Evaluating treatment options for calcific tendinitis of the rotator cuff

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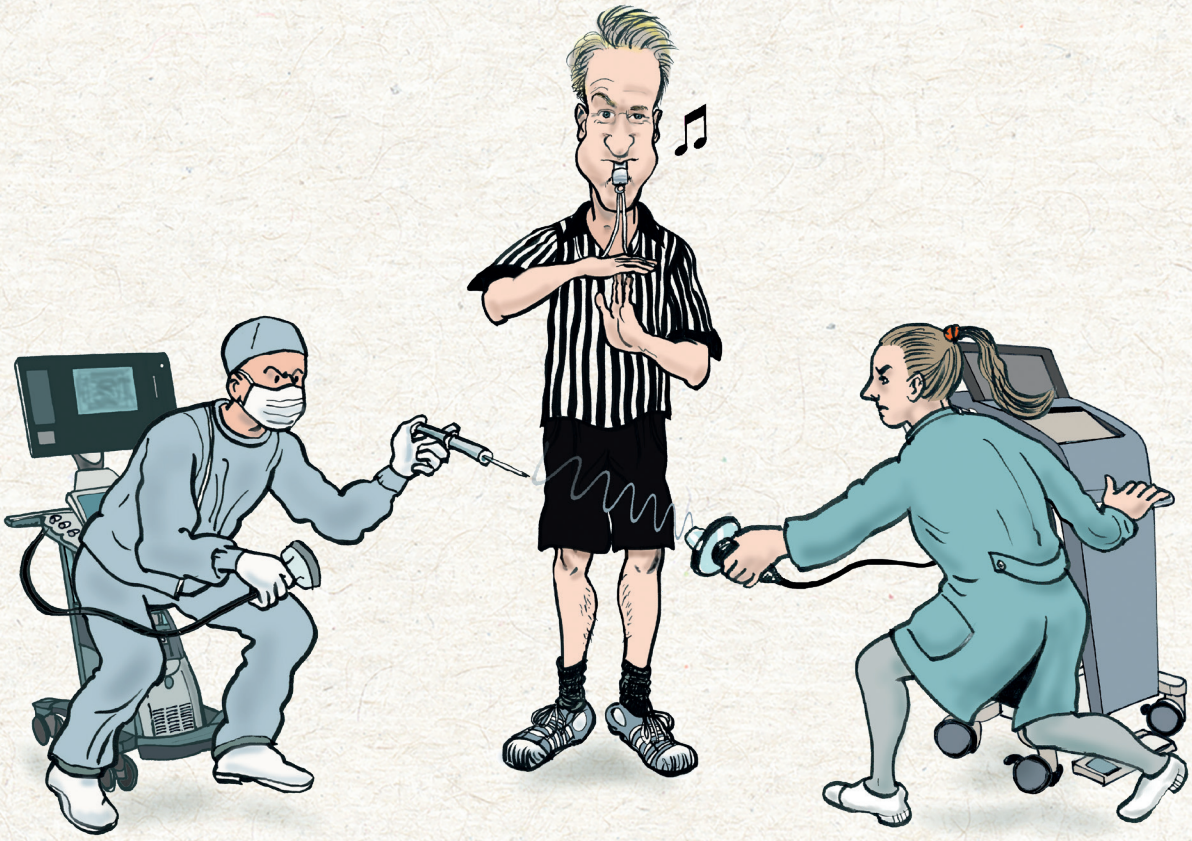

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General introduction and thesis outline

GENERAL INTRODUCTION

CALCIFIC TENDINITIS OF THE ROTATOR CUFF

Calcific tendinitis of the rotator cuff is a condition characterised by the deposition of hydroxyapatite crystals in tendons.[1] It is frequently encountered in the rotator cuff tendons.[2] The rotator cuff is a complex of four muscles and their tendons that act as important stabilizers of the glenohumeral joint and provide strength during abduction and rotation (figure 1). Rotator cuff calcific tendinitis (RCCT) is an important source of nontraumatic shoulder pain.[3] It is generally considered to be a self-limiting disease with spontaneous improvement of symptoms over time. However, in some individuals symptoms can be prolonged and intense. Its estimated prevalence in the population ranges from 2.7% to 20%.[2,4,5] The condition typically affects patients between 30 to 60 years of age, and women are more frequently affected than men.[5,6] Based on imaging studies, the supraspinatus tendon is affected in approximately 80%, the infraspinatus tendon in 15%, and the subscapularis tendon in 5%.[7] In up to 10% of patients, the pathology appears bilateral.[2,8]

PATHOPHYSIOLOGY

In calcific tendinitis, hydroxyapatite crystals deposits in the substance of a tendon (figure 2 & 3). The condition can affect any tendon at its insertion. Although calcific deposits are most frequently seen around the shoulder and in the Achilles tendon, they have also been described in other tissues such as the rectus femoris muscles or intra-osseous locations.[9–11] Radiographic and infrared spectrometry identified the consistency of the material as calcium carbonate apatite[12] and in more detail, two different types of carbonate apatite were identified, according to the position of the carbonate ions in the hydroxyapatite.[13] While macroscopically the material is frequently described as either a toothpaste like fluid or a mass of sandy material, there are conflicting reports in the literature whether there is also a chemical compositional change in the different phases of the disease.[1,14,15]

The presence of calcific deposits in the rotator cuff tendons is known under many names: calcific tendinitis, calcifying tendinopathy, tendinosis calcarea, calcareous tendinitis, calcific periarthritis and periarticular apatite deposit.[16] Some terms try to emphasize the extra-articular location of the calcium deposit while others mention the compound found in the calcification or the fact that there is a distinction between an inflammation or non-inflammatory degeneration of the tendon.[17] Painter[18] was the first to describe the radiographic findings in 1907. A few years before Harrington and Codman performed the first reported operative removal of a calcific deposit.[19]

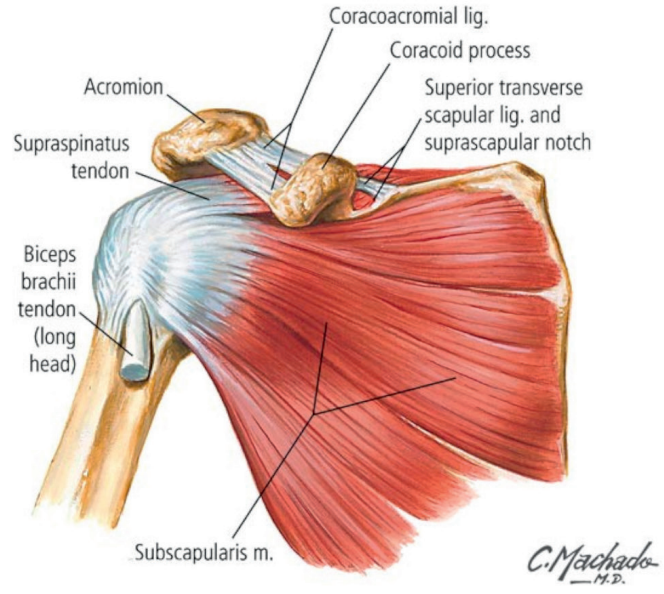

Figure 1. Anatomy of the rotator cuff. *Netter illustration used with permission of Elsevier Inc. All rights reserved. www.netterimages.com*

The precise pathogenetic mechanism of RCCT remains debated. In 1930, Codman[19] hypothesized that the formation of calcification was preceded by a degenerative process of the tendon. In 1938 Sandstrom[20] stated that local ischemia and vascular changes caused necrosis of the tendon which was the first step in the deposition of calcific material. Bishop[21] thought repetitive minor trauma could induce micro tears in the tendon tissue, hyaline degeneration and deposition of calcium. Bosworth[21] supported this theory in his classic study among 6061 volunteers. In 1997, the most advocated theory by Uhthoff and Loehr was published, suggesting the occurrence of a cell-mediated reactive calcifying process that is preceded by initial cartilage metaplasia.[7] Uhthoff divided the pathogenesis of RCCT in three stages (figure 4.):

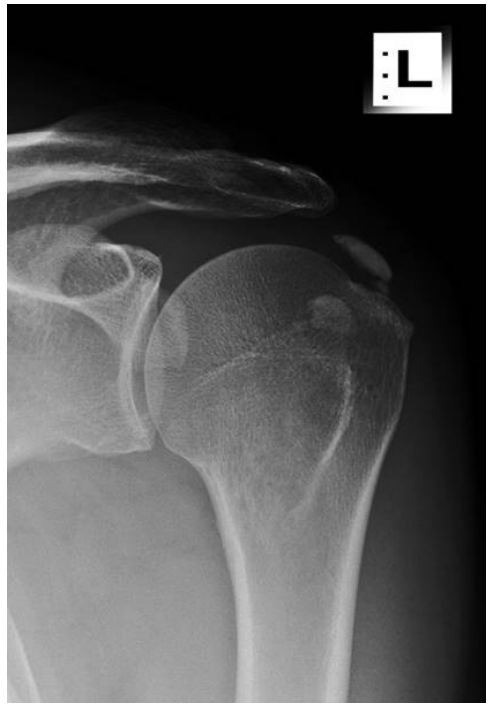

Figure 2. Antero-posterior radiograph of the left shoulder showing a calcific deposit in the supraspinatus tendon.

1. *Pre-calcific stage:* tendon transformation in fibrocartilaginous tissue in less vascular areas of the tendon, which acts as a substrate for calcium deposition.
2. *Calcific stage:* actual calcium deposition in the tendon. It is composed of the formative, resting and resorptive phase. In the formative phase the matrix vesicles unite to become calcific deposits that are separated by fibrocartilage or fibrocollagenous tissue. This process is mediated by the chondrocytes of the fibrocartilaginous metaplasia. The resting phase is noticeably dormant, with a lack of inflammation or vascular infiltration. The resorptive phase begins after a variable time period and correlates with the appearance of thin walled vascular channels, as well as macrophages phagocytosis of the calcium deposit. This phase is also characterized by oedema and increased intratendinous pressure with possible extravasation of calcium crystals in the subacromial bursa or greater tubercle.
3. *Post-calcific stage:* following resorption, fibroblasts and granulation tissue appear in the previous site of the deposits. This process usually ends with complete healing of the involved tendon and can take several months.

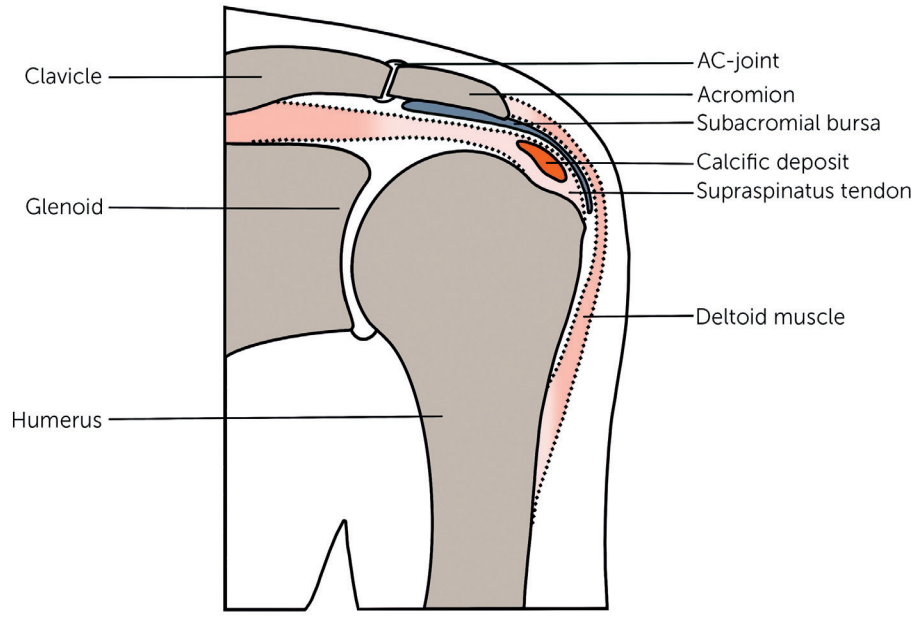

Figure 3. Corresponding illustration highlighting all relevant anatomical structures.

Since the paper from Uhthoff in the late 90s, Rui et al.[22,23] developed an alternative theory based on the erroneous differentiation of tendon cells. He identified a specific type of mesenchymal stem cells, based on animal models, which he called a tendon derived stem cell (TDSC). While in normal tendon healing, these TDSCs proliferate into normal tenocytes, in specific circumstances the TDSCs can differentiate into chondrocytes or osteoblasts, creating the deposition of the wrong extracellular matrix, and subsequentially the formation of calcific deposits. The exact mechanism of this failed healing response is unclear, but could be modulated by the expression of bone morphogenetic proteins, biglycan and fibromodulin.[24,25]

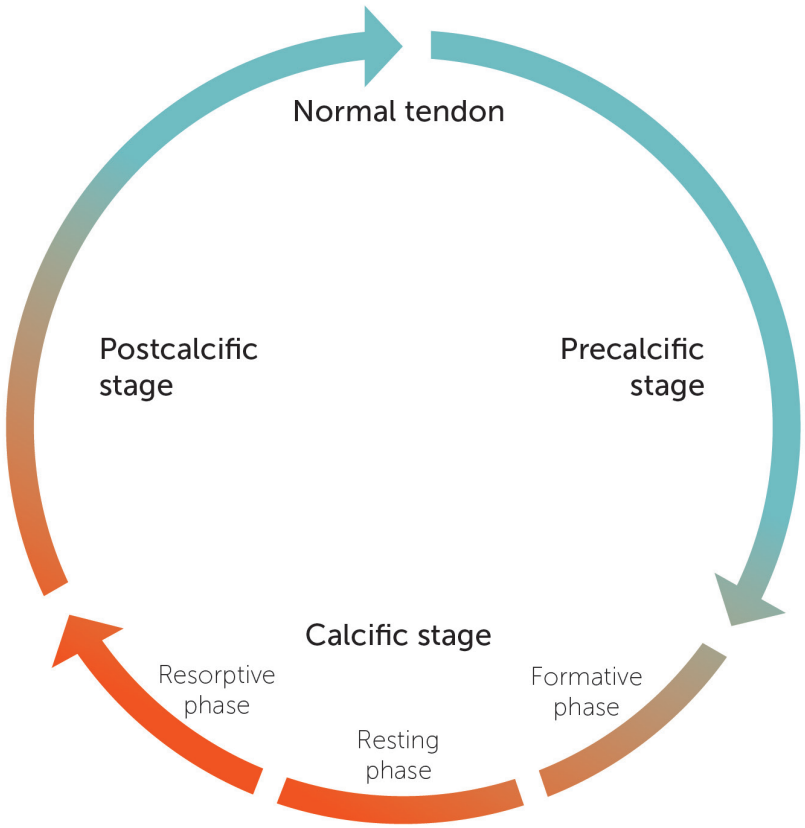

Figure 4: Schematic overview of the different stages of calcific tendinitis

CLINICAL PRESENTATION

The clinical presentation of patients with RCCT is variable. Patients generally experience pain that is similar to the clinical presentation of subacromial pain syndrome. The active range of motion is decreased and patients have adjusted their shoulder mechanism to avoid the pain. The scapular mechanism should be evaluated for dyskinesia and the rotator cuff tendons tested for possible tears. Other potential pathologies should be excluded before focussing solely on the calcific tendinopathy, given the high prevalence of asymptomatic calcific deposits.[2,4,26] Although there is no widely accepted clinical classification, attempts have been made to describe the different clinical presentation in four categories.[4,7,27] (1) The acute phase is characterized by severe pain and functional disability for about one to six weeks. This phase is usually associated with the resorption phase as described in Uhthoff's model. Symptoms can be so severe that patients seek help in the emergency department. (2) The chronic recurrent form is characterized by alternating pain and disability, without necessarily being preceded by the acute phase. It persists for six weeks to six months. (3) The persistent chronic form is characterized by a constant dull pain for at least six months without periods of remission or exacerbation. (4) The totally asymptomatic deposits. Bosworth reported that clinical symptoms occur in 34% - 45% of the patients with calcific deposits.[2] Usually the clinical evolution resolves spontaneously but symptoms can be prolonged and severe. Long-term data on the natural history of calcific tendinitis varies greatly. Gärtner et al.[1] reported a 85% chance of natural resolution after three years for type III deposits, as opposed to 33% for type I and II deposits.

IMAGING

Radiography

Radiography is widely available and usually sufficient to detect calcific deposits in the soft tissues around the glenohumeral joint. Standard radiographs include anterior-posterior, outlet and axillary views. These views allow assessment of the location, morphology and texture of the deposits. Additional anterior-posterior views in external rotation and internal rotation could help differentiate between a supraspinatus and infraspinatus deposit. Various classifications based on the size[2], morphology[1,28,29] and location[30] have been proposed (table I) of which the classification of Gartner et al. and Molé et al. are most frequently used.

The presence of an intra-osseous calcification in the greater tubercle, sometimes in combination with osteolysis, is a rare form of RCCT which is frequently misdiagnosed and is associated with significantly lower clinical outcome after treatment.[11,31]

Table 1. Classifications for calcifying tendinitis of the rotator cuff

Radiographic	Type	
Gärtner	Morphology	(I) well circumscribed, dense (II) soft contour/dense or sharp/ transparent. (III) translucent and cloudy appearance without clear circumscription
Molé	Morphology	(A) dense, homogeneous, sharp contours (B) dense segmented, sharp contours (C) heterogeneous, soft contours (D) dystrophic calcification at the insertion
DePalma	Morphology	(I) fluffy, amorphous and ill defined. (II) defined and homogeneous
Patte and Goutalier	Morphology	(I) localised and homogeneous (II) diffuse, disseminated, heterogeneous
Bosworth	Size	(Small) <0.5 cm (Medium) 0.5 – 1.5 cm (Large) 1.5 cm
Chiou	Morphology	(1) arc shaped (2) fragmented or punctate (3) nodular (4) cystic
	Activity	Color doppler signal. Grade 0 (no signal) to Grade 3 depending on activity.
Farin	Morphology	hyper echoic focus with a (A) well-defined shadow (B) faint shadow (C) without a shadow

Ultrasound

Ultrasound is a widely used imaging technique for the evaluation of shoulder pathology, especially the rotator cuff.[32,33] Without the need to expose the patient to radiation, ultrasound can accurately localize and categorize rotator cuff calcifications three dimensionally, while at the same time screen for concomitant rotator cuff tears, bursal and/or joint effusion and acromioclavicular joint pathology.[34,35] Ultrasound is just as sensitive as plain radiography for the detection of calcifications.[36,37] The deposits appear hyper echoic on ultrasound and Farin et al.[37] divided the deposits in three types (table 1 and figure 5) It is believed that these types correspond to the formative, resting and resorption phase of the disease respectively. Ogon et al. also stated that a prediction of the consistency can be made depending on the sound extinction.[30] Full sound extinction was correlated to a high-density eg. viscous solid deposit during arthroscopy, as opposed to the liquid-soft deposits that appeared to show no sound extinction. The role of power Doppler findings has been assessed by le Goff and Chiou.[38,39] They stated that a color/power Doppler signal was significantly associated with symptomatic calcifications and that none of the patients in the asymptomatic group showed a Doppler signal. Doppler techniques may therefore help the clinician in the differentiation between symptomatic and asymptomatic calcifications and predict whether or not symptoms will resolve with conservative treatment.

