial morphology detected on MRI in patients with subacromial pain syndrome are not related to symptoms (as determined by the Shoulder Pain and Disability Index (SPADI)) before and after exercise treatment.

METHODS

Study design, setting and participants
A prospective observational assessment of patients with subacromial pain syndrome who were included in a randomized controlled trial was undertaken. [14] The trial (clinicaltrials.gov registry number NCT01441830) included 143 patients aged 25 to 70 years old with subacromial pain syndrome lasting at least 3 months. The patients were enrolled between January 2012 and April 2014 at the outpatient shoulder clinic at the Department of Physical Medicine and Rehabilitation, Oslo University Hospital. All patients provided written informed consent. A brief description of the original trial participants follows.

The inclusion criteria were pain on one of two isometric tests (abduction or external rotation), positive Hawkins-Kennedy impingement sign [15] and normal passive glenohumeral range of motion. The exclusion criteria were previous surgery on the affected shoulder, instability, rheumatoid arthritis, full thickness tear of the rotator cuff, cervical radiculopathy, infection, patients considered unable to fill out questionnaires or follow the treatment, contraindications for shock wave therapy (use of anticoagulant drugs, bleeding disorder, epilepsy, pregnancy or pacemaker), previous experience with shock wave therapy, injection of cortisone in the affected shoulder in the last six weeks and a SPADI score below 20.

Patients were randomly assigned to one of two treatment groups; rESWT and supervised exercises (n=69) or sham rESWT and supervised exercises (n=74). The
rESWT/sham was conducted once a week in the first four weeks of the study. All patients were offered up to 20 supervised exercise sessions during the treatment period of 12 weeks, but for various reasons, many patients attended fewer sessions. The median number of sessions was 13 (range two to 20).

The primary study results after 24 weeks showed no significant differences in any outcome measures between the two treatment groups. [14] Of the 143 patients enrolled in the original trial, 115 had an available MRI of their painful shoulder and were included in the current study. For the patients with bilateral shoulder pain, the MRI of their most painful shoulder was included.

**Clinical evaluation and assessment**

At baseline, the patients completed a self-assessment questionnaire that included demographic and clinical prognostic factors and the SPADI. A clinical examination was performed, and the active range of motion in abduction and the external rotation were recorded. The first author (EK) did all the clinical assessments. Range of motion in abduction was assessed with the patient sitting on a chair in front of a panel with the degrees from 0-180 printed on. [16] External rotation was measured sitting on the same chair, with the chair placed on a similar panel and the arm in neutral position. The pain-provoking isometric strength test for abduction was performed with the shoulder in 30 degrees of abduction. The isometric external and internal rotation was performed in neutral position of the shoulder. The patients were asked whether the test was painful or not (yes/no) and the answer was recorded.

The SPADI is a self-assessment questionnaire with 13 questions divided into two subscales; one with five questions regarding shoulder pain and one with eight questions regarding shoulder function. Each question is scored on a visual analogue scale from 0 to 11. The total SPADI score ranges from 0 to 100, with 0 being no pain and disability and 100 being the worst possible pain and disability. [17]

For this study, the patients came to a follow-up visit after one year.

**MRI protocol and review**

The patients included in the randomized trial were referred for an MRI at the Radiologic Department at Oslo University Hospital (except for the patients with contraindications for
MRI and/or claustrophobia). MRIs taken before referral to the shoulder clinic at the Department of Physical Medicine and Rehabilitation at Oslo University Hospital were accepted if the images had been obtained within the last three months.

When the data were analyzed, the following variables from the MRI examinations were used: Acromion type (I, II, III, IV), AC-joint osteoarthritis (yes/no), bursitis (yes/no), tendinosis in one or more tendons of the rotator cuff (yes/no), partial tear in one or more tendons of the rotator cuff (yes/no) and calcification in one of more tendons of the rotator cuff (yes/no).

A previous study calculated an MRI total score for patients with low back pain and found no association between degenerative findings and pain and disability. [18] We therefore calculated a similar MRI total score for shoulder patients, using findings at the AC joint, subacromial bursa and rotator cuff and used this in the analysis in addition to each of the individual findings. Each of the following findings contributed one point to the total MRI score: tendinosis in one or more tendons of the rotator cuff (yes/no), partial tear in one or more tendons of the rotator cuff (yes/no), calcification in one or more tendons in the rotator cuff (yes/no), bursitis (yes/no) and AC-joint osteoarthritis. See figure 1. Thus, the score ranged from 0-5 points. As there were only three patients with all five findings, they were included in the group of patients with four findings on MRI, and the maximum MRI total score could be four points.

Images
Sixty-two (53.9%) patients had a shoulder MRI from our hospital; the rest of the patients had an MRI from a private center taken shortly before they were included in the study. The MRI examinations included the following sequences: 111 (96.5%) had transverse PDFS images, 66 (57.5%) had sagittal T1 weighted images, 100 (86.9%) had sagittal T2-weighted images, 41 (35.7%) had coronal PD images, 85 (73.9%) had coronal T2-weighted images and 101 (87.8%) had coronal PDFS images. Four (3.5%) examinations were MRI arthrograms.

Image evaluation
Two radiologists who were blinded to clinical data and experienced in musculoskeletal MRI evaluated the images retrospectively with a clinical Picture Archiving and Communication System (PACS). The imaging reading software used was the Siemens Syngo Studio and Syngo
Imaging VB36C. One observer had more than five years of experience, and the other had more than ten years. In a pilot study, the two observers evaluated ten shoulder MRIs to achieve a common understanding of the image evaluation criteria. The following criteria were used:

**AC joint osteoarthritis:** Degenerative changes of the AC joint are defined by the presence of joint space narrowing, periartricular sclerosis or bone marrow edema, subchondral cyst formation, marginal osteophyte formation, joint effusion and capsular distention. [19]

**Acromion morphology:** The shape of the acromion as seen in sagittal oblique MR images was assessed. Four morphologies have been identified. In type I, the acromion is flat; in type II, the acromion is curved; in type III; the acromion is hooked; and in type IV, the acromion has a convex inferior contour. [20]

**Subacromial-subdeltoid (SASD) bursitis:** SASD bursitis is defined by thickening or distention of the bursa. This can been seen as a low intensity signal in T1 and increased signal intensity on T2, PD-weighted images or PDFS- weighted sequences. [21]

**RC tendinosis:** On MRI, tendinosis appears as swelling and an increased signal on low TE images, such as PDFS, STIR or T2 with fat suppression or an intermediate signal on T2-weighted images. However, the signal is not as bright as fluid. [21, 22] Calcific tendinosis is defined as the deposition of calcium within or around the rotator cuff tendons. It has low signal intensity on all pulse sequences, and there is usually edema within the tendon and occasionally within subjacent bone. [21]

**RC Partial-Thickness Tears:** A partial rotator cuff tear involves only a portion of the tendon. Partial tears are seen as a focal fluid signal within the tendon, without complete extension from the bursal to articular surface. If a chronic partial tear has started to develop granulation tissue, the signal may be somewhat hypointense to fluid. Partial tear subtypes include articular-sided, bursal-sided, or intrasubstance tears and include both delaminating tears as well as focal tears confined within the footprint of the tendon. [21]
Statistical analysis

Statistical analysis was performed with SPSS software (IBM SPSS for Windows, version 23, Chicago IL, USA). The data were analyzed by an independent statistician not involved in the radiologic or clinical data collection. Multiple linear regression analysis was carried out with the SPADI score at baseline and the change in the SPADI score from baseline to the one year follow-up as dependent variables and with the MRI total score as a covariate. We adjusted for age, gender, education, work status and emotional distress (HSCL-25). The multicollinearity, residuals and influential data point checks showed that the assumptions of the regression models were not violated (Cook distance < 0.1, Centered Leverage value < 0.2). Analysis with treatment arm as an additional covariate was also run without influencing the results. All analyses were adjusted for the baseline value of the dependent variable. The same analyses were performed with the individual dichotomized MRI findings as covariates, with separate analyses for each MRI finding. The variance inflation factor (VIF) was checked, and was low for all variables. All analyses were also run separately in each treatment arm providing similar results as for the pooled analysis.