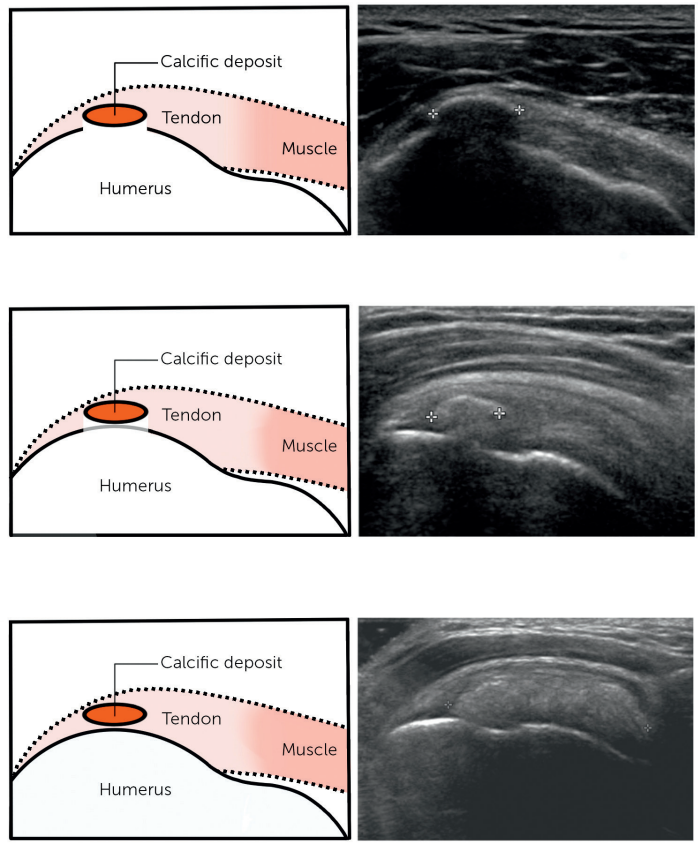

Figure 5. Ultrasound appearance of calcific tendinitis. Left, Schematic drawings; right, corresponding sonograms. Calcifications are indicated between calipers. A, Type 1 calcification appears as a well-defined hyperechoic structure with posterior acoustic shadowing. B, Type 2 calcification is shown as a hyperechoic focus, which shows minimal acoustic shadowing. C, Type 3 calcification appears as amorphous heterogeneous isoechoic-to-hyperechoic calcific deposits that replace the normal fibrillar tendon pattern. Note the absence of the acoustic shadow. *Used with written permission from dr. Becciolini, dr. Bianchi and John Wiley and Sons.*[35]

Computed-tomography

Various authors have advocated the use of CT in the work-up of calcific tendinitis.[30,31,40] Although it is more expensive than conventional radiography or ultrasound, CT can provide three-dimensional detailed information about the size, location and morphology of the calcific deposits. It can detect small calcifications that are missed on radiograph, and has a high positive and negative predictive value for the consistency of deposits by analyzing the attenuation levels (Hounsfield unit). Greater costs and higher

exposure to radiation for patients are reasons to not recommend CT in the standard work-up for patients with RCCT.

Magnetic resonance imaging (MRI)

Similar to ultrasound, MRI is useful in detecting concomitant pathology that may contribute to symptoms (e.g. subacromial bursitis, rotator cuff tears, joint effusion). The accuracy of detecting calcific deposits on MRI is around 95% and is most accurate with susceptibility- weighted imaging.[41] They have low signal intensity on all MRI sequences but can demonstrate perifocal edema on fluid sensitive settings. Loew et al. stated that perifocal edema around a deposit suggests an active phase of the disease and can mimic a rotator cuff lesion.[42] It is difficult to differentiate between the morphological characteristics on MRI. Generalized bone marrow edema can occur in the humeral head, in the rare case of an intra-osseous migration of the calcific deposit, either in the resorption phase of after an ultrasound-guided needling procedure.[11]

TREATMENT

Conservative

Conservative treatment is the mainstay for RCCT and can be successful in up to 80% of patients. The conservative management involves rest, physical therapy, oral nonsteroidal anti-inflammatory drugs and a corticosteroid injections when indicated.[43] Nonsteroidal anti-inflammatory drugs are widely prescribed in the primary care as a pragmatic first option to control subacromial pain, often before radiographic or ultrasound diagnosis of RCCT.[44] Physiotherapy includes range of motion exercises and concentric and eccentric rotator cuff strengthening exercises in combination with scapular stabilization. Corticosteroid injections in the subacromial bursa may also be used to relieve patient's symptoms.[45]

Approximately 10 to 20% of patients are resistant to conservative treatment and appear to remain in a prolonged formative phase with chronic symptoms.[43] When conservative treatment fails, other treatment option should be considered. The first papers on alternatives for surgery were published in the late 90s, in an attempt to look for less invasive treatment options. Multiple techniques were described such as extracorporeal shockwave therapy [46,47], radial shockwave therapy[48], therapeutic ultrasound[49] and ultrasound-guided percutaneous needling.[50]

Extracorporeal shockwave therapy (ESWT)

ESWT has become increasingly popular over the past 25 years for the management of RCCT.[51] With ESWT, a monophasic pressure pulse that has a high peak pressure and a short duration is produced and focussed on the target area via reflectors (figure 6). The shockwaves can be generated by electromagnetic, electrohydraulic, or piezoelectric mechanisms. The magnitude of the shockwaves is measured by its energy flux density (EFD), which is generally reported in millijoules per millimeters squared (mJ/mm2). The overall effect of ESWT is dependent on the numbers of pulses, the distribution of energy (focused or non-focused), targeted tissues and the EFD.[52–58] Efforts have been made to stratify ESWT in different energy groups.[56] While no consensus exists, high-energy shock waves are considered to have an EFD of >0.20 mJ/mm^2 and low-energy shockwaves an EFD of <0.08 mJ/mm^2.[57] The exact underlying therapeutic effect of ESWT on RCCT is still debated. It has a direct mechanical effect which might induce calcium deposit fragmentation due to increasing the pressure inside the deposit itself. The biological effect seems to be related to phagocytosis of the deposit induced by a neovascularization inflammatory response and leukocyte chemotaxis.

Ultrasound-guided needling

Ultrasound guided percutaneous needling is the most popular alternative for ESWT in persistent symptomatic RCCT. Different terminology is used in the literature: ultrasound guided percutaneous needle aspiration and lavage (UGN or USGN), barbotage and needle-guided aspiration of calcific deposit (NACD).[59] With this technique the calcific deposit is localized under ultrasound and a needle is introduced to or directly in the calcific deposit (figure 7). If lavage is used, the calcific deposit is then flushed with saline (lavage) and calcific minerals are aspirated through a one or two-needle technique.[60–63] This is followed by puncturing the deposit multiple times to manually break up the calcific deposit. Some authors advocate to keep the needle in the same place to minimize potential damage to the rotator cuff. Following the needling procedure, the needle is generally introduced in the subacromial bursa under ultrasound guidance where a corticosteroid solution is injected.[64] No consensus exists with regard to the number of needles that should be used, whether or not additional lavage is beneficial or the effect of the multiple perforations.[65,66]

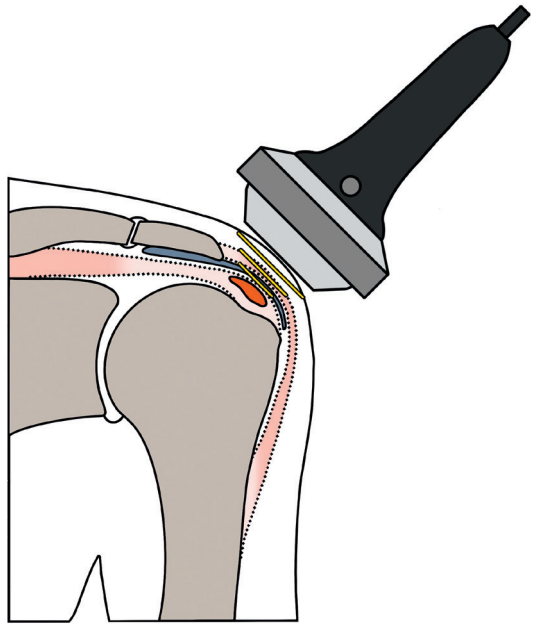

Figure 6. Illustration showing an extracorporeal shockwave setup: the therapy source sends focused pressure pulses to the targeted calcific deposit and surrounding tissues.

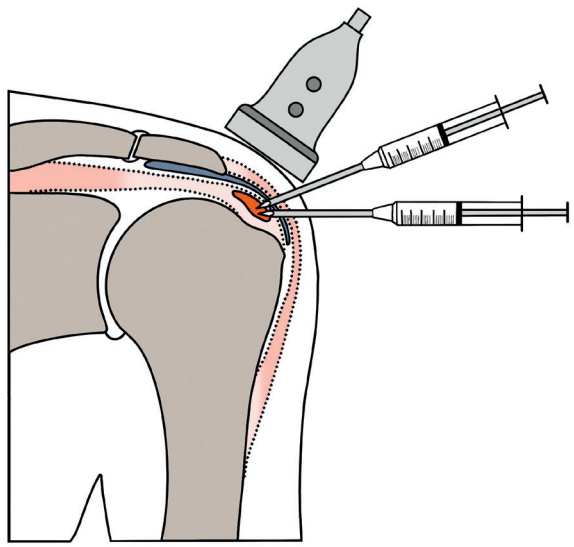

Figure 7. Illustration showing an ultrasound-guided needling setup: two needles with syringes perforating the calcific deposit under sonographic guidance.

Operative treatment

Surgery has long been the treatment of choice for RCCT patients who did not respond to a conservative treatment.[67] Surgical options include open or arthroscopic procedures to remove the calcific deposit, and to perform a subacromial bursectomy with or without a decompression. An arthroscopic procedure is currently the favoured method, because it is less invasive, and provides equivalent results as the open technique.[68] These procedures have been shown to have a high chance of success in restoring shoulder function and reducing pain. No consensus exists however regarding the extent of calcification removal, instrumentation, and beneficial effects of the additional subacromial decompression.[69]

OUTCOME MEASURES

Treatment effects in orthopaedic trials are generally measured by clinical outcome measures and patient-reported outcome measures. Region-specific instruments can measure disability, pain and problems related to a specific shoulder condition from the patients perspective.[70] Interpretation of these outcome scores can only be done adequately if the outcome measure has clearly defined measurement properties, such as the validity, reliability and responsiveness.[71,72] Furthermore, the term statistical significance is frequently used to describe a change in outcome of these clinical scores, which does not necessarily mean a clinical relevant benefit for the patient. To aid the researcher in the interpretation of the clinical relevance of an outcome, the concepts of minimal clinical important difference and substantial clinical benefit have been developed.[73,74]

OUTLINE OF THIS THESIS

AIM OF THIS THESIS

The general aim of this thesis is to improve the care for patients with calcific tendinitis of the rotator cuff with an emphasis on evaluating the effectiveness of extracorporeal shockwave therapy and ultrasound-guided needling. First, by giving insight in the prevalence and radiographic assessment of the condition. Secondly, by providing a comprehensive literature overview exploring all minimally invasive treatment options. And finally, by evaluating the outcome of a randomized controlled trial comparing high-energy shockwave therapy and ultrasound-guided needling in patients with refractory calcific tendinitis of the rotator cuff.

General introduction

Chapter 1 provides a general introduction to the subject of this thesis. The epidemiology, pathogenesis, various imaging techniques, and treatment options are discussed. Furthermore the aims of the thesis are described.

Epidemiological and radiological evaluation of rotator cuff calcific tendinitis

RCCT is one of the most frequent causes of subacromial pain syndrome. However calcific depositions have also been described in asymptomatic individuals. Only a few authors examined the prevalence of calcific depositions in the rotator cuff and their findings differed substantially. **Chapter 2** describes the clinical and radiological data of 1219 adults with, and without subacromial pain syndrome to assess the prevalence of calcific deposits in the rotator cuff. A multivariate analysis is used to define risk factors associated with the presence of symptomatic calcific deposits.

Although there are many radiological classification systems for RCCT, it remains unclear which of these systems are reliable and reproducible. In **Chapter 3** the interobserver and intraobserver reliability of the two most frequently used classification systems is measured.

Exploring minimally invasive treatment options

When the primary conservative treatment fails, alternative treatment options for RCCT may be considered. In **Chapter 4** a systematic review and meta-analysis is performed to explore the short-term and mid-term effectiveness of minimally invasive treatment options. After assessing the short-term to mid-term effectiveness in chapter 4, the mid- to long-term outcome of the most promising evidence-based minimally invasive treatment options are compared with arthroscopic surgery in **Chapter 5.**

Evaluating the effect of treatment with high-energy ESWT versus ultra-sound-guided needling

Based on chapters 4 and 5 a randomized controlled trial was conducted comparing high-energy ESWT and ultrasound-guided needling in patients with RCCT who did not responds to a conservative treatment. **Chapter 6** discusses the functional and radiological outcome of the randomized controlled trial. In **Chapter 7** we analyse the impact of RCCT on work ability and sick leave. Furthermore we analyse the change in work ability and sick leave after treatment and search for potential prognostic factors. **Chapter 8** discusses the responsiveness, minimal clinical important difference and substantial clinical benefit of the Constant and Disabilities of the Arm, Shoulder and Hand (DASH) scores.

Discussion and future perspectives

Chapters 9 and **10** present the general discussion and summary. In these chapters the most important findings of the thesis are summarized and compared with the literature. Clinical implications are formulated and future perspectives are discussed. A treatment flowchart is presented in the appendix as well as the Dutch summary.

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Part 1

Epidemiological and radiological evaluation of
calcific tendinitis of the rotator cuff

2

Prevalence of calcific deposits within the rotator cuff tendons in adults with and without subacromial pain syndrome: clinical and radiologic analysis of 1219 Patients

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ABSTRACT

BACKGROUND

Calcific tendinopathy is one of the most frequent causes of pain in the shoulder and is characterized by the presence of calcific deposits in the rotator cuff; however, calcific deposits have also been described in asymptomatic individuals. Only a few authors reported epidemiological data on the prevalence of calcific deposits in the rotator cuff.

METHODS

This study analyzed clinical and radiological data of 1219 adults with and without subacromial pain syndrome (SAPS) to assess the prevalence of calcific deposits in the rotator cuff. Multivariate analysis was used to define risk factors associated with the presence of symptomatic calcific tendinopathy.

RESULTS

Calcific deposits were found in the rotator cuff of 57 of 734 asymptomatic patients (7.8%). Of 485 patients with SAPS, 42.5% had calcific deposits. Age between 30 and 60 years old (odds ratio [OR], 8.0; 95% confidence interval [CI], 2.5–26.3, p <.001), subacromial pain (OR, 7.1; 95% CI, 5.1-9.9, p < .001) and female gender (OR, 1.5; 95% CI, 1.1 – 2.0, P = .014) were significantly associated with increased odds of calcific deposits.

CONCLUSION

This study demonstrates that women aged between 30 and 60 years with SAPS and a calcific deposit of >1.5 cm in length have the highest chance of suffering from symptomatic calcific tendinopathy of the rotator cuff. The prevalence rates of 7.8% in asymptomatic patients and 42.5% in patients with SAPS provide a current view on the epidemiology of calcific deposits in the rotator cuff.

LEVEL OF EVIDENCE: III, retrospective cohort study, epidemiology study

INTRODUCTION

Calcific tendinopathy is one of the most frequent causes of nontraumatic pain in the shoulder.[1] The condition is characterized by the presence of carbonate hydroxyapatite deposits in the rotator cuff tendons.[2] Most individuals with calcific tendinopathy are aged between 30 and 60 years, with women affected 1.5 times more often than men.[3,4] The clinical and radiological characteristics of calcific tendinopathy have been described in numerous papers since Painter[5] described the condition for the first time in 1907. However, calcific deposits have also been described in asymptomatic individuals and the presence of calcific deposits does not necessarily mean that a patient suffers from calcific tendinopathy.[6] Only a few authors have examined the prevalence of calcific deposits of the rotator cuff, and their findings differ substantially. Bosworth,[6] Welfing et al,[7] and Ruttiman[8] studied the prevalence of calcifications in patients without symptoms and reported a prevalence of 2.7% to 20%. Welfing et al,[7], Friedman,[9] and Harmon and Francisco[1] analyzed patients with shoulder pain and found a prevalence of calcific deposits of 6.8% to 40%.

Because most of this research was done in the 1940s to 1960s, we were interested in whether the prevalence of calcific deposits found in previous research was still relevant to our modern practice and whether risk factors for the prevalence of calcific deposits could be defined using modern statistical analyses. The first objective of this study was to screen a patient population without acute or chronic nontraumatic shoulder pain for the prevalence of radiologically detectable calcification in rotator cuff tendons, to evaluate their characteristics, and to compare these results with the historical reports. Furthermore, because the clinical presentation of a patient with calcific tendinopathy is similar to that of a patient with subacromial pain syndrome (SAPS), the second objective was to investigate the prevalence of calcific deposits in patient with SAPS. The results obtained could provide a current view on the epidemiology of rotator cuff calcific deposits.

MATERIAL AND METHODS

This study was a retrospective clinical analysis of adults with and without SAPS. Conventional radiographs of the shoulder, ultrasound findings and electronic patient records were used to assess the prevalence of calcific deposits in the rotator cuff tendons and to examine patient characteristics.

PATIENT GROUPS

The asymptomatic group consisted of patients who had presented to the emergency department of our clinic between January 2013 and April 2014 as a result of shoulder trauma, and had a shoulder radiograph available for analysis. Individuals were eligible for inclusion if they were >18 years and had a standard shoulder radiograph, consisting of an anteroposterior (AP) external rotation view, acromioclavicular view, axial view and outlet view, taken at the moment of consultation. Patients were excluded when their record showed a history of acute or chronic nontraumatic shoulder pain before the consultation.

The symptomatic group consisted of patients who were referred to our outpatient shoulder clinic with signs of SAPS and had a standard shoulder radiograph available for analysis. Individuals were eligible for inclusion if they were aged >18 years, showed clinical signs of pain in the deltoid region worsening with activities above shoulder level, had a positive painful arc, Hawkins test and Jobe test during physical examination, and had a standard shoulder radiograph taken at the moment of consultation. Exclusion criteria included clinical and sonographic evidence of a full thickness rotator cuff tear, symptomatic arthritis of the acromioclavicular joint or the glenohumeral joint, clinical signs of adhesive capsulitis, shoulder instability, scapular dyskinesis, cervicobrachialgia, cervical radiculopathy, chronic pain syndrome, Parsonage-Turner syndrome and suprascapular nerve entrapment.

PATIENT CHARACTERISTICS

Sex, age and affected side were reported for both groups. Duration of symptoms, hand dominance, comorbidity, treatment before consultation and the primary applied treatment after consultation were reported for the symptomatic group.

RADIOGRAPHIC AND ULTRASOUND ANALYSIS

Standard radiographs of the shoulder were made at the emergency department or at the outpatient clinic. One reviewer (J.L.) retrospectively assessed the presence and location of calcific deposits in the rotator cuff. The results were compared with the radiologist' original report. Disagreements were resolved through consensus or arbitration by a second observer (A.v.N.). The length of the calcific deposit was measured by using the IMPAX 6.5.2 Client caliper tool (Agfa Healthcare, Mortsel, Belgium) in the AP view. The number of affected tendons and calcific deposits were estimated by analyzing the AP, axial and outlet view. The size of the calcific deposits was categorized according to Bosworth[6] in 3 categories as small (<0.5cm), medium (0.5cm-1.5cm) and large (>1.5cm). In case of multiple calcific deposits the length of the largest calcific deposit was used for analysis. The Gärtner classification[2] was used for the morphological evaluation of calcific deposits (Table 1).

Electronic patient records were analyzed for shoulder ultrasound examinations and, when available, screened for the presence and location of calcific deposits. These results were compared to the radiographs, and any discrepancies were reported.

Table 1. Gärtner classification for radiographic appearance of calcific deposits [2]

Type	Radiographic appearance
I	Clearly circumscribed and dense
II	Soft contour/dense or sharp/transparent
III	Translucent and cloudy without clear circumscription

STATISTICAL ANALYSIS

Statistical analysis was performed by use of SPSS 21 software (IBM Corp, Armonk, NY, USA). Continuous data were checked for normality and are presented as means with standard deviations (SD) in case of normal distribution, otherwise as medians and interquartile ranges (IQR). Categorical data are described as frequencies with accompanying percentages.

Differences in patient demographics and clinical characteristics between the symptomatic and asymptomatic group were compared by use of Student *t* tests or Mann-Whitney *U* tests for continuous data where appropriate, and the χ^2 tests was used for categorical variables.

Univariate analyses were performed to identify factors associated with the presence of calcifications in the rotator cuff tendons. Candidate variables were sex, symptoms and age. Age was categorized in three levels; <30 years, 30-60 years and >60 years. The variables that were significantly associated with the presence of calcifications, at a significance level of 0.1, were entered in a logistic regression analysis with a backward selection procedure to model the multivariate relationship between patient characteristics and the presence of calcification. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to assess the strength of the association.

Additional subanalysis within the calcification group was performed to assess differences in the length of the calcific deposit and Gärtner types between patients with and without symptoms by use of a Mann-Whitney *U* test and χ^2, test, respectively. For all analyses, a *P* value <.05 was considered significant.