To assess the robustness of the results, we also did multiple linear regression analysis with all individual MRI findings in the same analysis, and manual backwards selection until all remaining variables had a p value of below 0.05. SPADI baseline, age, gender, education, work status and emotional distress were kept in the model.

RESULTS

Patient characteristics

Of the 115 patients included in this study, there were 62 women and 53 men. The mean age was 47 years. All patients had MRI and baseline data. Baseline data and comparisons with the 143 patients included in the original study are described in table 1.

One hundred and four of the 115 patients completed the study and had available SPADI scores after one year. The mean SPADI score at baseline was 52.4 (SD 17.0). There were 28 (24.3%) patients with acromion type I, 78 (67.8%) patients with acromion type II, four (3.5%) patients with acromion type III and five (4.3%) patients with acromion type IV. There were 28 patients (24.3%) with calcification in the rotator cuff, 85 (73.9%) with tendinosis, 40 (34.8%) with a partial tear in the rotator cuff, 65 (56.4%) with subacromial bursal effusion and 82 (71.3%) with AC joint osteoarthritis. There were eight patients with
none of these structural findings on MRI, and three patients with all, i.e. calcification, tendinosis, subacromial bursal effusion, AC joint osteoarthritis and partial tear in the rotator cuff.

After one year, the mean SPADI score was 29.7 (SD 26.1), and the mean change in the SPADI score from baseline to the one year follow-up was 22.1 (SD 25.7).

Clinical examination
The only variable from the clinical examination at baseline associated with a higher SPADI score at baseline was the active range of motion in abduction. For each 11 degree increase in AROM abduction, the SPADI score would decrease by 1.7 points (p < 0.001, 95% confidence interval (CI) -1.0 to -0.30). No recorded variables from the clinical examination had any predictive value when evaluating the change in the SPADI score during one year follow-up.

MRI findings vs. SPADI baseline
The MRI total score was weakly correlated to the SPADI score at baseline (β=-3.1, with 95% CI -5.9 to -0.34; p=0.03, R² 1.9%), as seen in table 2. There were no significant correlations between the SPADI score at baseline and individual structural changes on MRI, except for calcification in the rotator cuff (β=-8.2, with 95% CI -15.4 to -1.1; p=0.03, R² 4.4%) (table 2). For both the MRI total score and the individual calcification in the rotator cuff the correlation was inverse, i.e., the patients with calcification or high MRI total score had a lower SPADI score at baseline than the patients without calcification or a low MRI total score.

We also did analysis with all the individual MRI findings in a single model and manual backwards selection. The only remaining variable with a p value below 0.05 in this analysis was calcification in the rotator cuff (with the same result as presented above).

MRI findings vs. change in the SPADI score after one year
After one year, the MRI total score was significantly correlated to the change in the SPADI score, with an 8.1 point decrease in the change in the SPADI score for each structural change that was detected at MRI (95% CI -12.3 to -3.8; p< 0.001, R² 8.8%), see table 3 and figure 2.
Of the individual structural changes, tendinosis ($\beta=14.1$, with 95% CI 3.3 to 25.0; $p=0.01$, $R^2$ 4.5%) in the rotator cuff and bursitis ($\beta=10.2$, with 95% CI 0.3 to 20.1; $p=0.04$, $R^2$ 3.0%) at baseline was associated with a poorer outcome. There was also a tendency towards a poorer outcome for the patients with AC joint osteoarthritis and calcification in the rotator cuff at baseline, but this difference was not statistically significant (table 3). We also did analysis with all the individual MRI findings in a single model and manual backwards selection. The only remaining variable with a $p$ value below 0.05 in this analysis was tendinosis in the rotator cuff (with the same result as presented above).

There was no difference in the mean change in the SPADI score after one year for the patients with a flat/upward acromion (type I and IV) vs. the patients with a hooked acromion (type II and III); $\beta=-1.1$, 95% CI -12.2 to 9.9, $p=0.84$.