RESULTS

ASYMPTOMATIC GROUP

Demographics and prevalence of calcific deposits in asymptomatic patients categorized by age group and sex are shown in Table 2 and shown in Fig. 1. During the inclusion period, conventional shoulder radiographs were obtained in 734 patients in the emergency department after trauma. Of these, 57 patients (7.8%) had calcific deposits in the rotator cuff and were included for further radiographic analyses. These results were compared with previous studies[1,4,6,8,9] and summarized in table 3. The calcific group consisted of 30 men (52.6%) and 27 women (47.4%) with a mean age of 59.3 (SD, 15.1) years. The right side was affected in 56%. The prevalence of calcific deposits in the rotator cuff was 7.4% in men and in 8.2% in women.

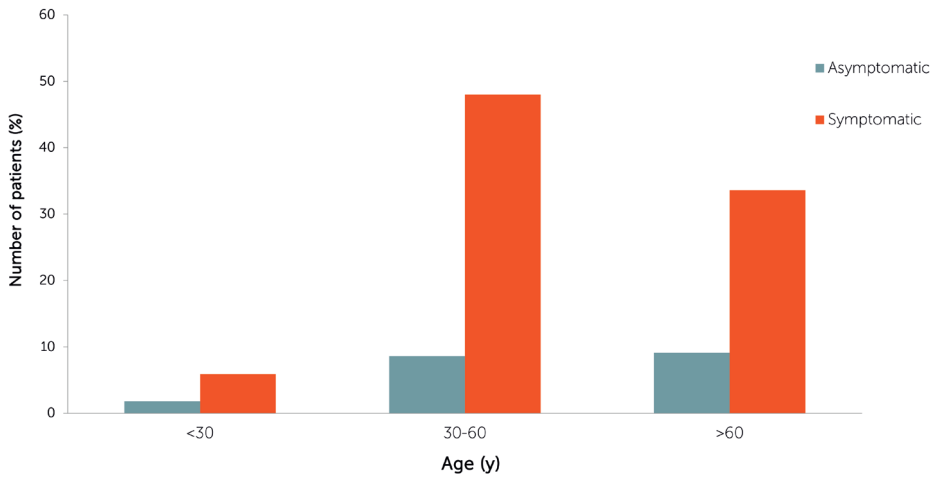

Figure 1. Prevalence of calcific deposits in the rotator cuff in symptomatic and asymptomatic patients within each age group.

Radiographic analysis

Of the 57 calcific deposits, 50 (87.7%) were located in the supraspinatus tendon, 6 (10.5%) were in the infraspinatus tendon, and 1 deposit was found in the subscapularis tendon. Just 1 calcific deposit was present in 48 patients (82.8%) with affected tendons compared with 2 deposits in 8 patients (13.8%), 4 deposits in 1 patient (1.7%), and 5 deposits in 1 patient (1.7%). The deposits were a median length of 0.42cm (IQR, 3.0-6.7 cm), and 59.6% were <0.5 cm, 40.4% were 0.5-1.5 cm, and 0% were >1.5 cm. These calcific deposits were categorized according to Gärtner as type I in 21%, type II in 54.4%, and type III in 24.6%.

Table 2. Demographic data and prevalence of calcific deposits in symptomatic and asymptomatic group according to age and sex.

	Symptomatic group			
	Total		Calcific depots	
	N (%)	Male/female (ratio)	N (%)	Male/female (ratio)
	485 (100)	185/300 (1.6)	206 (42.5)	62/144 (2.3)
Age (y)				
<30	17 (3.5)	9 / 8 (0.9)	1 (5.9)	1 / 0 (-)
30-60	331 (68.2)	121 / 210 (1.7)	159 (48.0)	45 / 114 (2.5)
>60	137 (28.2)	55 / 82 (1.5)	46 (33.6)	16 / 30 (1.9)
	Asymptomatic group			
	Total		Calcific depots	
	N (%)	Male/female (ratio)	N (%)	Male/female (ratio)
	734 (100)	403/331 (0.8)	57 (7.8)	31/28 (0.9)
Age (y)				
<30	111 (15.1)	91 / 20 (0.2)	2 (1.8)	2 / 0 (-)
30-60	315 (42.9)	195 / 120 (0.6)	27 (8.6)	15 / 12 (0.8)
>60	308 (42.0)	117 / 191 (1.6)	28 (9.1)	13 / 15 (1.2)

N (%) = number and percentage of individuals within the age group; male/female = number and ratio males and females.

SYMPTOMATIC GROUP

Demographics and prevalence of calcific deposits in symptomatic patients categorized by age group and sex are shown in fig. 1 and reported in Table 2. During the inclusion period, radiographs were obtained for 647 individuals who presented to the outpatient shoulder clinic with signs of SAPS. Of these, 162 patients were excluded, resulting in 485 inclusions. Overall, 206 patients with SAPS had a calcific deposit in the rotator cuff tendons resulting in a prevalence of 42.5%. The calcific group consisted of 62 men (30.1%) and 144 women (69.9%) with a mean age of 52.4 (SD, 10.3) years. The prevalence of calcific deposits was 33% in men and 48% in women. Compared with the asymptomatic group, a significant difference was found in the age ($P < .001$) and sex distribution ($P = .04$) in this symptomatic group. The left-right distribution was 45% vs 55%, and the dominant side was affected in 54% of the patients. The mean duration of SAPS symptoms was 32.7 months. The initiated treatment after consultation is provided in Table 4. A relevant medical history was noted in 37 patients (17%), consisting of cardiovascular pathology (40%), metabolic pathology (19%), and psychiatric diseases (19%) or a combination of these conditions (22%). The history of 17 patients reported previous calcific tendinopathy on the contralateral side. Before consultation, 87.4% of

the patients had received some form of therapy, comprising physiotherapy in 73%, subacromial infiltrations in 40%, therapy with nonsteroidal anti-inflammatory drugs in 31%, extracorporeal shockwave therapy in 13%, and ultrasound-guided needling therapy in 4%.

Radiographic analysis

Two or more tendons were affected in eighteen cases (9%). Of the 225 affected tendons, 198 tendons contained 1 calcific deposit (88%), 20 (8.9%) contained 2 calficiations, 5 (2.2%) contained 3 calcifications, and 2 (0.9%) contained 4 calcifications. The supraspinatus was the most frequently affected tendon, in 186 patients (82.7%), followed by the infraspinatus in 19 (8.4%) and the subscapularis tendon in 20 (8.9%). Median length of the deposit was 1.16cm (IQR 7.2-16cm) and was <0.5 cm in 15,5%, 0.5 to 1.5cm in 55.8%, and >1.5 cm in 28.6%. Categorization according to morphology resulted in Gärtner type I in 38.4%, type II in 47.0% and type III in 14.6%.

Ultrasound assessment

Ultrasound imaging was available in 154 patients (65%) in the symptomatic group. There were 21 (13.4%) discrepancies between the interpretation of conventional radiographs and ultrasound in the symptomatic group. Discrepancies varied from an additional small deposit in other rotator cuff tendons (52%), a different affected tendon (19%), no calcium found during ultrasound examinations (19%) to a higher amount of fragments of the calcific deposit (9.5%).

Table 3. Comparison of the prevalence data of calcific deposits in the current study with the available literature.

Study / year	n	Prevalence	Symptoms	X-ray / US	Mean age	Female (%)	Size calcific deposit
Bosworth '41	6,061	2.7% (n=165)	Asymptomatic	US	89.4% <40y	76.7	16.3% >1.5cm 54.4% 0.5 – 1.5cm 50% <0.5 cm
Rutimann '59	100	20% (n=20)	Asymptomatic	-	-	-	-
Welfing '65	200	7.5% (n=15)	Asymptomatic	X-ray	51.5y	-	-
Present study	**734**	**7.7% (n=57)**	**Asymptomatic**	**X-ray**	**55.3y**	**45.1**	**0.42cm**
Friedman '57	228	32.9% (n=75)	Symptomatic	X-ray	45.1y	44	> 0.5 cm
Harmon '58	1496	40% (n=609)	Symptomatic	X-ray	-	-	0.5 – 1.5 cm >1.5 cm
Welfing '65	925	6.8% (n=63)	Symptomatic	X-ray	53.7y	45	-
Present study	**485**	**42.5% (=206)**	**Symptomatic**	**X-ray**	**53.2y**	**61.9**	**1.16 cm**

cm = centimeter; n = number of patients; US = ultrasound; y = years; % = percentage

FACTORS ASSOCIATED WITH CALCIFIC TENDINOPATHY

The odds of a calcific deposits being present on radiographs increased for patients who were older compared with patients younger than 30. For patients between 30 and 60 years, the OR was 8.0 (95% CI, 2.5-26.3, $P < .001$), and for patients older than 60 years, the OR was 5.4 (95% CI 1.6-17.8, $P = .006$). Pain (OR, 7.1; 95% CI, 5.1-9.9; $P < .001$) and female gender (OR, 1.5, 95% CI 1.1 – 2.0, $P = .014$) were both significantly associated with increased odds of calcific deposits.

DISCUSSION

This study retrospectively analyzed 1219 patients for the prevalence of calcific deposits in the rotator cuff visualized by conventional radiograph. The prevalence was 7.8% in 734 asymptomatic patients and 42.5% in 485 symptomatic patients with SAPS. The supraspinatus tendon was affected in 83.7%, followed by the infraspinatus tendon in 8.9% and the subscapularis tendon in 7.4%. There was a significant difference in the median size of the deposit between the asymptomatic (0.42 cm) and the symptomatic group (1.16 cm). Sex distribution and age in this SAPS group were significantly different from the asymptomatic group. The SAPS group with calcific deposits had a lower mean age (55.3 vs. 59.3 years) and contained more women (69.9% vs. 47.4%) compared with the asymptomatic group. Multivariate regression analysis showed that the odds of the presence of a calcific deposit in the rotator cuff tendons were significantly associated with female gender, age between 30 and 60 years, and subacromial pain.

This study showed no difference in the distribution of the Gärtner classification between the symptomatic and asymptomatic patients. All patients with a large calcific deposit (>1.5 cm) were symptomatic. This supports Bosworth's[6] theory that large calcific deposits always result in a painful shoulder sooner or later, though they may remain quiescent and symptomless for months or years.

The prevalence of calcific deposits in the SAPS group was 42.5%. This is a high percentage compared to previous studies (Table 3). Welfing et al.[7] found a surprisingly low percentage of 6.5% in a group of 925 patients with shoulder pain. An explanation for this discrepancy might be that Welfing et al. included a variety of other painful shoulder conditions (eg, adhesive capsulitis) and excluded calcific deposits that were located at the insertion of the greater tubercle, automatically decreasing the total prevalence.

Table 4. Initiated treatment for calcific tendinopathy after consultation

Treatment modality initiated	Primary visit N=206	Second visit N=78	Third visit N=26
No treatment	20 / 9.7%	1 / 1.3%	1 / 3.8%
NSAID	5 / 2.4%	3 / 3.8%	-/-
+ physiotherapy	42 / 20.4%	20 / 25.6%	9 / 34.6%
+ subacromial infiltration	28 / 13.6%	19 / 24.4%	5 / 19.2%
+ physiotherapy and subacromial infiltration	5 / 2.4%	2 / 2.5%	-/-
US-guided needling	78 / 37.9%	21 / 26.9%	4 / 15.4%
ESWT	27 / 13.1%	4 / 5.1%	3 / 11.5%
Arthroscopic surgery	1 / 0.5%	8 / 10.3%	4 / 15.4%

N = number of patients treated during the first, second and third visit; NSAID = nonsteroidal anti-inflammatory drug; ESWT = extracorporeal shockwave therapy; US = ultrasound

In this study, the SAPS group was a mean age of 55.3 years (range, 28-79 years), with most patients between the age of 30 and 60 (68.2%). The majority of the persons with calcific deposits were females (69.9%) with a frequency of calcific deposits within females of 48%, and 33% within men. Logistic regression analysis showed that women had a higher risk for the presence of a calcific deposit. These results are consistent with previous statements that women are affected more than men[3,4,10].

Imaging of the shoulder is necessary to confirm the diagnosis of calcific tendinitis. In this study, radiography was the primary method of examining the rotator cuff for calcific deposits. Radiography is a practical, cost effective and useful modality to detect and locate calcific deposits as well as for the assessment of their extent, delineation and density.[11] Characterizing the shape and contour of the calcific deposit in three categories as suggested by Gärtner[2] is important. It is likely that a transparent, fluffy radiographic appearance with poorly defined borders of the calcific deposit, Gärtner type III, is an indicator for the resorptive phase of the disease and therefore has a higher chance of self-healing.[12,13] However, discriminating between these morphologic types remains a challenge in daily practice. Also, current literature shows that reliable classification of the stage of the disease cannot be achieved by radiologic measures only.[14] The discrepancies between ultrasound and radiographs suggests that ultrasound is more sensitive in finding small calcific deposits in the subscapularis tendons, as well as discriminating whether a calcific deposit is located at the insertion of the supraspinatus or the infraspinatus tendon. Ultrasound provides an excellent means of identifying and localizing the calcification within the rotator cuff, while at the same time evaluating the integrity of the rotator cuff tendons, biceps tendon and subacromial

bursa. The calcific deposit is seen as a hyperechoic focus, with or without posterior acoustic shadowing.[15] These morphological characteristics were classified by Farin et al.[2] The conclusion of their study is that ultrasound proved to be reliable in the detection and localization of rotator cuff calcifications, but is yet unable to classify the pathophysiologic phase. Because of this and the possibility of pathologic conditions of bone, it is advisable to obtain radiographs in conjunction with ultrasound examination for calcific tendinopathy[16].

The symptomatic patients had a mean duration of SAPS symptoms of 32 months. Because 87% of the patients had already received some sort of conservative treatment, minimally invasive treatment options such as US-guided needling and ESWT were initiated frequently. Arthroscopic decompression was reserved for thirteen patients (6.8%) with persistent symptoms that were resistant to maximum conservative therapy. These results are illustrative for a condition in which surgical treatment should only be performed in patients that do not respond to conservative and minimally invasive therapies[17].

No correlation was found between the distribution of the dominant arm and the affected shoulder. Metabolic disorders such as diabetes mellitus type II, are a risk factor for calcific tendinopathy as stated by Hurt and Baker[18]. In this study, metabolic disorders were reported in only 6 patients and were therefore not found to be a risk factor for the presence of calcific deposits.

The retrospective design of this study provided the opportunity to study a large group of patients, to study the prevalence of calcific deposits and to analyze risk factors associated with the development of symptomatic calcific tendinopathy of the rotator cuff. However, a prospective cohort study should be conducted to identify patients with asymptomatic calcific deposits and follow them over a longer period of time to study if, and if possible why, they develop symptomatic calcific tendinopathy.

This study had some limitations. A perfect cross-section of the general population to examine the prevalence of this disease would be ideal. This study model tried to serve that purpose, but the group defined as 'asymptomatic patients' constituted a selected portion of the general population. Compared with the general age distribution in the municipality of our clinic (Haarlemmermeer, the Netherlands, n=144061)[19] the percentage of individuals aged between 30-60 years was comparable with this study population, but there was a higher amount of men aged <30 years, probably due to sports trauma, and individuals aged >80 years due to increased chance of falling, both of which can be explained by the emergency department as screening location.

Extrapolation of these results to the general population should therefore be done with caution. Bosworth[6] also studied a specific portion of the general population (76.7% women, 89.4% aged <40, 94.1% clerks or typists) containing a number of young female manual laborers. Nevertheless, Bosworth's method involved obtaining physical and bilateral fluoroscopic examinations of both shoulders in 6,061 unselected individuals, which was more thorough than our method. The relative young age of Bosworth's study population might explain the low (2.7%) prevalence of calcific tendinopathy as compared with the 7.7% found in this study, where the mean age was 55 years. Furthermore, it would have been interesting to see if occupational health is also a risk factor in our study population. Unfortunately, too little occupational data were available to use this in this study.

CONCLUSION

This study demonstrates that women in the fourth, fifth and sixth decade of their life with SAPS and a calcific deposit of >1.5 cm in length have the highest chance of suffering from symptomatic calcific tendinopathy of the rotator cuff. In this study, the prevalence of calcific deposits in the rotator cuff in a patient population without acute or chronic nontraumatic shoulder pain was 7.8%. Furthermore, 42.5% of all the patients with SAPS who were analyzed had calcific deposits in the rotator cuff. These results differ from previous studies and provide a current view on the epidemiology of calcific rotator cuff deposits. Determining if the calcific deposit in the rotator cuff in a patient with SAPS is the primary cause of symptoms remains a challenge. At the same time, the presence of a calcific deposit in the rotator cuff is not a condition that requires immediate treatment or referral to an orthopaedic surgeon when a patient does not have symptoms of tendinopathy.

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3

Radiographic assessment of calcifying tendinitis of the rotator cuff: an inter- and intraobserver study

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ABSTRACT

BACKGROUND

The radiographic appearance of calcific tendinitis of the rotator cuff varies according to the stage of the disease. We compared currently used classification systems in a large group of observers to identify the most reliable classification system.

METHODS

Thirty-seven orthopaedic surgeons evaluated shoulder radiographs of 25 patients to classify the stage of the calcific tendinitis according to the classifications by (1) Gärtner and (2) Molé using a Web-based study platform. Inter and intraobserver agreement among observers was measured using the Siegel and Castellan multirater κ.

RESULTS

Both classification systems had fair interobserver agreement; κ was 0.25 for the Molé classification and 0.34 for the Gärtner classification. The Gärtner classification was significantly more reliable than the Molé classification

CONCLUSION

Currently, there is no radiographic classification that can serve the purpose of guiding treatment in a reliable way.

INTRODUCTION

Calcific tendinitis is a frequently encountered cause of subacromial pain syndrome, and its pathogenesis is still under debate.[1] The prevalence of calcific deposits in the rotator cuff tendons in either the general population (2.7% to 7.8%), as well as in a population with a painful shoulder (8% to 40%), is high[2]. The supraspinatus tendon is most frequently affected. It is postulated by Uhthoff et al. that calcific tendinitis can be divided into three main stages; the pre-calcific stage, the calcific or formative phase and the resorption stage.[3] These stages are characterized by differences in size, shape and appearance on imaging techniques.[4] Different treatment options are advised depending on the stage of the disease, and previous studies have suggested that there is a relationship between the size, location and morphology of calcifications, and clinical outcome.[5,6] Imaging techniques can help the physician to localize and classify the calcific deposits and guide treatment by combining this information with clinical parameters.[6,7] Among these imaging techniques, radiography of the shoulder is widely available, inexpensive, fast and in most cases sufficient to diagnose calcific deposits in the rotator cuff. Standard radiographs include anterior-posterior, outlet and axillary view.[7] These views allow multidirectional assessment of the location and morphology of the deposits. Additional anterior-posterior views in external rotation and internal rotation could help in differentiating between a supraspinatus and infraspinatus located deposit. Various classifications systems exist to categorize radiographic signs of calcific tendinitis of which the Gärtner [4] and Molé [8] classification are most frequently used. (Table 1).

Table 1. Radiographic classifications for calcific tendinitis of the rotator cuff

Title	*Definitions*	*Inter- / intraobserver agreement: κ (range)*
Gärtner [4]	(I) well circumscribed, dense (II) soft contour/dense or sharp/transparent. (III) translucent and cloudy appearance without clear circumscription	0.33 - 0.48 / 0.36 - 0.42 [9,10,13]
Molé [8]	(A) dense, homogeneous, sharp contours (B) dense segmented, sharp contours (C) heterogeneous, soft contours (D) dystrophic calcification at the insertion	0.18 – 0.22 / 0.34 – 0.40 [13,14]
DePalma [11]	(I) fluffy, amorphous and ill defined. (II) defined and homogeneous	0.25 - 0.34 / 0.24 - 0.49 [13,14]
Patte and Goutallier [12]	(I) localised and homogeneous (II) diffuse, disseminated, heterogeneous	0.24 - 0.38 / 0.28 - 0.46 [13,15]

κ = Fleiss kappa

There is some knowledge on the psychometric properties of the classification systems in smaller observer groups and these studies did not show satisfactory inter- and intraobserver agreement.[9,10] The primary objective of this study was therefore to investigate whether the interobserver agreement of the Gärtner classification[4] and the Molé classification[8], could be improved by using a large group of observers. The second objective was to assess whether the observers were able to correctly locate the deposit on the radiographs and the third objective was to re-assess the intraobserver agreement. The primary hypothesis was that both the Gärtner classification and the Molé classification systems would have a low inter- and intraobserver agreement. Our secondary hypothesis was that the interobserver agreement with respect to deposit location in the rotator cuff would be high.