**DISCUSSION**

The main finding of the current study was that a higher MRI total score (more structural findings) predicted a poorer outcome after one year. Of the individual structural findings, tendinosis in one or more tendons of the rotator cuff and bursitis predicted a poorer outcome.

Few previous studies have evaluated whether structural changes detected on MRI influence prognosis after conservative treatment in this patient group. Ekeberg et al. found no contribution to their predictive model on short term outcome (six weeks) after corticosteroid injection when considering rotator cuff or bursal abnormalities detected on MRI and sonography. [11] However, their study had a short follow-up and no standardized description of the MRIs. Ertan et al. found that patients with “minor-grade” MRI findings presented a more favorable course in the long term, which supports our findings, even though their study used a different MRI classification than ours. [12] Hambly et al. reported similar findings as Ertan et al. and used even another MRI classification system. [13] Ketola et al. found that patients with AC joint degeneration had more pain five years after surgery for shoulder impingement syndrome. [23] However, AC joint degeneration is very common, and there is poor evidence for the effectiveness of surgery. [24-26]

In contrast to our study, some previous studies have reported a poorer outcome after conservative treatment in patients with a hooked acromion (type II and III), [27, 28]
while other studies have called into question the relevance of the shape of acromion, and reported low interobserver reliability for assessing acromial shape. [29-31]

At baseline, we found a weak inverse correlation between the SPADI score and the MRI total score. The MRI total score explained only 1.9% of the variance in baseline SPADI and the observed weak association has no clinical significance. We speculate however that one possible explanation may be that the general practitioners refer more patients with several structural changes on MRI, including patients with a low symptom burden. Previous studies have shown conflicting results regarding the association between structural changes detected on MRI and symptoms, but an inverse relation has not been reported. Reuter et al. found no significant differences in the prevalence of partial tears, AC joint degeneration or tendinosis in symptomatic vs. asymptomatic Ironman Triathletes. [6] One review reported that partial thickness tears of the rotator cuff were more common in asymptomatic volunteers than in individuals with painful shoulders. [7] Enhancement of the subacromial/subdeltoid bursa was not found to have any relationship to shoulder symptoms in individuals with symptomatic and asymptomatic rotator cuff tears in two studies, [8, 9] but in contrast, Ardic et al. reported that subacromial bursal effusion was correlated to the reported severity of shoulder disability in a small cohort including patients with subacromial impingement syndrome. [10]

Results in the present study suggest inferior clinical results after one year in patients with more degenerative changes of the subacromial structures detected on MRI (in particular tendinosis and bursitis). However, the variance explained by MRI findings was low, the total score explained less than 10 % and tendinosis or bursitis less than 5 %. Still, future studies should evaluate tendon morphology before and after exercises and examine the relation between exercise type, load, intensity and duration. We may hypothesize that patients with more degenerative findings may benefit from slower progression and longer duration and that this was not obtained in the present study. Compliance with exercise therapy varied as suggested by the range of sessions reported and reasons for lack of compliance may include low motivation and difficulties in fitting exercise sessions with the work schedule.

The main strengths of the present study are that we included a large number of patients with subacromial pain syndrome diagnosed according to prespecified criteria. Two experienced radiologists that were blinded for clinical data reexamined all MRIs in
conference, and conclusions were reached by consensus. We used the SPADI score, which is a reliable and validated shoulder questionnaire for the evaluation of the patient’s pain and function. [32]

The major limitation of this study is that the MRI total score used in this study is not previously validated. Second, the patients were not blinded to the result of their MRI scan. We cannot exclude that the interpretation of MRI findings, how patients are informed about the findings, and how they finally attribute findings to their complaints, may influence the observed association between MRI findings and self-reported pain and disability after one year. It is not unlikely that patients with a higher number of more pronounced degenerative findings to a larger extent are informed that pain is caused by the observed MRI findings as compared to those with fewer degenerative findings. Ideally, in studies that evaluate the association between degenerative findings and symptoms, patients should be blinded to the description of MRI during follow-up.