MATERIALS AND METHODS

DESIGN

This study was approved by the institutional research board at the principal investigator's hospital and, has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its amendments.

CASE SELECTION

Radiographs of calcific tendinitis patients were selected from a database of patients treated for shoulder pain at the senior investigator's hospital. This database was composed for an earlier epidemiological study on the prevalence of calcific deposits in symptomatic and asymptomatic patients.[2] Each series contained three radiographs (anterior-posterior (AP), supraspinatus outlet view and axillary view). The AP radiographs were taken with the arm in neutral rotation and the scapula positioned parallel to the film (True AP / Grasney view). In total 154 radiographs with correlative ultrasound examinations were available in the database.[2] Inclusion criteria for this study were: a single calcific deposit of at least 10 mm in a rotator cuff tendon, and clinical signs of non-traumatic subacromial pain syndrome. One of the authors (J.L.) selected twenty-five non-consecutive cases with calcific deposits of different size, morphology, and location, representing a wide spectrum of radiographic presentations. The distribution among the supraspinatus, the infraspinatus and subscapularis tendon was 17:5:3 (Fig 1a-c). The standard of reference with regard to the location of the deposit was the ultrasound examination which was available in every case. Radiographs were anonymized, converted to DICOM files and uploaded to the research group's web-based survey platform.

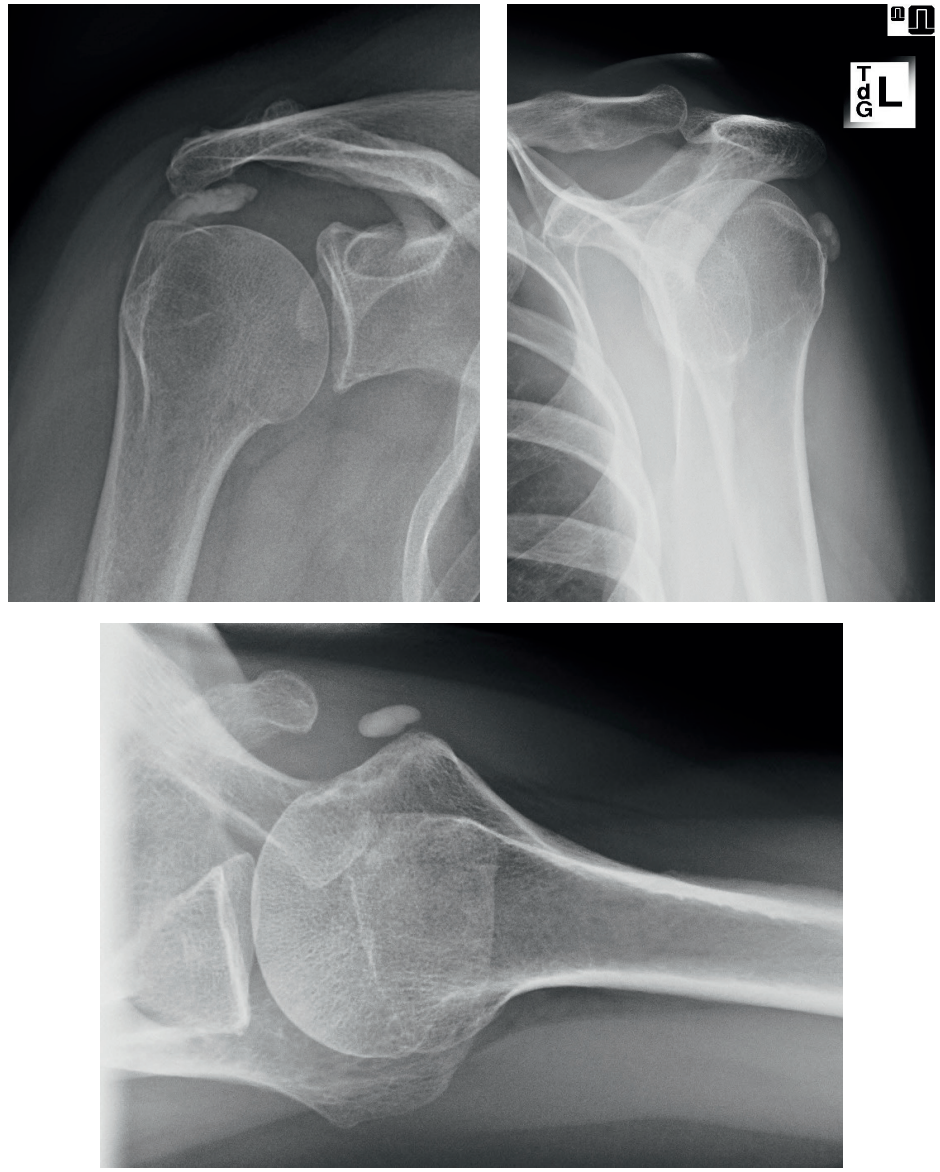

Figure 1a. Axial view shoulder radiograph, showing a calcific deposit in the subscapular tendon located at its insertion on the lesser tubercle.
Figure 1b. AP view shoulder radiograph, showing a calcific deposit in the supraspinatus tendon located at its insertion on the greater tubercle.
Figure 1c. Outlet view shoulder radiograph, showing a calcific deposit on the dorsal side of the shoulder, located in the infraspinatus tendon.

PARTICIPANTS

Independent members of the Shoulder Elbow Platform[16] were invited by an invitation e-mail that included a short study description. They were asked to evaluate 25 shoulder radiograph series from patients with calcific rotator cuff tendinitis on a web-based study platform. Other than an acknowledgment as part of the author collaborative in the paper, no incentives were provided. The goal of the Shoulderelbow Platform is to facilitate online interobserver agreement and diagnostic accuracy studies in the field of orthopedic shoulder and elbow injuries. Members of the Shoulderelbow Platform are fully trained, actively practicing surgeons from different countries. The observers independently logged in to the website. After login they received an instruction on the use of the classification systems and were asked to provide the following demographic and professional data: observer's gender, location of practice, years of practice, observer's clinical specialty, and number of treated calcific tendinitis patients a year. For the interobserver agreement, observers were asked to classify the deposit according to the Gärtner[4] and the Molé classification[8] (Table 1.).The observers were then asked to answer a multiple option question on the location of the deposit. Options were: supraspinatus tendon, infraspinatus / teres minor tendon, subscapularis tendon. Observers evaluated radiographs using a built-in Digital Imaging and Communications in Medicine viewer (MedDream, Softneta, Kaunas, Lithuania) and were able to zoom and adjust brightness, contrast, and window levelling. A case had to be completed to continue with the next case. Observers completed the study at their own pace, in their own time on various computers if necessary. Six months later randomly selected senior surgeons were contacted until six agreed to re-asses the previous cases to determine the intraobserver agreement.

STATISTICAL ANALYSIS

Statistical analysis was performed by use of SPSS 21 software (IBM Corp, Armonk, NY, USA). Observer characteristics are described as frequencies with accompanying percentages. Agreement among observers was determined using absolute agreement and the Fleiss kappa measure described by Siegel and Castellan.[17] The Fleiss kappa measure is a frequently used statistics measure to describe chance- corrected agreement between ratings made by multiple observers. [18–20] The generated kappa values were interpreted according to the guidelines by Landis and Koch[18]: values of 0.01 to 0.20 indicate poor agreement; 0.21 to 0.40 fair agreement; 0.41 to 0.60, moderate agreement; 0.61 to 0.80, substantial agreement; and more than 0.81, almost perfect agreement. Kappa values were compared by use of a two sample Z-test. A *P*-value <.05 was considered statistically significant. A subgroup analysis was performed on the interobserver data to assess whether differences in observer characteristics (years

in practice, number of treated cases a year or continent of residence) influenced the Fleiss kappa measure.

Post-hoc power analysis revealed that a minimum sample of 25 patients evaluated by a minimum of 37 observers would provide 97% power (α = 0.05, ß = 0.20) in a two-sample Z-test to detect a clinically significant difference of one categorical rating of kappa (κ = 0.10).

RESULTS

PARTICIPANTS

In total 150 invitations were send. Fifty-seven surgeons logged in to the Shoulder Elbow Platform. Thirty-seven observers (25%) completed the survey. The majority of the observers worked in Continental Europe (59%), were in practice 5 years or more (68%) and treated >25 cases of calcific tendinitis patients a year.

INTEROBSERVER AGREEMENT

Surgeons had fair interobserver agreement for both the Molé classification (κ =0.25) and the Gärtner classification (κ =0.34). The Gärtner classification was more reliable than the Molé classification system (*P* = .014*)*. A moderate interobserver agreement was found for the presence of calcific deposits in the supraspinatus tendon (κ =0.47) and the subscapularis tendon (κ =0.53), whereas a fair interobserver agreement was found for the presence of a calcific deposit in the infraspinatus tendon (κ =0.38) on radiographs. Table 2. shows the kappa and the absolute agreement values.

INTRAOBSERVER AGREEMENT

There was substantial intraobserver agreement for both the Molé (κ =0.65) and the Gärtner classification (κ =0.70) ranging from moderate (κ = 0.55) to almost perfect (κ = 0.85). With regard to the localization of the deposits on the radiograph, substantial intraobserver agreement was achieved for the supraspinatus (κ = 0,79), infraspinatus (κ =0,65) and subscapularis (κ =0,76).

FACTORS ASSOCIATED WITH INTEROBSERVER AGREEMENT

Various subgroup analyses were performed based on demographic parameters of the observers but no significant differences were observed. (supplementary Table 3-5)

Table 2. Interobserver / intraobserver agreement

Classification	Categorical kappa	κ* (inter / intra)	abs ǂ (inter / intra)
Gartner & Simons	fair / substantial	0.34 / 0.70	0.58 / 0.79
Molé	fair / substantial	0.25 / 0.65	0.46 / 0.75
Location			
Supraspinatus	moderate / substantial	0.47 / 0.79	0.75 / 0.93
Infraspinatus / teres minor	fair / substantial	0.38 / 0.60	0.72 / 0.82
Subscapularis	moderate / substantial	0.53 / 0.76	0.90 / 0.95

* = Fleiss kappa
ǂ = absolute agreement

Table 3. Interobserver agreement by country provider

	Europe (n=22)		USA (n=9)		Other (n=6)	
Classification	Categorical	κ * / abs ǂ	Categorical	κ * / abs ǂ	Categorical	κ * / abs ǂ
Gartner & Simons	fair	0.39 / 0.60	fair	0.32 / 0.60	fair	0.30 / 0.56
Molé	fair	0.26 / 0.47	fair	0.28 / 0.51	fair	0.22 / 0.43
Location						
Supraspinatus	moderate	0.44 / 0.73	moderate	0.52 / 0.77	moderate	0.50 / 0.78
Infraspinatus	fair	0.39 / 0.73	moderate	0.42 / 0.73	fair	0.28 / 0.65
Subscapularis	moderate	0.47 / 0.88	substantial	0.74 / 0.95	moderate	0.54 / 0.88

* = Fleiss kappa
ǂ = absolute agreement

Table 4. Interobserver agreement for years in practice

	0-5 y (n=12)		6-10 y (n=7)		10-20 y (n=18)	
Classification	Categorical	κ * / abs ǂ	Categorical	κ * / abs ǂ	Categorical	κ * / abs ǂ
Gartner & Simons	fair	0.35 / 0.59	fair	0.35 / 0.59	fair	0.34 / 0.58
Molé	fair	0.26 / 0.48	fair	0.22 / 0.44	fair	0.24 / 0.45
Location						
Supraspinatus	moderate	0.43 / 0.73	fair	0.29 / 0.65	moderate	0.59 / 0.82
Infraspinatus	moderate	0.47 / 0.78	moderate	0.40 / 0.71	fair	0.31 / 0.78
Subscapularis	moderate	0.42 / 0.82	substantial	0.77 / 0.96	moderate	0.54 / 0.89

* = Fleiss kappa
ǂ = absolute agreement

Table 5. Interobserver agreement for number of treated patients a year

	0-25 (n=14)		25-50 (n=11)		> 50 (n=12)	
Classification	Categorical	κ * / abs ǂ	Categorical	κ * / abs ǂ	Categorical	κ * / abs ǂ
Gartner & Simons	fair	0.28 / 0.55	fair	0.27 / 0.53	moderate	0.47 / 0.66
Molé	fair	0.22 / 0.44	fair	0.28 / 0.49	fair	0.27 / 0.47
Location						
Supraspinatus	moderate	0.53 / 0.78	substantial	0.67 / 0.88	fair	0.31 / 0.67
Infraspinatus	fair	0.35 / 0.71	fair	0.35 / 0.72	moderate	0.41 / 0.72
Subscapularis	moderate	0.54 / 0.90	moderate	0.54 / 0.90	moderate	0.54 / 0.89

* = Fleiss kappa
ǂ = absolute agreement

DISCUSSION

In the current study we showed that the radiographic classification systems as developed by Gärtner and Molé lack interobserver agreement. Therefore these classifications are not reliable enough to classify calcific tendinitis of the rotator cuff. The intraobserver agreement was acceptable with a substantial agreement, surgeons tend to agree with themselves more than with each other, but the interobserver agreement for the Gärtner classification was only fair according to the criteria by Landis and Koch. The Gärtner classification showed a higher (*P* = .014*)* interobserver reliability (**κ** = 0.34) than the classification by Molé (**κ** =0.24). The highest agreement among observers was seen among observers who treat >50 patients a year (**κ** = 0.47 / moderate agreement). Increasing the amount of observers to thirty seven, compared to previous studies with lower numbers, did not improve interobserver agreement. In these studies, with 4 and 6 observers respectively, a fair to moderate agreement was found (Table 1).[9,10] These results are consistent with previous studies in which alternative classification systems for calcific tendinitis have been tested (Table 1). While the results between these studies differ, the interobserver data never exceeds moderate agreement. Patte and de Palma both suggested a system with only 2 options but this did not result in a more reliable classification. It seems that observers can't agree on vague terms such as 'ill-defined, cloudy, inhomogeneous and localised or diffuse'.

In this study, agreement between observers was fair to substantial with regard to the location of the calcific deposit on radiographs, with absolute agreement ranging from 0.72 to 0.90. It appeared easier for observers to differentiate if a deposit was in the supraspinatus or the subscapularis than in the infraspinatus. This could be due to the fact that both tendons have their insertion on the greater tuberosity. Additional AP external and internal rotation views, supplementary to the outlet view, could have made the

differentiation more easy but these radiograph were not routinely available in current database. Furthermore, deposits in the subscapularis tendon can be identified on the anterior aspect of the humeral head on the axillary-view radiographs, making it easier to determine the location.

A limitation of most interobserver studies, is the use of only a few observers. Strengths of this study include the use of a web-based study platform and it provides insight in how interobserver agreement studies can benefit from an international web-based study platform. While in this study the results between the small and large observer groups were similar, a web-based platform has the potential to gather a large amount of data from an international collaboration of surgeons, makes it easier to recruit observers, and provides the observers the tools to assess the radiographs, or other imaging modalities, in an uniform way. In comparison to smaller observer studies this provides researchers the possibility to perform additional subgroup analyses.

The study should however be interpreted in light of several limitations. First, the results would be more generalizable if the observers included a range of clinical staff including residents and reporting radiologists who may also be responsible for diagnosis, triage and delivery of appropriate care. Second, observers received an explanation on the classification systems prior to the survey but did not receive any specific training. Third, there may be a difference in quality between the web interface that was utilized and the usual way in which physicians view radiographs. However, the DICOM viewer provides all the usual tools that are required for an appropriate assessment. Fourth, for practical purposes we chose to limit the study to two classification systems although other, less frequently used, systems are available (Table 1). Fifth, additional AP in internal rotation views might have increased the detection rate of infraspinatus deposits. Finally, the data may be subject to the so-called ''kappa paradox'' because the kappa measure was considerably lower than the overall percentage of agreement (Table 2.). If the prevalence of an outcome is low, it causes an imbalance in the marginal totals, generating a lower kappa than one might expect.[21,22]

CONCLUSION

We conclude that interobserver radiographic classifications for calcific tendinitis of the rotator cuff are not reliable enough, and would need more precise and simplified criteria to improve reliability. This would be of importance since tools, whether imaging or clinical, are needed to guide physicians in their treatment algorithm for patients with symptomatic calcific tendinitis. Development of these tools however is difficult, because there are no clear clinical or radiographic cut-off points between the different phases

of the disease and patients may even have multiple calcific deposits in different phases. Currently there is no classification that can serve this purpose and physicians remain largely dependent on the development of symptoms over time and a combination of screening examinations to determine what phase of the disease a patient is in.

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Part 2

Exploring minimally invasive treatment options

4

Evidence for minimally invasive therapies in the management of chronic calcific tendinopathy of the rotator cuff: a systematic review and meta-analysis

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ABSTRACT

BACKGROUND

This meta-analysis assessed the short-term to midterm effectiveness of minimally invasive treatment modalities in the management of calcifying tendinopathy of the shoulder, a common source of chronic shoulder pain that leads to pain, a decreased active range of motion and loss of muscular strength. When conservative therapies fail, minimally invasive treatment options can be considered before resulting to surgery.

MATERIALS AND METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed to conduct this review. A systematic literature search was conducted in May 2013 to identify all studies that examined the short-term to midterm effectiveness of minimal invasive treatment modalities for chronic calcifying tendinopathy. The primary end points were identified as function, pain and total resorption rates. Grades of Recommendation Assessment, Development and Evaluation (GRADE) was used to assess the quality of evidence.

RESULTS

Included were twenty studies (1544 participants). Common methodological flaws were related to randomization. In general, there is moderate quality GRADE evidence that high-energy ESWT has a significant effect on pain relief and functional status compared to other interventions. There is variable quality GRADE evidence on the efficiency of other interventions.

CONCLUSION

High-energy extracorporeal shockwave therapy is the most thoroughly investigated minimal invasive treatment option in the short-term to midterm and has proven to be a safe and effective treatment modality. Ultrasound-guided needling is safe but has not been proven to be more effective than an ultrasound-guided subacromial corticosteroid injection in recent level-1 research, and further research will have to prove its effectiveness.

LEVEL OF EVIDENCE: II, systematic review and meta-analysis.

INTRODUCTION

Calcific tendinopathy of the rotator cuff is a disorder characterized by inflammation around deposits of calcium carbonate apatite crystals in the tendons and is a common source of pain in the shoulder. Calcific deposits are found in between 2.7% to 22% of subjects during routine examination[1], and clinical symptoms occur in 34% to 45% of patients[2]. Approximately 80% of the depositions are located in the supraspinatus tendon[2–4]. Most individuals with calcific tendinopathy are aged between 30 and 50 years, with women affected 1.5 times more often than men[5–7]. Clinical features of the disease are shoulder pain, a decrease in active range of motion, and loss of muscular strength. The disease in some cases is self-limiting without therapy. The natural course of spontaneous resolution of the calcific deposit is variable, however, and was reported in 9.3% after 3 years and 27% after 10 years.[4] Uhthoff et al.[56] described that the progress of the disorder passes through 4 phases in the following order: cell-mediated calcification/formative stage, resting stage, resorptive stage/deposit phagocytosis, and ending with complete recovery of the tendon. Most patients can be treated conservatively with pain medication, physiotherapy and prudent use of subacromial corticosteroid injections. Approximately 10% of patients are resistant to conservative treatment and appear to remain in a prolonged formative phase with chronic symptoms.[8] These patients can be treated with other modalities such as surgery whereby an open or arthroscopic surgical procedure can achieve complete clinical improvement in 80% to 100%.[9] Surgery however is costly, requires a long rehabilitation and perioperative complications may occur.[10]

There are nonsurgical alternatives such as extracorporeal shockwave therapy (ESWT),[11,12,21,22,13–20] transcutaneous electronic nerve stimulation (TENS)[40] and ultrasound-guided percutaneous needling.[23–28] Because the natural course of calcific tendinopathy is variable and the time required for a spontaneous disappearance often is too long and unacceptable for the patient´s quality of life the treatment should be effective in the short-term and midterm, minimally invasive, with minimal risk on complications, and inexpensive. The aim of this systematic review is therefore to present an evidence-based overview of the short-term and midterm (3 – 6 month) effectiveness of various nonsurgical and minimally invasive treatment modalities in pain reduction, improvement of shoulder function and reduction in size of calcific deposits for patients with chronic calcific tendinopathy of the shoulder. This information can support the development of evidence-based guidelines and give direction to future research on calcifying tendinopathy of the rotator cuff.

MATERIALS AND METHODS

INCLUSION CRITERIA

Types of study

The literature search of the literature performed for this review was limited to published original randomised or quasi-randomised controlled (RCT) and controlled clinical trials (CCT) concerning the minimally invasive treatment of chronic calcifying tendinopathy of the rotator cuff with at least 3 months follow-up.

Types of participants

Inclusion was limited to articles reporting on patients over 18 years old with symptoms of calcific tendinopathy of the rotator cuff consisting for more than six months who did not respond to conservative treatment with NSAID's, physiotherapy or subacromial corticosteroid injections. The diagnosis of calcifying tendinopathy had to be established by analysis of standard radiographs and/or ultra-sonograms of the shoulder with morphological type-I and type-II deposits corresponding to the classification of Gartner and Simons.[16] Trials involving patients with evidence of a rotator cuff tear (physical examination, sonographic and/or MRI), systemic inflammatory disorders, previous surgery to the shoulder, instability of the shoulder, neurological disorders or dysfunction of the upper limb, ESWT/needling within the last year, acute bursitis and osteoarthritis of the glenohumeral or acromioclavicular joint were excluded.

Types of intervention

Six interventions were included in the study: Extracorporeal shockwave therapy (ESWT), radial shockwave therapy (RSWT), ultrasound guided percutaneous needling, transcutaneous electronic nerve stimulation (TENS), laser therapy and ultrasound therapy. Shockwave therapies can be classified according to the amount of energy released by the sonic pulses expressed as energy flux density (EFD) in mJ/mm2.[29] There is no universal agreement concerning the thresholds of these subdivisions. For the present study we distinguished between low-energy shockwave therapy having an EFD of <0.20 mJ/mm2 and high-energy shockwave therapy having an EFD of >0.20 mJ/mm2.[30,31]

Types of outcome measures

This study focused on outcome measures for pain, shoulder function and change of the size of calcific deposit pertaining to the effect of the different treatment modalities for calcifying tendinopathy of the rotator cuff.

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES FOR THIS REVIEW

To identify all studies pertaining the treatment of calcifying tendinopathy of the rotator cuff in adults the following databases were searched: Medline (1966 to May 2013), Cochrane Database of Systematic Reviews (1988 to May 2013), Cochrane Clinical Trial Register (1988 to May 2013), PEDRO (1988 to May 2013), CINAHL (1988 to May 2013) and Embase (1988 to May 2013). A range of keywords relevant to the review was grouped into four categories to maximize the search result. The Pubmed/Medline search is defined in Table 1. The search was independently performed by two reviewers (J.L. and I.S.).

The 'find similar' function in Medline and EMBASE and references of retrieved publications were also used to add studies potentially meeting the inclusion criteria, missed by the electronic search. Papers outside the English language were considered if translation was possible. Abstracts from scientific meetings, unpublished reports, and review articles were excluded.

Table 1. Pubmed/Medline search strategy

#1	(calcif*[All Fields])
#2	("tendinopathy"[MeSH Terms] OR "tendinopathy"[All Fields] OR "tendinosis"[All Fields] OR "tendinitis"[All Fields])
#3	("shoulder"[MeSH Terms] OR "shoulder"[All Fields]) OR ("rotator cuff"[MeSH Terms] OR ("rotator"[All Fields] AND "cuff"[All Fields]) OR "rotator cuff"[All Fields]) OR supraspinatus[All Fields])
#4	("shock*"[All Fields] OR "needling"[All Fields] OR " percutaneous" OR "ultrasound"[All Fields] OR "laser"[All Fields])

METHODS OF THE REVIEW

Selection of trials

Trial selection was performed by reviewing title and abstract to identify potentially relevant articles for our review. The full manuscript was retrieved when the title, keywords or abstract revealed insufficient information to determine appropriateness for inclusion. All identified studies were independently assessed by 2 reviewers (J.L. and I.S.) for inclusion using the above-mentioned criteria. Disagreement was resolved by discussion, with arbitration by a third reviewer (A.N.) when differences remained.

Data collection

Information was extracted from each included trail by one reviewer (J.L.). The following data was extracted: study design (RCT / QRCT / Non-RCT), study characteristics (e.g.

country where the study was conducted, risk of bias), patient characteristics (e.g. number of participants, age, gender), description of the experimental and control interventions, co-interventions, duration of follow-up, types of outcomes assessed and the authors' results and conclusions. Studies that included more than 2 treatment arms were treated as separate interventions for the purpose of this review. Extraction was verified by the second reviewer (M.B.). Disagreements were resolved in a consensus meeting or, if necessary, by third party adjudication (A.N.). Reviewers were not blinded for author, affiliation, and source.[32–34] If necessary, authors were contacted for additional information. If final value scores were not reported the change from baseline scores were extracted. Outcomes were assessed at 3 and 6 months and data included according to the time closest to these intervals.

ASSESSMENT OF RISK OF BIAS IN INCLUDED STUDIES

Differences in quality amongst trials indicate a possible difference in bias between these trials. Therefore, evaluating the risk of bias of the trials when evaluating the effectiveness of an intervention. Two independent reviewers (J.L. and I.S.) obtained the full text of all potentially eligible articles for independent methodological assessment. Articles were not blinded for author, affiliation, and source.[32–34] Studies were independently evaluated for their risk of bias using the 6 recommended criteria by the Cochrane Review Group[35] and scored as 'low risk', 'high risk' of 'unclear risk'. Any disagreement was resolved by consensus or third-party adjudication (A.N.).

Quantitative analysis

The synthesis approach was data-driven. Treatment effect was examined through meta-analyses, but these were only conducted if studies were determined to be clinically homogenous. Clinical homogeneity was defined a priori by setting, population and comparison group. If the study arms were all heterogeneous, a qualitative/narrative data synthesis approach would be performed. The results of comparable studies were pooled using fixed or random effects models when appropriate. When heterogeneity is present, a random-effects meta-analysis weights the studies relatively more equally than a fixed-effect analysis.[35] Individual and pooled statistics were reported as relative risks with 95% confidence intervals for dichotomous outcomes. Weighted mean differences (WMD) or, where different scales have been used, standardized mean differences (SMD) and 95% confidence intervals were reported for continuous outcomes measurements. Heterogeneity was explored in two manners, informally by vision (eye-ball test) and formally tested by the Q-test (chi-square) and I^2. Substantial heterogeneity was defined as $I^2 \geq 80\%$.[36] Regardless of possible heterogeneity of the included studies the following stratified analysis were conducted: 1) by type of intervention 2) by follow-up time (e.g. three and six months). All analyses were conducted in Review Manager 5.2.[37]

Unit of analysis issues / dealing with missing data

The method according to Walter et al [38] was used to calculate the SD in cases where authors did not provide the standard deviation. If a mean and 95% confidence interval was reported the standard deviation for each group was estimated by dividing the length of the confidence interval by 3.92, and then multiplying by the square root of the sample size.[35]

Qualitative analysis

The overall quality of evidence and the strength of recommendations was evaluated using Grades of Recommendation Assessment, Development and Evaluation (GRADE).[36] The quality of evidence is described in Table 2.

Table 2. GRADE quality of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect. There are sufficient data with narrow confidence intervals. There are no known or suspected reporting biases.
Moderate quality: Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate; one of the domains is not met.
Low quality: Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate; two of the domains are not met.
Very low quality: Great uncertainty about the estimate; three of the domains are not met.
No evidence: No evidence from RCTs.

RESULTS

SEARCH RESULTS

The search of Medline, Embase, CINAHL, Pubmed, Cochrane, PEDro and SPORTDiscus databases provided a total of 772 citations. The search was performed on May 25, 2013, with a final search update on August 24, 2013. After adjusting for duplicates 306 studies remained. Of these, 254 studies were discarded for not meeting the inclusion criteria after reviewing the abstracts. The full text of the remaining 52 studies was examined in more detail, and we identified 20 studies for inclusion in the review. [11,12,22,25,28,39–45,13,15–21] No additional studies were identified by the 'find similar' function in Medline and Embase databases or by checking the references of retrieved publications. (Fig. 1)

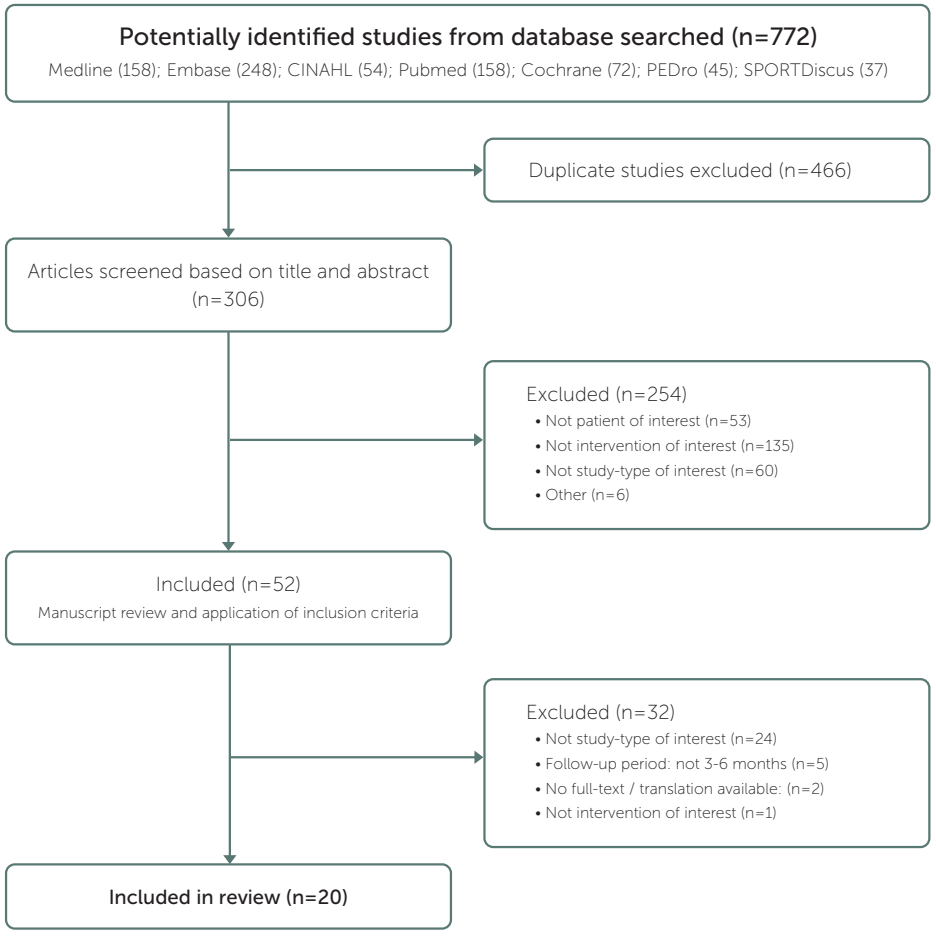

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[62] flow diagram of the search process.

CHARACTERISTICS OF INCLUDED STUDIES

Study characteristics and interventions are summarized in Table 3. Nineteen studies were constructed as prospective randomised controlled trials and 1 as a prospective non-randomised controlled trial.[28] The sample size ranged from 20 to 287 patients with a total of 1544 participants. All but one study [43] provided baseline characteristics. The age ranged from 28 to 82 years. The mean duration of symptoms reported varied from 11.1 to 42.8 months. The studies were published between 1998 and 2013 and most studies were of Western European origin except for the studies from Hsu et al [20] and Pan et al. [19]

OUTCOME MEASURES: TYPE, TIMING

Assessment of pain, shoulder function and radiological appearance of the calcific resorption after treatment were the most common reported outcome measures.

All but one study[16] reported shoulder function. The Constant Murley Scale (CMS) was the most common reported shoulder function outcome measure. In addition to the CMS, de Witte et al[45] used the Disabilities of the Arm, Shoulder and Hand questionnaire (DASH) and the Western Ontario Rotator Cuff index (WORC). Cacchio et al [41] reported the University of California Los Angeles scale (UCLA).

Sixteen out of 20 studies provided explicit data on changes in pain either by reporting the CMS subset scores [17,22,25,40], VAS-pain levels, (13,14,16,18–22,24,28,52,54) or by reporting the recurrence of pain.[16] Four out of 20 studies [11,39,43,45] used a primary outcome measure which included pain assessment as a sub score (CMS, DASH, WORC, ULCA) but did not provide the exact data. Three studies [21,44,45] differentiated between pain during rest and stress, whereas Pleiner et al[13] made a difference between day and night. Hsu et al [20] only provided visual analog data for the treatment group.

All but one study [28] reported changes in radiological size, or appearance, or both. Sixteen studies described if there was no change, partial resorption or total resorption of the calcific deposit. Gerdesmeyer et al[17] described the change in mm^2, Pan et al[19] described the change in sonographic morphology, and Far et al[44] only reported if there was an improvement without elaborating what the exact criteria for improvement were.

TREATMENT PARAMETERS: TYPE, PRACTITIONER, NUMBER AND DOSAGE OF TREATMENT

This review reports 17 trials concerning the use of ESWT, 1 trial using RSWT and 2 trials concerning the use of ultrasound-guided percutaneous needling. The SWT trials reported a wide variety of energy flux density (0.06 - 0.78 mJ/mm^2), the number of pulses applied (1000-6000) as well as the number of sessions (1-5). Nine studies (12–14,17–19,23,50,54) compared high-energy ESWT with low-energy ESWT. Six studies [11,16,17,20,40,43] compared high-energy ESWT with sham,- or no treatment. Three studies [11,16,17] compared low-energy ESWT with sham or no treatment. Cacchio et al[41] compared RSWT with sham treatment. Pan et al[19] compared high-energy ESWT with TENS. Krasny et al[25] compared high-energy ESWT with high-energy ESWT combined with ultrasound-guided needling. Serafini et al[28] compared needling with no treatment, and de Witte[45] compared needling with a subacromial injection with steroids. Haake et al [21] included a treatment arm with high-energy ESWT directed on the insertion of the supraspinatus tendon rather than focussing directly on the calcific deposit. Sabetti et al [15] compared

focussing the low-ESWT on the maximum point of tenderness with focussing directly on the calcific deposit.

SAFETY

All studies reported on adverse effects. After treatment with SWT the most reported side effects were pain during treatment [17,22,40], soreness [19], local subcutaneous hematomas [11,39] and small petechial haemorrhages [17,25]. All of which affected only a small amount of the treated participants and all the side effects resolved within a few days. No clinically relevant adverse events such as avascular necrosis, bone oedema or rotator cuff tears were reported. Serafini et al[28] reported a few mild vagal reactions during treatment in their needling group and a painful bursitis in 13.2% of their patients within 3 months. de Witte et al[45] did not find a similar incidence of post-treatment bursitis and reported 2 frozen shoulders after needling.

RISK OF BIAS IN INCLUDED STUDIES

Of the 20 trials included in this review, the risk of bias was high in 4, [28,39,40,43], unclear in 16, and none had a low risk. The results of the risk of bias assessment for the individual studies are summarized in Table 4. In 17 of the 20 included trials, the generation or the concealment of the sequence randomization (or both) were inadequately described. No trials were able to blind the caregiver. Seven of the 20 trials adequately blinded patients and outcome assessors. [13,16,17,21,40,41,45] The proportion of missing outcome data was large enough to affect the results in four studies.[20,28,39,40] Three studies did report all of the prespecified primary outcomes in detail.[20,40,43]

Table 3. Summary of study characteristics

First author, year, type	Pts No.	Mean age in years (range or ±SD)	Mean duration of symptoms (range or ±SD in mo)	Follow-up (mo)	Intervention	Focus	Dosage in (impulses x EFD in mJ/mm²)	No. of sessions	Interval between sessions	Outcome measure
Rompe 1998 RCT [44]	100	49 (29 to 68)	25 (12 to 84)	1.5 + 6	ESWT low energy	Calcific deposit	1500 x 0.06	1	NA	CMS, resorption calcific deposits
		47 (29 to 60)	33 (12 to 120)		ESWT high energy	Calcific deposit	1500 x 0.28	1	NA	
Loew 1999 RCT [33]	80	46 (28 to 77)	36	3	No treatment	NA	NA	NA	NA	CMS, resorption calcific deposits
					ESWT low energy	Calcific deposit	2000 x 0.1	1		
					ESWT high energy	Calcific deposit	2000 x 0.3	1		
					ESWT high energy	Calcific deposit	2000 x 0.3	2	1 wk	
Haake 2002 RCT [19]	50	50 (29 to 68)	>6 months	3 + 12	ESWT high energy	Calcific deposit	2000 x 0.78	1	NA	CMS, VAS (rest/stress),
					ESWT high energy	Tuber-culum majus	2000 x 0.78	1		subjective improvement, resorption calcific deposits
Perlick 2003 RCT [41]	80	48.4 (38 to 64)	32	3 + 12	ESWT high energy	Calcific deposit	2000 x 0.42	2	3	CMS, resorption calcific deposits
					ESWT low energy	Calcific deposit	2000 x 0.23	2	3	

Table 3. Continued.

First author, year, type	Pts No.	Mean age in years (range or ±SD)	Mean duration of symptoms (range or ±SD in mo)	Follow-up (mo)	Intervention	Focus	Dosage in (impulses x EFD in mJ/mm²)	No. of sessions	Interval between sessions	Outcome measure
Gerdesmeyer 2003 RCT [17]	144	51.6 ± 8.5	42.6 ± 23.2	3 + 6 + 12	ESWT high energy	Calcific deposit	1500 x 0.32	2	12-16 days	CMS, VAS, resorption calcific deposits
		47.3 ± 8.5	42.8 ± 35.2		ESWT low energy	Calcific deposit	6000 x 0.08	2	12-16 days	
		52.3 ± 9.8	41.3 ± 28.6		Sham treatment - blocking polyethylene foil	Calcific deposit	1500 x 0.32	2	12-16 days	
Cosentino 2003 RCT [9]	70	51.8 (35 to 68)	15 (10 to 20)	6	ESWT high energy	Direction of calcific deposit	1200 x 0.28	4	4-7 days	CMS, resorption calcific deposits
			14.5 (10 to 18)		Sham treatment	No details reported	1200 x 0.0	4	4-7 days	
Pan 2003 RCT [40]	60 (63 shoulders)	55.21 ± 2.01	24.55 ± 6.45	0,5 + 1 + 3	ESWT high energy	Marked painful area	2000 x 0.26-0.32	3 times a week for 4 weeks = 12	2-3 days	CMS, VAS, sonographic morphology assessment
		58.00 ± 1.83	23.90 ± 5.32		TENS	Painful suba-cromial area	NA			
Peters 2004 RCT [42]	90	52 ± 6 (29 to 68)	NR	6	ESWT low energy	Calcific deposit	1500 x 0.15	Maximum of 5 sessions till no symptoms	6 wks	Pain, resorption calcific deposits
					ESWT high energy	Calcific deposit	1500 x 0.44	Maximum of 5 sessions till no symptoms	6 wks	

Table 3. Continued.

First author, year, type	Pts No.	Mean age in years (range or ±SD)	Mean duration of symptoms (range or ±SD in mo)	Follow-up (mo)	Intervention	Focus	Dosage in (impulses x EFD in mJ/mm²)	No. of sessions	Interval between sessions	Outcome measure
					Sham treatment	Calcific deposit	0.00	Maximum of 5 sessions till no symptoms	6 wks	
Pleiner 2004 RCT [43]	43 (57 shoulders)	54 ± 11	>6	3 + 7	ESWT high energy	Focused on point of maximum pain	2000 x 0.28	2	2 wks	CMS, VAS, resorption calcific deposits
		50 ± 8			ESWT low energy / sham treatment	Point of maximum tenderness	2000 x <0.07	2	2 wks	
Krasny 2005 RCT [29]	80	47.3 (32.5 to 67.3)	36.3 (13.0 to 96.0)	4.1	ESWT high energy + US-guided percuteneous needling	Calcific deposit	2500 x 0.36	1	NA	CMS, VAS, resorption calcific deposits
		49.4 (32.4 to 63.5)	30.5 (12.0 to 60.0)		ESWT high energy	Calcific deposit	2500 x 0.36	1	NA	
Sabetti-Aschraf 2005 RCT [47]	50	52.96 ± 8.77	NR	3	ESWT low energy	Point of max tenderness	1000 x 0.08	3	1	CMS. VAS, resorption calcific deposits
		52.4 ± 7.74	NR		ESWT low energy	Calcific deposit	1000 x 0.08	3	1	
Cacchio 2006 RCT [6]	90	56.12 ± 1.98	14 ± 4.95	6	RSWT low energy	Calcific deposit	2500 x 0.1	4	1 wk	UCLA, VAS, resorption calcific deposits
		56.42 ± 2.09	13 ± 5.03		Control	Calcific deposit	25 x 0.1	4	1 wk	

Table 3. Continued.