In addition, different MRI scanners were used for the imaging. Moreover, the structural changes detected on MRI have not been confirmed by surgery. Previous studies have reported variable results regarding the diagnostic accuracy of shoulder MRI, especially when evaluating partial thickness tears and tendinosis, [33, 34] but we used a consensus between two experienced radiologists to improve the validity of the MRI evaluation. Also, we did not obtain MRIs at one year follow-up to assess the evaluation between an eventual reversal of morphology and changes in symptoms.

In addition, the high prevalence of degenerative findings in the asymptomatic population are consistently reported for the shoulder[5-7] and other musculoskeletal locations. [35-37] Thus, degenerative findings similar to those observed in the present study are normally found in persons with no pain or disability. [38]

Moreover, some of the confidence intervals were quite wide, suggesting more uncertainty and the sample size should have been larger. Further studies with more patients are needed to confirm the results.

Accordingly, the results from the present study should be interpreted with caution.

In summary, we found that the combined MRI findings were statistically significantly associated with the change in the SPADI score from baseline to the one year follow-up, with a poorer outcome for the patients with several findings on MRI. Of the individual findings, tendinosis in the rotator cuff and bursitis were associated with a poorer outcome. Further
studies are warranted to evaluate the association between degenerative and clinical findings. In particular tendon morphology should be assessed before and after treatment and related to load, intensity, type and duration of exercise treatment.

**LIST OF ABBREVIATIONS**

RESWT: Radial Extracorporeal Shock Wave Therapy  
MRI: Magnetic Resonance Imaging  
SPADI: The Shoulder Pain and Disability Index  
AC joint: Acromio-clavicular joint

**DECLARATIONS**

**Acknowledgements**

We thank all the participants for their valuable contribution to this study and Sophies Minde Ortopedi for funding of the project.

**Funding**

The trial was funded by Sophies Minde Ortopedi. The funder of the study had no role in the design of the study, data collection, data analysis, data interpretation, or writing of the article.

**Availability of data and materials**

- The datasets generated and analysed during the current study are not publicly available due to Norwegian personal data protection laws, but are available from the corresponding author on reasonable request.
Authors’ contributions

EK contributed to the design of the study, enrolment of patients, data gathering, analysis, interpretation and writing of the manuscript. MA and ACK were the radiologists, and re-examined all MRIs, in addition they contributed to data interpretation and writing of the manuscript. JIB, HLS, and EB-H contributed to the design of the study, data interpretation and writing of the manuscript. KBE contributed to the design of the study and conducted some of the supervised exercise treatment of the patients, data interpretation and writing of the manuscript. NGJ contributed to the design of the study, enrolment of patients, data interpretation and writing of the manuscript. LS was the statistician and contributed to the data analysis, interpretation and writing of the manuscript. CR contributed to the literature search, design of the study, data analysis, interpretation and writing of the manuscript. All authors have seen and approved the final version of the manuscript.

Competing interests

EK received non-personal research grants from Sophies Minde Ortoped; MA, ACK, JIB, KBE, HLS, NGJ, EB-H, LS and CR declare no competing interests. None of the authors have financial relationships with any organisations that might have an interest in the submitted work.

Consent for publication

Not applicable.

Ethics approval and consent to participate

This study was approved by the regional committee for medical and health research ethics (No 2011/755). All participants provided written informed consent.


3. Juel NG, Natvig B: **Shoulder diagnoses in secondary care, a one year cohort.** *BMC Musculoskelet Disord* 2014, 15:89.


16. Brox JI, Brevik JI, Ljunggren AE, Staff PH: **Influence of anthropometric and psychological variables pain and disability on isometric endurance of shoulder


Figure 1A-H. Oblique coronal PDFS-weighted (A, C, E, G), oblique coronal T2-weighted (B, D, H), and axial PDFS-weighted (F) MRI images in five different patients (A-B, C-D, E-F, G, H) illustrating typical MRI findings assessed in this study. A and B demonstrate tendinosis with thickening and increased intermediate signal within the supraspinatus tendon (black and white arrows). C and D demonstrate partial tears with signal abnormality in the undersurface extending to the intrasubstance in the supraspinatus tendon (black and white arrows). E and F demonstrate calcific tendinosis of the supraspinatus tendon with low density areas (white and black arrows) and edema in tendon and the subjacent bone. In addition there is slightly fluid in the subacromial/subdeltoid bursa. G demonstrates subacromial/subdeltoid bursitis with increased fluid and slightly thickening of the wall (white arrow). H demonstrates AC joint osteoarthritis with prominent undersurface osteophyte formation causing narrowing of the supraspinatus outlet (white arrows).
Figure 2. Change in SPADI score from baseline to one year follow up for the patients with zero to four points on the MRI total score, from multiple linear regression analysis.