First author, year, type	Pts No.	Mean age in years (range or ±SD)	Mean duration of symptoms (range or ±SD in mo)	Follow-up (mo)	Intervention	Focus	Dosage in (impulses x EFD in mJ/mm²)	No. of sessions	Interval between sessions	Outcome measure
Sabetti 2007 RCT [46]	47	53.57 ± 8.80	> 6	3	ESWT high energy	Calcific deposit	2000 x 0.2	2	1 wk	CMS, VAS, resorption calcific deposits
		49.38 ± 8.37			ESWT low energy	Calcific deposit (three dimensional localization device)	1000 x 0.08	3	1 wk	
Albert 2007 RCT [2]	80	46.6 (31 to 74)	41.2 (6 to 120)	3	ESWT high energy	NR	2500 x 0.45 (max)	2	2 wks	CMS, VAS, resorption calcific deposits
		47.5 (32 to 69)	36.4 (7 to 160)		ESWT low energy	NR	2500 x 0.02-0.06	2	2 wks	
Hsu 2008 RCT [25]	46	54.4 (30 to 70)	12.3 (6 to 72)	1.5 + 3 + 6 + 12	ESWT high energy	Delivered at affected area	1000 x 0.55	2	2 wks	CMS, VAS, resorption calcific deposits
		57.8 (44 to 82)	11.1 (6 to 30)		Sham treatment	Dummy electrode	NR	NR	NR	NA
Hearnden 2009 RCT [22]	20	NR	NR	0.25 + 1.5 + 6	ESWT high energy	Calcific deposit	2000 x 0.28	1	NA	CMS, VAS, resorption calcific deposits
			NR		Sham treatment	Calcific deposit	20 x 0.03	1	NA	
Serafini 2009 NRCT [52]	219 (235 shoulders)	40.3 ± 10.9	NR	1 + 3 + 12 + 60 + 120	US-guided percuteneous needling	NA	NA	1	NA	CMS, VAS
	68	40.2 ± 11.3	NR		No treatment	NA	NA	NA	NA	

Table 3. Continued.

First author, year, type	Pts No.	Mean age in years (range or ±SD)	Mean duration of symptoms (range or ±SD in mo)	Follow-up (mo)	Intervention	Focus	Dosage in (impulses x EFD in mJ/mm²)	No. of sessions	Interval between sessions	Outcome measure
Far 2011 RCT [15]	30	49.7 ± 9	>6	1.5 + 3	ESWT high energy	Calcific deposit with 3D fluoroscopy	3200 x 0.3	1		CMS, VAS, resorption calcific deposits
		48.6 ± 7.3			ESWT low energy	Calcific deposit with 3D fluoroscopy	1600 x 0.2	2	1 wk	
Ioppollo 2013 RCT [27]	46	57.09 ± 16.4	6.95 ± 1.06	3 + 6	ESWT high energy	Calcific deposit	2400 x 0.2	4	1 wk	CMS, VAS, resorption calcific deposits
		51.65 ± 12.23	7.22 ± 1.2		ESWT low energy	Calcific deposit	2400 x 0.1	4	1 wk	
De Witte 2013 RCT [61]	48	50.4 ± 7.2	>3	1,5 + 3 + 6 + 12	US-guided percutaneous needling	NA	NA	1	NA	CMS, VAS, DASH, WORC,
		53.7 ± 7.3	>3		US-guided SAI with corticosteroids	NA	NA	1	NA	resorption calcific deposits

CMS = Constant Murley scale, DASH = Disabilities of the Arm, Shoulder and Hand questionnaire, EFD = energy flux density in mJ/mm², ESWT = extracorporeal shockwave therapy, Mo = months, NA = not applicable, NR = not reported, NRCT = non randomized controlled trial, RCT = randomized controlled trial, RSWT = radial shockwave therapy, SD = standard deviation, SAI = subacromial bursa injection, TENS = transcutaneous electric nerve stimulation, UCLA = University of California Los Angeles scale, VAS = visual analogue scale, WORC = Western Ontario Rotator Cuff Index

Table 4. Risk of bias assessment

= High risk
= Low risk
= Unclear

	Random sequence generationn	Allocation concealment	Blinding of patients (performance bias and detection bias)	Blinding of treatment providers (performance bias and detection bias)	Blinding of outcome assessors (performance bias and detection bias)	Blinding of functional outcome assessment (performance bias and detection bias)	Blinding of radiographic assessment	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Group similarity at baseline (other source of bias)	Influence of co-intervention (other source of bias)
Rompe '98	?	?	?	-	?	?	?	-	+	+	+
Loew '99	-	?	?	-	?	?	?	+	+	+	+
Haake '02	?	+	+	-	+	+	?	+	+	?	+
Cosentino '03	?	?	+	-	+	+	+	-	-	+	+
Gerdesmeyer '03	+	+	+	-	+	+	+	+	+	+	+
Perlick '03	?	?	?	-	?	?	?	+	+	+	+
Pan '03	+	?	-	-	?	-	+	+	+	+	+
Peters '04	+	?	+	-	+	+	?	+	+	+	+
Pleiner '04	?	?	+	-	+	+	+	+	+	+	+
Krasny '05	+	?	-	-	+	-	+	+	+	+	+
Sabetti '05	?	?	?	-	-	?	+	+	+	+	+
Cacchio '06	+	?	+	-	+	+	+	+	+	+	+
Sabetti '06	+	?	?	-	?	?	?	+	+	+	+
Albert '07	?	+	+	-	-	?	+	+	+	+	+
Hsu '08	?	?	?	-	?	?	+	-	-	+	+
Hearden '09	+	+	+	-	?	?	?	+	-	?	+
Serafini '09	-	-	-	-	-	-	-	-	+	+	-
Far '11	?	?	?	-	+	?	?	+	+	+	+
Ioppollo '12	+	+	?	-	+	+	+	+	+	+	+
De Witte '13	+	?	+	-	+	+	?	+	+	+	+

The Cochrane risk of bias tool consists of six items for which there is empirical evidence for their biasing influence on the estimates of an intervention's effectiveness in randomised trials: 1) sequence generation, 2) allocation concealment, 3) blinding, 4) incomplete outcome data, 5) selective outcome reporting and 6) a catch-all item called "other sources of bias". The criteria were scored as 'low risk', 'high risk' of 'unclear risk'.

CLINICAL RESULTS

FUNCTION

Table 5 presents the mean difference in improvement of functional CMS outcome scores at 3 and 6 months follow-up with GRADE quality assessment for the studies that were included in the meta-analysis. Nine different treatment comparisons were evaluated. All but 1 study [45] reported a significant difference in shoulder function between the compared treatment arms. Two studies that compared low-energy SWT with sham treatment could not be included in the analysis due to different outcome parameters: Gerdesmeyer et al[17] reported a significant difference in CMS outcome at 6 months (mean difference, 8.4; 95% CI, 15.4 to 1.4, P = .02) whereas Cacchio et al [41] reported a significant difference in the UCLA score at 6 months (mean difference, 21.55; 95% CI, 20.09 to 23.01, P < .0001).

PAIN

The quantitative results of pain reduction found in the different studies are summarized in Table 5. Eight different comparative treatments were included. Four analyses describe non-significant differences with substantial heterogeneity (I^2 > 80%) resulting in low-level GRADE evidence. Hsu et al [20], comparing high-energy SWT vs sham treatment, demonstrated a significant (P < .001) decrease in pain in the treatment group at 3 and 6 months but did not provide data of the control group and did not report 95% CIs. Cosentino et al, [40] comparing high-energy SWT vs sham treatment, reported a significant decrease in pain in the treatment group at 6 months follow-up (P < .001) but only provided CMS subset scores. Peters et al[16] only provided data on the recurrence of pain in the low-energy SWT and treatment group (87% and 100% respectively).

FULL RESORPTION RATE

The difference in chance, provided as relative risk + 95% confidence interval, of full resorption of the calcific deposit after treatment is reported in Table V. Seven different treatment comparisons were available for analysis. Four out of 7 comparisons resulted in significant outcome differences.

Table 5. Clinical results

Outcomes	Studies and participants (No.)	Effect (MD + 95% confidence interval)	P-value	Hetero-geneity (I^2)	GRADE level of evidence	Grade Quality assessment
Function 3 months (Difference in CMS outcome, 0-100 higher = better)						
High ESWT vs. low ESWT [2,15,17,33,46]	5 (148/143)	7.02 [1.28 to 12.76]	0.02	57%	Moderate	1
High ESWT vs. placebo / sham treatment [17,33,43]	3 (99/94)	17.14 [12.8 to 21.48]	<0.0001	0%	Moderate	1
Low ESWT vs. placebo / sham treatment [17,33]	2 (68/68)	5.94 [0.53 to 11.36]	0.03	0%	Moderate	1
High ESWT + US-guided needling vs. high ESWT [29]	1 (40/40)	9.50 [0.49 to 18.51]	0.04		Moderate	1
ESWT focused on calcific deposit vs. greater trochantor [19]	1 (25/25)	31.51 [16.84 to 46.18]	<0.0001		Moderate	1
ESWT focused on calcific deposit vs. point of max. pain [15]	1 (25/25)	12.72 [4.5 to 20.94]	0.002		Moderate	1
US-guided needling vs. no treatment [52]	1 (192/50)	22.20 [20.17 to 24.23]	<0.0001		Very low	1,6
US-guided needling vs US-guided subacromial steroid injection [61]	1 (23/25)	-1.79 [-11.97 to 8.39]	0.73		Moderate	1
Function 6 months (Difference in CMS outcome 0-100, higher = better)						
High ESWT vs. low ESWT [17,27,44]	3 (127/121)	18.30 [15.05 to 21.55]	<0.0001,	19%	Moderate	1
High ESWT vs. placebo / sham treatment [9,17,43]	3 (114/86)	22.75 [11.98 to 33.51]	<0.0001	78%	Low	1,5
High ESWT vs. TENS [40]	1 (33/30)	16.45 [9.92 to 22.98]	<0.0001		Moderate	1
US-guided needling vs US-guided subacromial steroid injection [61]	1 (23/25)	6.42 [-2.56 to 15.4]	0.16		Moderate	1
Pain 3 months (Difference in VAS 0-10, lower = better)						
High ESWT vs. low ESWT [2,15,17,46]	4 (123/122)	-0.95 [-2.5 to 0.59]	0.23	74%	Low	1,2
High ESWT vs. placebo / sham treatment [17,43]	2 (79/74)	-2.10 [-4.35 to 0.15]	0.07	86%	Low	1,3
Low ESWT vs. sham treatment [17]	1 (48/48)	-0.90 [-1.71 to -0.09]	0.03		Moderate	1
High ESWT + US-guided needling vs. high ESWT [29]	1 (40/40)	-1.10 [-2.18 to -0.02]	0.05		Moderate	1
ESWT focused on calcific deposit vs. greater tuberculum [19]	1 (25/25)	-2.86 [-4.46 to -1.26]	0.0005		Moderate	1

Table 5. Continued.

Outcomes	Studies and participants (No.)	Effect (MD + 95% confidence interval)	P-value	Hetero-geneity (I^2)	GRADE level of evidence	Grade Quality assessment
ESWT focused on calcific deposit vs. point of max. tenderness [47]	1 (25/25)	-15.15 [-3.68 to -26.62]*	0.01		Moderate	1
US-guided needling vs. no treatment [52]	1 (192/50)	-4.00 [-4.5 to -3.5]	<0.0001		Very low	1,6
Pain 6 months (Difference in VAS 0-10, lower = better)						
High ESWT vs. low ESWT [17,27]	2 (71/71)	-3.21 [-3.78 to -2.64]	<0.0001	0%	Moderate	1
High ESWT vs. placebo / sham treatment [17,43]	2 (79/74)	-2.47 [-6.29 to 1.35]	0.20	96%	Low	1,3
Low ESWT vs. sham treatment [6,17]	2 (93/93)	-3.60 [-8.10 to 0.90]	0.12	98%	Low	1,3
High ESWT vs. TENS [40]	1 (33/30)	-2.34 [-1.16 to- 3.52]	<0.0001		Moderate	1
Full resorption rate		RR (95% CI)				
High ESWT vs. low ESWT [2,17,27,41,42,44,46]	7 (255/253)	RR: 2.02 [1.04 to 3.92]	0.04	71%	Low	4
High ESWT vs. placebo / sham treatment [9,17,22,25]	4 (127/105)	RR: 6.76 [3.17 to 14.44]	<0.0001	0	Low	4,5
High ESWT + US-guided needling vs. high ESWT [29]	1 (40/40)	RR: 1.69 [1.09 to 2.61]	0.02		Moderate	4
High ESWT vs. TENS [40]	1 (33/30)	RR: 1.76[0.17 to 18.39]	0.64		Moderate	4
ESWT focused on calcific deposit vs. greater trochantor [19]	1 (25/25)	RR: 1.60 [0.84 to 3.07]	0.64		Moderate	4
ESWT focused on calcific deposit vs. point of max. pain [47]	1 (25/25)	RR: 6.00 (0.78 to 46.29)	0.09		Moderate	4
US-guided needling vs US-guided subacromial steroid injection [61]	1 (23/23)	RR 2.17 [1 to 3.17]	0.05		Moderate	4

CI, confidence interval; EWST, extracorporeal shockwave therapy; MD, mean difference; RR, relative risk; US, ultrasound.
* = Numerical rating score (0-100), lower = better,
1. Total number of participants <400
2. Positive and negative effects across studies
3. $I^2 > 80\%$
4. Total number of events <300
5. >25% of studies contain high risk of bias
6. Study design: non-randomized controlled tr

DISCUSSION

The objective of this systematic review was to assess the effectiveness of different minimally invasive treatment modalities for patients with chronic calcifying tendinopathy after a short-term to midterm follow-up. This review was primarily focused on functional outcome and secondarily on the change in pain and resorption of the calcific deposit. The quantitative analysis provided moderate-quality GRADE evidence that high-energy ESWT is superior to low-energy ESWT and to no,- or sham treatment. Moderate-quality GRADE evidence is provided that ultrasound-guided needling in addition to high-energy ESWT is more effective than high-energy ESWT alone and that ESWT was more effective when focussed on the calcific deposit instead of focussing on the greater tubercle or the point of maximum tenderness. Concerning the effectiveness of ultrasound-guided needling there is very low-quality GRADE evidence that needling is more effective than no treatment and moderate-quality GRADE evidence for a nonsignificant effect in favour of needling compared to a subacromial corticosteroid injection.

STRONG POINTS AND LIMITATIONS

This is the first systematic review that applies an evidence based approach to analyze all available minimal invasive treatment modalities and provides the optimal treatment option in the short-term- to midterm for patients with chronic calcifying tendinopathy of the rotator cuff. The analysis was performed at 3 and 6 months of follow-up. By applying the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines, the Cochrane risk of bias assessment and GRADE level of evidence tool, this study uses a transparent method of assessing and reporting the evidence synthesis. The short-term to midterm follow-up of this review is also the most important limitation. Based on the current available literature it remains unclear if the positive effect of the different treatment modalities carries through on the long-term (>1 year). Unfortunately, only one small prospective clinical study has a follow-up of 2 year.[46]

Other limitations of this study were primarily related to the heterogeneity between the interventions used and the relative small number of studies and patients available for the meta-analysis. Since the majority of the included studies analyzed the effectiveness of ESWT it is difficult to draw far-reaching conclusions on the effectiveness of US-guided needling and TENS. Another limitation might be the use of the CMS as an outcome instrument. This review reports statistical significant differences in CMS outcome scores but a minimal clinically important difference for the CMS remains unknown.[47] Methods to improve standardization and measurement precision are needed and particularly

errors of measurement and minimal clinically important differences need to be further evaluated.[48]

COMPARISON WITH THE LITERATURE

In the past years a few comprehensive reviews were published about the pathology and etiology of calcifying tendinopathy[49,50]; however, the exact pathophysiological mechanism is still not completely known. Degenerative changes, the limited vascularity of the rotator cuff, metabolic changes and overuse may be triggers for calcifications of the tendon tissue.[51] We investigated but did not find a relation between the size of the calcific deposit and the severity of functional restriction or pain. Several therapies have been proposed as the optimal treatment for this condition. Surgery is generally considered the procedure of last resort carrying with it a higher cost, a greater risk of complications, and a longer recovery time.[10] During the search we came across several alternative minimally invasive treatment options such as therapeutic ultrasound[52], laser therapy[53,54], and platelet-rich plasma therapy.[55] Unfortunately, most of these studies were of lower quality and did not meet the inclusion criteria. According to our findings, high-energy ESWT is effective to treat rotator cuff calcific tendinopathy. The quantitative analysis in this review underlines earlier statements from descriptive reviews[56,57] that high-energy ESWT is superior to low-energy ESWT and sham treatment. Further research is needed to determine dose-response relationship of SWT. Owing to the wide variety in energy levels, intervals between sessions and number of sessions a clear guidance for the dose-effect cannot be provided. Ultrasound-guided needling has been performed since the 1980s, but to our knowledge, a review concerning the effectiveness of this treatment modality has not been published yet. Several retrospective and non-controlled studies[24,26,58–61] have reported good midterm and long-term result for this treatment but de Witte et al[45] was the first to provide level 1 data of needling compared to a control treatment in calcifying tendinopathy and found no statistical significant difference at 3 and 6 months.

CONCLUSION

High-energy ESWT is the most thoroughly investigated minimally invasive treatment option in the short-term to midterm, and SWT has proven to be a safe and effective treatment. With regard to the other treatment options, ultrasound-guided needling has proven to be safe but not proven to be more effective than an ultrasound-guided subacromial corticosteroid injection in recent level 1 research. In theory this technique directly addresses the source of pain by removing as much intratendinous calcification as possible and further fragmenting any remaining calcification, but up to this point, there is not enough high-quality evidence to give an evidence-based recommendation.

No RCTs that compare ESWT with ultrasound-guided needling have been performed, making a direct comparison difficult. Our primary recommendation for further research would therefore be to conduct a high-quality placebo controlled RCT with patient-related outcome measures to compare these 2 modalities. Furthermore, there is no evidence as to what the best US-guided needling technique is as single-needling and double-needling techniques are both used in modern practice. Finally, this review once more highlights the heterogeneity in different treatment protocols, outcome measures, and follow-up periods used in shockwave research and we would like to encourage the development of a best-evidence high-energy ESWT protocol with clear guidance of the dose-related effectiveness.

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5

The effectiveness of high-energy extracorporeal shockwave therapy versus ultrasound-guided needling versus arthroscopic surgery in the management of chronic calcific rotator cuff tendinopathy: a systematic review

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ABSTRACT

PURPOSE

The objectives of this comprehensive quantitative review of the treatment of calcific tendinopathy of the rotator cuff were to investigate if there is a sustainable positive effect in outcome after treatment with high-energy extracorporeal shockwave therapy (ESWT) or ultrasound (US) -guided needling and to compare these results with those of treatment with arthroscopic surgery.

METHODS

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed to conduct this review. A systematic literature search was conducted in December 2014 to identify relevant clinical articles in peer-reviewed journals with at least 6 months' follow-up. Each article was scored using the Coleman Methodology Score. The primary endpoints were functional outcome and radiological change in size of the calcific deposit.

RESULTS

Twenty-two studies were included (1258 shoulders). The Coleman Methodology Score for the included studies was 77.1 ± 9.1. Overall, good to excellent clinical outcomes were achieved after treatment with either high-energy ESWT, US-guided needling or arthroscopic surgery, with an improvement in Constant-Murley score ranging between 26.3 to 41.5 points after 1 year. No severe side effects or long-term complications were encountered.

CONCLUSIONS

Patients can achieve good to excellent clinical outcome after high-energy ESWT, US-guided needling and arthroscopy for calcific tendinopathy of the shoulder. Side effects and post treatment complications should be taken into account when making a decision for each individual patient. Physicians should consider high-energy ESWT and US-guided needling as minimally invasive treatment options when primary conservative treatment fails. Arthroscopy can safely be used as a very effective but more invasive secondary option, although the extent of deposit removal and the additional benefit of subacromial decompression remains unclear.