Table 1. Demographic and clinical factors at baseline. Values are numbers (percentages) unless stated otherwise.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Population with MRI (n=115)</th>
<th>Original population (n=143)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>47.0 (10.2)</td>
<td>46.7 (10.5)</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤12 years at school</td>
<td>10 (8.7)</td>
<td>13 (9.1)</td>
</tr>
<tr>
<td>University/college</td>
<td>60 (52.2)</td>
<td>74 (51.7)</td>
</tr>
<tr>
<td>Full- or part time work</td>
<td>80 (69.6)</td>
<td>130 (65.2)</td>
</tr>
<tr>
<td>Female sex</td>
<td>62 (54.4)</td>
<td>78 (54.4)</td>
</tr>
<tr>
<td>Emotional distress (1-4). Mean (SD)</td>
<td>1.6 (0.5)</td>
<td>1.6 (0.5)</td>
</tr>
<tr>
<td>SPADI baseline. Mean (SD)</td>
<td>52.4 (17.0)</td>
<td>51.9 (17.0)</td>
</tr>
</tbody>
</table>
Table 2. Analysis of the relationship between baseline SPADI and the MRI total score and individual structural changes at MRI, calculated by multiple regression analysis, adjusting for age, gender, work status, education and emotional distress.

*Values are mean (SD)

<table>
<thead>
<tr>
<th>Structural change present</th>
<th>SPADI baseline*</th>
<th>Diff SPADI baseline (β)</th>
<th>P value</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI total score</td>
<td>-</td>
<td>-</td>
<td>-3.1</td>
<td>0.03</td>
</tr>
<tr>
<td>Bursitis</td>
<td>YES</td>
<td>51.5 (17.1)</td>
<td>-3.1</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td>53.9 (16.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tendinosis in rotator cuff</td>
<td>YES</td>
<td>52.8 (16.8)</td>
<td>2.1</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td>51.2 (17.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcification in rotator cuff</td>
<td>YES</td>
<td>46.1 (12.8)</td>
<td>-8.2</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td>54.4 (17.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial tear in rotator cuff</td>
<td>YES</td>
<td>50.1 (15.0)</td>
<td>-3.6</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td>53.6 (17.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AC joint osteoarthritis</td>
<td>YES</td>
<td>51.8 (17.8)</td>
<td>-3.5</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td>53.9 (14.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Analysis of the relationship between the change in SPADI over one year and the MRI total score and individual structural changes at MRI, calculated by multiple regression analysis, adjusting for baseline SPADI, age, gender, work status, education and emotional distress.

*Values are mean (SD)

<table>
<thead>
<tr>
<th>Structural change present</th>
<th>Change in SPADI from baseline to one year follow up*</th>
<th>Diff change SPADI (β)</th>
<th>P value</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI total score</td>
<td>-</td>
<td>-8.1</td>
<td>&lt; 0.001</td>
<td>-12.3 to -3.8</td>
</tr>
<tr>
<td>Bursitis</td>
<td>YES</td>
<td>18.4 (26.0)</td>
<td>10.2</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td>28.0 (24.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tendinosis in rotator cuff</td>
<td>YES</td>
<td>18.8 (25.7)</td>
<td>14.1</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td>31.1 (23.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcification in rotator cuff</td>
<td>YES</td>
<td>13.9 (27.4)</td>
<td>7.0</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td>24.9 (24.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial tear in rotator cuff</td>
<td>YES</td>
<td>20.2 (24.2)</td>
<td>2.4</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td>23.1 (26.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AC joint osteoarthritis</td>
<td>YES</td>
<td>19.2 (24.9)</td>
<td>10.8</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td>29.8 (26.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>