LEVEL OF EVIDENCE: IV, systematic review of level I, II and IV studies.

INTRODUCTION

Calcific rotator cuff tendinopathy is a common cause of subacromial pain syndrome.[1] It is thought to be an active, cell-mediated process, although the exact pathophysiology remains unclear.[2] The disease mainly affects individuals in the third to fifth decade of life, with women being affected more often than men.[3-5] The condition is generally self-limiting and can be managed with appropriate nonoperative treatment such as nonsteroidal anti-inflammatory drugs, physical therapy and subacromial corticosteroid injections.[2, 6] Some cases, however, progress to a chronic symptomatic phase despite conservative treatment.[7] Minimally invasive treatment modalities such as high-energy extracorporeal shockwave therapy (ESWT) and ultrasound (US) -guided needling have been developed for patients in whom nonoperative treatment fails.[8] Several recent studies have shown the short-term effectiveness of these treatment options.[8-10] Treatment resistant cases may, however, necessitate surgical removal of the calcific deposit and surgery has long been the treatment of choice for patients with calcific rotator cuff tendinopathy.[4] Surgical management options include arthroscopic procedures to remove the calcified deposit and to perform subacromial decompression.[11-15] These procedures have been shown to have a high chance of success in restoring shoulder function and reducing pain. Controversies exist however regarding the extent of calcification removal, the long-term impact on the rotator cuff tendons and the use of subacromial decompression.[9, 14]

The recent focus on minimally invasive treatment modalities suggests that surgery is gradually being superseded by these new options in the management of chronic rotator cuff tendinopathy. The objective of this study was to investigate if there is a sustainable positive effect in terms of functional outcome and resorption of calcific deposits after treatment with high-energy ESWT and US-guided needling and to compare these results with those of treatment with arthroscopic surgery. A systematic review of the currently available literature was conducted to search for evidence pertaining the effectiveness and safety of these treatment modalities with a minimum follow-up of 6 months.

MATERIAL AND METHODS

This review was performed and reported following the principles of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)guidelines.[16] The literature search conducted for this systematic review was limited to clinical studies concerning the minimally invasive and arthroscopic treatment of chronic calcific tendinopathy of the rotator cuff with at least 6 months follow-up. Three interventions were included: high-energy ESWT, US-guided needling and arthroscopic surgery. ESWT

can be classified in low energy and high energy according to the amount of energy released by the sonic pulses expressed as energy flux density (EFD) in millijoules per square millimeter. There is no universal agreement concerning the threshold of these subdivisions. For this study we defined high-energy ESWT as having an EFD of greater than > 0.20 mJ/mm^2. Several recent systematic reviews have shown the superiority of high-energy ESWT to low-energy ESWT in the treatment of calcific rotator cuff tendinopathy.[8, 9, 17] We therefore focused solely on high-energy ESWT.

Study inclusion was limited to trials involving patients aged 18 years or older with symptoms of subacromial pain syndrome in combination with radiographically or sonographically proven calcific tendinopathy who did not respond to conservative treatment with nonsteroidal anti-inflammatory drugs, physiotherapy, or subacromial corticosteroid injections. Studies involving patients with evidence of a full thickness rotator cuff tear (physical examination, sonographic and/or MRI), systemic inflammatory disorders, previous surgery to the shoulder, instability of the shoulder, dysfunction of the upper limb, ESWT/needling within the last year, acute bursitis and osteoarthritis of the glenohumeral or acromioclavicular joint were excluded. Our study focussed on validated outcome measures for shoulder function and change in radiological size of the calcific deposit. Baseline outcome parameters in combination with post-treatment results had to be reported. Studies that did not report both of these parameters were excluded from this study.

Table 1. **PubMed/Medline Search Strategy**

#1	(calcif*[All Fields])
#2	("tendinopathy"[MeSH Terms] OR "tendinopathy"[All Fields] OR "tendinosis"[All Fields] OR "tendinitis"[All Fields])
#3	("shoulder"[MeSH Terms] OR "shoulder"[All Fields]) OR ("rotator cuff"[MeSH Terms] OR ("rotator"[All Fields] AND "cuff"[All Fields]) OR "rotator cuff"[All Fields]) OR supraspinatus[All Fields])
#4	("shock*"[All Fields] OR "needling"[All Fields] OR " percutaneous"[All Fields] OR "ultrasound"[All Fields] OR "arthroscopy"[MeSH Terms] OR "arthroscopy*" [All Fields])

A search term with Boolean operators was constructed (Table 1) and the following databases were searched from 1978 to 2014: Medline, Embase, PEDro, CINAHL (Cumulative Index to Nursing and Allied Health Literature), SPORTDiscus and the Cochrane Database of Systematic Reviews. A range of keywords (calcific tendinopathy, shoulder, rotator cuff, shockwave, ultrasound guided, needling , arthroscopy) relevant to the review was grouped into 4 categories to maximize search results and the search

was independently performed by 2 reviewers (J.L. and E.V.). The lists of references of retrieved publications and the "find similar" function in Medline and Embase were manually checked for additional studies potentially meeting the inclusion criteria. The search was restricted to articles written in the English, German, or Dutch language.

Studies were selected by reviewing the title and abstract to identify potentially relevant articles. The full manuscript was retrieved when the title or abstract included insufficient information to determine appropriateness for inclusion. All identified studies were independently assessed by 2 reviewers (J.L. and E.V.) for inclusion using the above-mentioned criteria. Disagreement was resolved by discussion, with arbitration by a third reviewer (M.B.) when differences remained.

Two reviewers (J.L. and E.V.) independently extracted the following information from each included study: study design; patient characteristics (e.g. number of participants, age, sex, mean duration of symptoms); study characteristics (e.g. follow-up period; types of outcome measures, baseline measurements) and treatment characteristics (e.g. treatment technique, effects of treatment at various periods of follow-up, post-treatment regime and complications). Studies that included more than 2 treatment arms were treated as separate interventions for the purpose of this review. Reviewers were not blinded for author, affiliation, or source.[18] Disagreement between reviewers was resolved by discussion with arbitration by a third author (M.B.) when differences remained.

The criteria developed by Coleman et al[19] were used to assess the methodological quality of each article. The Coleman scoring system is a method of analyzing the quality of the studies reviewed. It has been validated[20] and proved accurate and reproducible in systematic reviews.[19, 21, 22] Each study was independently assessed by 2 reviewers (J.L., E.V.), and any discrepancies were resolved by discussion; a total Coleman Methodology Score of between 0-100 was given (Table 2). A perfect score of 100 would represent a study design that largely avoids the influence of chance, various biases, and confounding factors. The synthesis approach was data-driven. Treatment effect was examined through meta-analyses, but these were conducted only if studies were determined to be clinically homogenous. Clinical homogeneity was defined a priori by setting, treatment technique, duration of follow-up and outcome measure used. If the study arms were heterogeneous, a qualitative/narrative data synthesis approach was performed.

Table 2. Study characteristics

	Author (year)	LoE / CS	No pts (shoulders)	Age †	Gender (ratio f/m)	Duration of symptoms	Follow-up (months)	Technique *	Outcome measures
High energy ESWT	Kim (2014)	1/87	29	57.4 (47-78)	8.7	NR	1.5, 3, 6, 12, 24	1000 * 0.36 * 3 / maximum sore spot	ASES, SST, VAS, resolution of deposit
	Ioppolo (2012)	1/83	23	57.1 ± 16.4	1.9	6.9 ±1	3,6	2400 * 0.20 * 4 / calcific deposit	CMS, VAS, resolution of deposit
	Hsu (2008)	1/77	33	54.4 (30-70)	1.2	12.3 (6-72)	1.5, 3, 6, 12	1000 * 0.55 * 2 / affected area	CMS, VAS, resolution of deposit
	Perlick (2004)	1/80	40	48.4 (38-64)	1.2	32	3,12	2000 * 0.42 * 2 / calcific deposit	CMS, resolution of deposit
	Pleiner (2003)	1/85	23 (31)	54 ± 11	1.9	>6	3,7	2000 * 0.28 * 2 / maximum point of tenderness	CMS, VAS, resolution of deposit
	Gerdesmeyer (2003)	1/94	48	51.6 ± 8.5	2.7	51.6 ± 8.5	3, 6, 12	1500 * 0.32 * 2 / calcific deposit	CMS, VAS, resolution of deposit
	Cosentino (2003)	1/62	35	51.8 (35-68)	1.3	15 (10-20)	6	1200 * 0.28 * 4 / calcific deposit	CMS, resolution of deposit
	Daecke (2002)	4/83	115	49 (28-77)	0.7	5y (1-36 y)	3, 6, 48	2000 * 0.3 * 1 (Group I) / calcific deposit 2000 * 0.3 * 2 (Group II) / calcific deposit	CMS, resolution of deposit
	Rompe (1998)	1/81	50	47 (29-60)	1.6	33 (12-120)	1.5, 6	1500 * 0.28 * 1 / calcific deposit	CMS, resolution of deposit
US-guided needling	Kim (2014)	1/87	25	53.9 (45-76)	11.5	NR	1.5, 3, 6, 12, 24	Single needle	ASES, SST, VAS, resolution of deposit
	De Witte (2013)	1/91	23	53.7 ± 7.3	1.1	NR	1.5, 3, 6, 12	Single needle	CMS, DASH, WORC, resolution of deposit

Table 2. Continued.

	Author (year)	LoE / CS	No pts (shoulders)	Age †	Gender (ratiof/m)	Duration of symptoms	Follow-up (months)	Technique *	Outcome measures
	Yoo (2010)	4/70	30 (35)	51.3 (34-77)	2	44.8m (6-240)	0.3, 3, 6	Singe needle	CMS, ASES, resolution of deposit
	De Conti (2010)	4/76	123	48.0 (31-65)	1.7	11 (6-15)	6	Double needle with lavage and aspiration	CMS
	Serafini (2009)	2/84	219 (235)	40.3 (29-72)	1.5	NR	0.3,3,12, 60,120	Double needle with lavage and aspiration	CMS, VAS
	Del Cura (2007)	4/63	65 (67)	47.0 (31-72)	1.6	30 (1-168)	2.5, 12	Double needle with lavage and aspiration	SPADI
Arthroscopy	Sabeti (2014)	1/70	20	47.6	NR	31.5m	1.5, 9	Bursectomy, fluoroscopy, needling, blunt removal, no tendon repair	CMS, VAS, resolution of deposit
	Balke (2012)	4/71	62 (70)	54.0 (39-74)	1.6	2.6y (1.5-15y)	72	Bursal debridement, ASD on indication, removal with resector / curvette	CMS, ASES, resolution of deposit
	El Shewy (2011)	4/76	56	48.6 (37-54)	0.5	5.2 (3.5-7.1)	90 (90-120)	Bursectomy, ASD on indication, removal with arthroscopy knife / shaver	CMS, ASES, UCLA, resolution of deposit
	Yoo (2010)	4/68	35	49.8	1.4	39.1	31	Bursectomy, acromioplasty on indication, full removal of deposit	CMS, ASES, VAS
	Seyahi (2009)	4/61	28 (30)	48.3	1.8	15	38	Bursectomy, section CA ligament, curvette / resector, full removal of deposit	CMS, VAS, resolution of deposit
	Seil (2006)	4/85	54 (58)	45.4	0.8	52	3, 6, 12, 24	Longitudinal incision, blunt exploration and removal	CMS, resolution of deposit

Table 2. Continued.

Author (year)	LoE / CS	No pts (shoulders)	Age †	Gender (ratio f/m)	Duration of symptoms	Follow-up (months)	Technique *	Outcome measures
Porcellini (2004)	4/74	63	37.0	2	20 (14-60)	36	Bursal debridement, resector / curvette, full removal of deposit	CMS, resolution of deposit
						17.1		
Rubenthaler (2003)	2/76	14	50.4	6	NR		Removal of deposit, no tendon repair, ASD in all cases.	CMS, patte score, resolution of deposit

ASD = arthroscopic subacromial decompression, ASES = American Shoulder and Elbow Surgeons score, CA = coracoacromial ligament, CS = Coleman Methodology Score, CMS = Constant Murley Scale, DASH = Disability of the Arm, LoE = Level of Evidence, pts no = number of patients, Shoulder and Hand score, SST = Simple Shoulder Test, SPADI = Shoulder Pain and Disability Index, UCLA = University of California Los Angeles score, mm = millimetre, mm^2 = millimetre squared, % = percent, ± = standard deviation

† Data presented as mean (range) or mean ± SD

* ESWT data are presented as pulses x energy flux density (in millijoules per square millimeter) x sessions/focus shockwaves

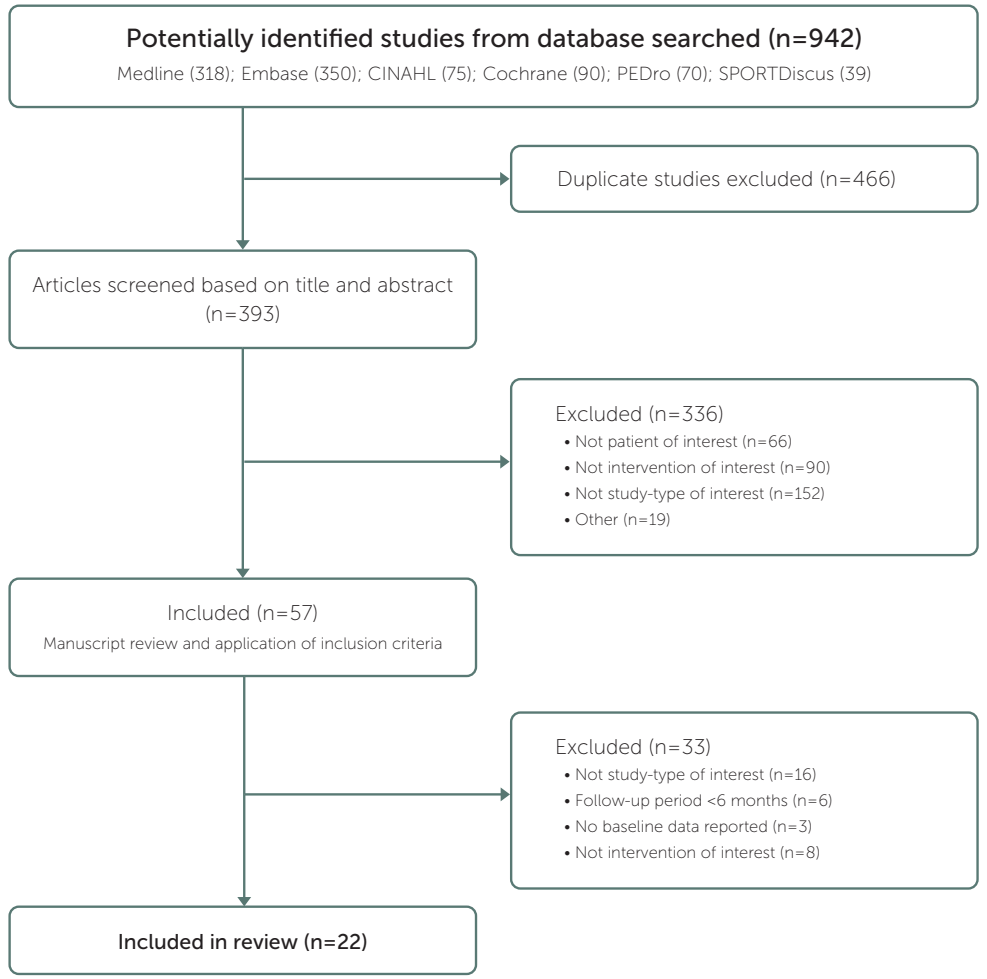

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement flow diagram of the search process. (CINAHL, Cumulative Index to Nursing and Allied Health Literature.)

RESULTS

SEARCH RESULTS

The search of Medline, Embase, CINAHL, Cochrane, PEDro and SPORTDiscus databases provided a total of 942 citations (Figure 1). The search was performed on December 9, 2014. After adjusting for duplicates, 393 studies remained. Of these studies, 336 were discarded for not meeting the inclusion criteria after review of the abstracts. The full text of the remaining 57 studies was examined in more detail. Twenty-two studies, including 1258 treated shoulders,

met the inclusion criteria and were included in the systematic review.[11, 13, 14, 23-41] Of the studies, 8 involved treatment with high-energy ESWT[23, 24, 29-31, 33, 34, 36], 5 concerned treatment with US-guided needling[25-27, 39, 41], 1 involved a group treated with high-energy ESWT and a group treated with US-guided needling[32] and 8 concerned the use of arthroscopic surgery.[11, 13, 14, 28, 35, 37, 38, 40]

No additional studies were identified by the 'find similar' function in the Medline and Embase databases or by checking the references of retrieved publications.

CHARACTERISTICS

General patient characteristics and interventions are summarized in Table 2. The longest mean follow-up time was 4 years for the ESWT studies, 10 years for the US-guided needling studies and 6 years for the arthroscopy studies.

METHODOLOGICAL QUALITY

The Coleman Methodology Score for the included studies varied from 61 to 94 with a mean score of 77.1 and a SD of 9.1. Eleven studies were constructed as prospective randomised controlled trials, 1 as a prospective non-randomised controlled trial, 6 as prospective cohort studies and 4 as retrospective cohort studies. A mean Coleman score of 81.8 was given to the ESWT studies and 76.0 and 72.6 given to the needling and arthroscopy studies, respectively. The number of patients in the various studies and differences in follow-up times in combination with the different type of studies accounted for the differences in Coleman scores given to the studies.

OUTCOME MEASURES: TYPE, TIMING

Assessment of pain, shoulder function and radiological appearance of the calcific resorption after treatment were the most frequent reported outcome measures. All studies reported on shoulder function. The Constant-Murley Scale (CMS)[42] was the most common reported shoulder function outcome measure. In addition to the CMS, 5 authors used the American Shoulder and Elbow Surgeons (ASES)[43] assessment form. A single study used each of the following measures: The Disability of the Arm, Shoulder and Hand (DASH)[44], Patte score[45], Shoulder Pain and Disability Index (SPADI)[46], Simple Shoulder Test (SST)[47], University of Los Angeles (UCLA) scale[48] and the Western Ontario Rotator Cuff (WORC) index.[49]

Of the 22 studies, 18 reported changes in radiologic size or appearance of the calcific deposit. [13, 23-25, 27-37, 40, 41] Sixteen studies reported whether there was no change, partial resorption, or total resorption. [13, 23, 25, 27-37, 40] Four studies described the change in length in millimeters, [25, 30, 32, 41] whereas Gerdesmeyer et al. [29] and Ioppollo et al. [31] described the change in size in mm^2.

HIGH-ENERGY ESWT

TECHNIQUES

Nine studies (8 RCTs), including a total of 346 patients, used high-energy ESWT as the treatment modality.[23, 24, 29-34, 36] Although these trials all used high-energy ESWT, the reported EFD (0.2 - 0.55 mJ/mm^2), number of pulses applied (1000 - 2400), and number of sessions (1 - 4) varied. The shockwave energy was focused on the calcific deposit in 6 trials and on the maximum point of tenderness in 2 trials. Hsu et al.[30] did not report details on the focus area.

CLINICAL OUTCOME

Functional outcome scores after treatment with high-energy ESWT are summarized in Table 3. Compared with baseline parameters, high-energy ESWT significantly improved shoulder function in 7 trials at 6 months' follow-up. Based on 5 trials, the improvement in shoulder function remained at 1 year. Kim et al.[32] reported a significant increase in ASES score (78.3 vs 49.9 points) and Simple Shoulder Test score (78.6% vs 34%) in 29 patients after 2 years. Daecke et al.[24] reported promising results on the CMS in 2 high-energy ESWT series (88 $\pm$ 8 vs 49 $\pm$ 13 and 85 $\pm$ 8 vs 44 $\pm$ 12 respectively) in 115 patients after 4 years in their prospective non-RCT.

SAFETY

All studies reported on adverse effects. A summary is provided in Table 4. All complications affected only a small number of participants and the effects resolved within a few days after treatment. No clinically relevant post treatment complications were reported.

ULTRASOUND-GUIDED NEEDLING

Techniques

Six US-guided needling studies[25-27, 32, 39, 41] (2 RCTs) comprising a total of 485 patients were included in this study. Three studies used a double-needle technique and 3 studies used a single needle technique. Lavage and aspiration was performed in all trials using 2 needles. The needle gauge ranged between 16 and 25, with 16-gauge needles most commonly used. In all studies a subacromial corticosteroid injection was performed after the needling procedure. All US-guided needling procedures were performed with patients under local anesthesia.

Clinical outcome

Outcome scores after treatment with US-guided needling are summarized in Table 3. At 6 months follow-up, 3 out of 4 trials reported significant improvement on functional outcome scales while De Witte et al[25] did not find a significant improvement on the CMS, DASH or WORC after 6 months. Based on the 4 trials, the functional outcome after 1 year was significantly improved in all trials, including that of de Witte et al.[25] Kim et al[32] and Serafini et al[39] reported excellent long term results after two years and five to ten years respectively.

SAFETY

Two trials reported a re-needling rate of 45% and 25%. Yoo et al. [41] reported a 28% clinical failure rate at 6 months' follow-up and conversion to arthroscopy in 17% of the cases. All studies reported on side effects and complications after US-guided needling. These results are summarized in Table 4. All of these side effects were minor with no reported long-term disability

Table 3. Results

	Author (year)	No pts (shoulders)	Baseline	6 months	1 year	2 year	>2 year	>5 year	Resorption / change in size
High-energy ESWT	Kim (2014)	29	ASES: 49.9 SST: 34%	ASES: 76.4 SST: 70.8%	ASES: 74.6 SST: 70.8%	ASES: 78.3 SST: 78.6			Partial 16.7%, full 42.6%, none 41.7%. Pre: 11±1mm Post: 5.6±0.8mm
	Ioppolo (2012)	23	CMS: 49.26±8.6	CMS: 79.4±0.33					Full 42.6%. Size reduction in mm^2: 135.91±71.69
	Hsu (2008)	33	CMS: 57.3	CMS: 85	CMS: 88				Partial 36.3%, full 21.2%, none 45.5% Pre: 11.9±5.4 mm Post: 5.5±6.3 mm
	Perlick (2004)	40	CMS: 48.4		CMS: 73.2				Partial 20.0%, full 25%, none 45%
	Pleiner (2003)	23 (31)	CMS: 46±21	CMS: 70					Partial 19.4%, full 19.4%, none 61.2%
	Gerdes-meyer (2003)	48	CMS: 60±11	CMS: 91.0 (86.7-95.3) 95% CI	CMS: 91.6 (87.3-96.0) 95% CI				Full 60.4%. Size reduction in mm^2: 128.9 (170-87.7)
	Cosentino (2003)	35	CMS: 45±18	CMS: 76±16					Partial: 40%, full 31.5%, none 28.5%
	Daecke group I (2002) group II	56 59	CMS: 49±13 CMS: 44±12		CMS: 67±17 CMS: 69±19		CMS: 88±8 CMS: 85±8		Radiologic changes 47% (6m), 93% (4y) Radiologic changes 77% (6m), 93% (4y)
	Rompe (1998)	50	CMS: 53±13.1	CMS: 88±11.5					Partial 42%, full 22%, none
Total / mean		346	CMS 50.2	CMS: 82.9	CMS: 76.5		CMS: 86.5		

Table 3. Continued.

	Author (year)	No pts (shoulders)	Baseline	6 months	1 year	2 year	>2 year	>5 year	Resorption / change in size
US-guided needling	Kim (2014)	25	ASES: 41.5 SST: 38.2	ASES: 85.2 SST: 74.1	ASES: 90.1 SST: 83.3	ASES: 91.1 SST: 91.7			Partial 11.1%, full 72.2%, none 16.7% Pre: 14.8±1.7mm Post: 0.45±0.3
	De Witte (2013)	23	CMS: 71.6±12.3 DASH: 32.6±18.5 WORC:49.6±20.3	CMS: 78.6±16.7 DASH: 24.6±20.7 WORC:63.5±26.2	CMS: 86.0 (80.3–91.6) DASH: 19.6 (9.5–29.8) WORC: 69.7 (57.6–81.8)				Partial 39%, full 56%, none 5% Pre: 11.6±6.4, Post 5.1±5.7
	Yoo group I (2010) group II	24 (30) 6	CMS: 53.7±16.3 ASES: 48.0±14.5 CMS: 55.4±7.4 ASES: 48.6±9.4	CMS 87.9±8.7 ASES 84.6±12.8 CMS 92±16.9 ASES 47.5±17.5					Pre: 13.6±5mm Post: 5.6±6.5 Pre: 13.1±4.8mm Post: 12.7±7.1
	De Conti group I (2010) group II	123	CMS: 28.6 CMS: 34.1	CMS: 81.4 CMS: 71.1					
	Serafini (2009)	219 (235)	CMS: 57.3±3.4		CMS: 91.7±3.1		CMS: 90.9±3.6	CMS:91.8 ±5.0	
	Del Cura (2007)	65 (67)	SPADI: 50.2 (10-90.1)		SPADI: 14.7 (0-62.8)				Partial 18.8, full 78.1%, none 3.1%
Total/ Mean		485	CMS: 49.9	CMS: 79.4	CMS: 91.2		CMS: 90.9	CMS: 91.8	

Table 3. Continued.

	Author (year)	No pts (shoulders)	Baseline	6 months	1 year	2 year	>2 year	>5 year	Resorption / change in size
Arthros-copy	Sabeti (2014)	20	CMS: 44.9±14.4		CMS: 90.33±14.7				Partial 6%, full 94%
	Balke (2012)	62 (70)	ASES: 38.3					ASES: 81.5 CMS: 74.4	
	El Shewy (2011)	56	CMS: 63.3 ASES: 57.2 UCLA: 52.8					CMS: 97.8 ASES: 95 UCLA: 95	Partial 26%, full 74%
	Yoo (2010)	35	CMS: 63.2±20 ASES: 39±17				CMS: 87±15 ASES: 89±13		
	Seyahi (2009)	28 (30)	CMS: 42				CMS: 100		Partial 3%, full 97%
	Seil (2006)	54 (58)	CMS: 32.8			CMS: 90.9			
	Porcellini (2004)	63	CMS: 55.1				CMS: 86,4±7.2		Full resorption 21%, microcalcifications 71%, deposits <10mm in size 8%
	Rubenthaler (2003)	14	CMS: 64.1			CMS: 97.6			Partial 42%, full 58%
Total/ Mean		332	CMS: 48.8		CMS: 90.3	CMS: 92.2	CMS 89.8	CMS 84.4	

ASES = American Shoulder and Elbow Surgeons score, CMS = Constant Murley Scale, DASH = Disability of the Arm, Shoulder and Hand score, SST = Simple Shoulder Test, SPADI = Shoulder Pain and Disability Index, UCLA = University of California Los Angeles score, mm = millimetre, mm^2 = millimetre squared, % = percent, ± = standard deviation

ARTHROSCOPY

Techniques

Eight arthroscopic surgery studies[11, 13, 14, 28, 35, 37, 38, 40] including a total of 332 patients were included in this review. In 4 studies[11, 28, 35, 40] the anesthesia protocol was reported. In 3 studies the operation was performed under general anesthesia and 1 trial[35] used a combined scalene block with general anesthesia. All surgeons started the surgical procedure with a diagnostic intra-articular arthroscopy. Seven studies proceeded with a subacromial bursectomy; one article[38] did not provide additional data on this particular phase. Rubenthaler et al.[13] subsequently proceeded with an acromioplasty and coracoacromial ligament incision. Seyahi and Demirhan[40] only performed a section of the coracoacromial ligament without acromioplasty. Four authors only performed decompression on indication such as signs of mechanical impingement, fraying of the coracoacromial ligament or erosions on the undersurface of the acromion. [11, 14, 35, 38] The calcific deposit was localized with fluoroscopy in 2 studies[37, 40], with US in 1 study[37] and by needling in the remaining studies. The means of calcific deposit removal differed and included use of an arthroscopic knife and shaver, the use of a curette and synovial resector, and use of blunt instruments. Seyahi and Demirhan[40] used side-to-side stitches in all cases after removal of the deposit. Yoo et al.[14] and Porcellini et al.[35] used side-to-side sutures or suture anchors depending on the size of the rotator cuff lesion. Three authors reported no additional use of sutures.

Clinical outcome

Outcome scores after treatment with arthroscopic surgery are summarized in Table 3. None of the studies reported data at 6 months follow-up. Sabeti et al.[37] found an improvement of 45.5 points on the CMS in 20 patients after 1 year. Five trials reported data after 1.5 to 3 year follow-up with improvement on the CMS ranging from 23.8 to 58.1 points. Balke et al[11] reported a significant improvement on the ASES assessment of 43.2 points at six year follow-up. At seven year follow-up El Shewy et al[28] reported a significant improvement on the ASES assessment of 37.8 points and on the UCLA scale of 42.2 points.

SIDE EFFECTS, COMPLICATIONS AND REHABILITATION PROTOCOL

Adverse events were reported by all authors but one[35]. The most commonly reported complications after surgery were prolonged post-operative pain and stiffness (Table 4). All cases of shoulder stiffness could be treated with subacromial or intra-articular infiltrations with corticosteroids and/or nonsteroidal anti-inflammatory drugs, with no reported long lasting disability. Yoo et al[14] reported intraoperative rotator cuff tears in most cases because of extensive debridement of the calcific deposit, all of

which were immediately repaired with suture anchors or side-to-side stitches with good clinical outcome. Balke et al.[11] reported 11 partial supraspinatus ruptures during ultrasound examinations at last follow-up. No serious adverse events such as infection, hyperesthesia or secondary operations were reported.

Four authors used an immediate passive and active exercise rehabilitation protocol.[11, 13, 38, 40] Porcellini et al.[35] started with 3 weeks of passive training before adding active exercises, el Shewy[28] chose to immobilize the shoulder with a sling for 2 weeks in combination with passive motion exercise, and Yoo et al chose to immobilize the shoulder with an abduction brace for 3 weeks.[14]

Tabel 4. Treatment side effects and post treatment complications

Treatment modality	Peri treatment side effects	Post treatment complications
High-energy ESWT (n=404)	Frequent : pain, erythema, local intracutaneous petechial bleeding, subcutaneous hematomas	None reported
US-guided needling (n=508)	Frequent: pain, discomfort Rare: vagal reactions, fainting	Rare: frozen shoulder (2.4%), subacromial bursitis (5%)
Arthroscopy (n=346)	Frequent: pain, RC defects due to extensive debridement requiring intraoperative RC repair.	Frequent: post-operative pain Rare: frozen shoulder (3.7%), partial RC tears (3.5%), subacromial bursitis (<1%), secondary surgical RC repair (<1%)

ESWT = extracorporeal shockwave therapy, N= number of shoulders treated, RC = rotator cuff, US = ultrasound

DISCUSSION

The results of treatment with high-energy ESWT, US-guided needling and arthroscopy in patients with calcific tendinitis of the shoulder were evaluated. Good results concerning improvement of shoulder function and resorption of the calcific deposit at final follow-up were achieved by all three treatment modalities, with an improvement in Constant-Murley score ranging between 26.3 to 41.5 points after one year.

ESWT has been studied extensively, with a large heterogeneity in reported treatment protocols and large difference in shockwave intensity. ESWT uses monophasic pressure pulses that have a high peak pressure and a short duration that is focused onto a small target through reflectors. The exact mechanism by which ESWT relieves tendon associated pain is still unclear. The theoretical benefits are the stimulation of

tissue healing[50] and the fragmentation of calcifications.[51] The intensity of the ESWT is measured by the EFD which is reported in millijoules per square millimeter, and the overall effect is dependent on the EFD, the number of pulses and focus of the focal point. Several attempts have been made to stratify the energy into 2 or 3 groups but no consensus currently exists on what the exact cut-off point is between low- and high-energy shockwaves. In general, an EFD of <0.08 mJ/mm^2 corresponds to low energy whereas high-energy extracorporeal shockwaves have an EFD of >0.28 mJ/mm^2. Although a clear dose-response relationship between low- and high-energy ESWT has not been defined, studies have shown that high-energy ESWT (>0.28 mJ/mm^2) has a better chance of improving shoulder function and pain reduction in patient with chronic calcific tendinopathy than low-energy ESWT (<0.08 mJ/mm^2). The advantage of high-energy ESWT is that it is widely applicable in out of hospital settings and is relatively inexpensive. Good clinical results can be achieved and treatment is without any severe side effects or long-term complications. However, in general, the patients have to receive multiple ESWT sessions in order to achieve this result, which makes this treatment more time consuming than US-guided needling.

US-guided needling uses sonographic guidance to visualize the calcific deposit, which is then punctured and irrigated with a needle to break them down. The procedure removes part of the calcific deposit and promotes further reabsorption of the remaining calcific material. Some authors prefer a single needle to prevent damage to the surrounding tendon tissue, whereas others describe a 2-needle technique including aspiration and lavage to promote resorption and create a continuous flow of fluid in which the calcific deposits are dissolved. A recent review by Gatt and Charalambous[10] showed no difference in outcome when comparing a 1-needle technique versus a 2-needle technique. Two authors reported a re-needling rate of 28% and 45% respectively. Most reported side-effects were discomfort during treatment and shoulder pain after treatment, which resolved with nonoperative treatment. US-guided needling can be performed in an outpatient clinical setting under local anesthesia and is therefore widely applicable. The costs are similar to that of high-energy ESWT and the included studies did not report serious side effects or long-term complication. This review showed that, based on the available level of evidence, US-guided needling is a safe and effective treatment modality in the midterm to long-term.

Surgical removal of the calcific deposit has been the preferred treatment for chronic calcific rotator cuff tendinopathy for several years. Open and endoscopic techniques are available for this purpose but arthroscopy is currently favored because it is minimally invasive and provides clinical results equivalent to open techniques.[13] The arthroscopic techniques used by the authors in this review differed primarily on the choice of

additional subacromial decompression and the extent of calcific deposit removal. Up to this point, numerous studies failed to prove a benefit of additional acromioplasty. The extent to which the calcific deposit has to be removed is another issue. Maier et al stated that calcific removal with preservation of the rotator cuff yielded to excellent results and that arthroscopic techniques with complete removal of the calcific deposit often requires repair of the rotator cuff defects.[14] Prolonged immobilization because of a rotator cuff repair can also add to a higher chance of postoperative shoulder stiffness.[52] Arthrofibrosis and postoperative pain were the most commonly reported complications and must be taken into account when one is appreciating the high clinical success rate of arthroscopic removal.

Pooling of data was not possible due to the heterogeneity of the included studies. However, we were able to provide a clear overview of the literature reporting outcomes after treatment for calcific tendinopathy of the shoulder. Arthroscopy and US-guided needling resulted in different complications compared to ESWT, the most important complication being postoperative pain and shoulder stiffness. All frozen shoulders responded well to nonoperative treatment.

LIMITATIONS

A limitation of this study is the heterogeneity of the methodological quality of the included studies. Shockwave therapy was the only modality for which extensive level I evidence was available. The results for arthroscopic surgery group were primarily based on level IV studies with an emphasis on the long-term results. The flaws of these individual studies are reflected in our results and in the difference in Coleman score. It remains under considerable debate whether the good clinical results and resorption of the calcific deposit after treatment with either of the 3 treatment modalities is due to the effect of the treatment or due to the natural course of the condition.[53] A pearl of this study is that it gives a comprehensive overview on the available literature for the top 3 treatment modalities for calcific rotator cuff tendinopathy. Arthroscopy, high-energy ESWT and US-guided needling have all proved to provide good clinical outcome at mid- to long-term follow-up.

Future research should focus on comparative studies reporting the long-term clinical (patient-reported) outcome and assessment of patients' quality of life after ESWT, US-guided needling and arthroscopy for calcific tendinopathy of the rotator cuff.

CONCLUSION

Patients can achieve good to excellent clinical outcome after high-energy ESWT, US-guided needling and arthroscopy for calcific tendinopathy of the shoulder. Side effects and post treatment complications should be taken into account when making a decision for each individual patient. Physicians should consider high-energy ESWT and US-guided needling as minimally invasive treatment options when the primary conservative treatment fails. Arthroscopy can safely be used as a very effective but more invasive secondary option although the extent of deposit removal and the additional benefit of subacromial decompression remains unclear.

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Part 3

Evaluating the effectiveness of high-energy ESWT versus ultrasound-guided needling

6

Comparing ultrasound-guided needling combined with a subacromial corticosteroid injection versus high-energy extracorporeal shockwave therapy for calcific tendinitis of the rotator cuff: a randomized controlled trial

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ABSTRACT

PURPOSE

To compare clinical and radiographic outcomes after treatment with standardized high-energy extracorporeal shock wave therapy (ESWT) and ultrasound guided needling (UGN) in patients with symptomatic calcific tendinitis of the rotator cuff who were nonresponsive to conservative treatment.

METHODS

The study was designed as a randomized controlled trial. The ESWT group received ESWT (2000 pulses, energy flux density 0.35mJ/mm2) in four sessions with one week intervals. UGN was combined with a corticosteroid US-guided subacromial bursa injection. Shoulder function was assessed at standardized follow-up intervals (6 weeks and 3, 6 and 12 months) using the Constant Murley Score (CMS), the Disabilities of the Arm, Shoulder and Hand questionnaire and visual analogue score for pain and satisfaction. The size, location and morphology of the deposits were evaluated on radiographs. The a priori sample size calculation computed that 44 participants randomized in each treatment group was required to achieve a power of 80%.

RESULTS

Eighty-two patients were treated (56 female, 65%; mean age 52.1 ± 9 years) with a mean baseline CMS of 66.8 ± 12 and mean calcification size of 15.1 ± 4.7mm. One patient was lost to follow-up. At 1-year follow-up the UGN group showed similar results as the ESWT group with regard to the change from baseline CMS (20.9 versus 15.7; p=0.23), Disabilities of the Arm, Shoulder and Hand questionnaire (-20.1 versus -20.7; p=0.78) and visual analogue scale for pain (-3.9 and -2.6; p=0.12). The mean calcification size decreased by 13 ± 3.9 mm in the UGN group and 6.7 ± 8.2 mm in the ESWT group (<p=0.001). 22% of the UGN and 41% of the ESWT patients received an additional treatment during follow-up because of persistent symptoms.

CONCLUSIONS

This RCT compares the clinical and radiographic results of UGN and high-energy ESWT in the treatment of calcific tendinitis of the rotator cuff. Both techniques are successful in improving function and pain with high satisfaction rates after one-year follow-up. However, UGN is more effective in eliminating the calcific deposit, and the amount of additional treatments was greater in the ESWT group.

LEVEL OF EVIDENCE: II, randomized controlled trial.

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INTRODUCTION

Calcific tendinitis of the rotator cuff is a common cause of pain in the shoulder. The condition is characterized by the deposition of calcium carbonate hydroxyapatite crystals in the rotator cuff tendons. The prevalence of calcific tendinitis in either the general population (2.7% - 7.8%) or in a population with a painful shoulder (8% - 40%) is high.[1] In calcific tendinitis of the rotator cuff, the supraspinatus tendon is most frequently affected. Typically, individuals with calcific tendinitis are aged between 30 and 60 years with women affected 1.5 times more than men.[1] Patients experience activity-related pain in the deltoid region, a decrease in active range of motion as well as pain at night with variable functional impairment. Although it is considered to be a self-limiting disease with spontaneous improvement over time symptoms can be severe and long-lasting.[2–4] The exact etiology remains unclear but the most widely accepted theory is by Uhthoff et al and describes an active, cell-mediated reactive process that is divided in 3 distinct stages: the precalcific, calcific (with a formative, resting and resorptive phase) and postcalcific stage.[5] Symptoms generally worsen during the resorptive phase. The patients in this phase have the highest chance of non-operative recovery.[6] Primary treatment consists of non-steroidal anti-inflammatory drugs, physiotherapy and a subacromial corticosteroid injection (SAI) when indicated.[6–8] When primary treatment fails more invasive techniques are available.[9] Extracorporeal shockwave therapy (ESWT) and ultrasound guided needling (UGN) are among the most frequently applied treatments in refractory cases and can be considered as an alternative for a surgical intervention.[10,11] These treatments are minimally invasive, inexpensive, relatively easy to perform with low complication rates and have shown promising results in previous studies.[9,12–16] However, previous systematic reviews also concluded that there is a lack of level 1 evidence comparing UGN with ESWT.[8,13]

The primary objective of this study was to compare clinical and radiographic outcomes after treatment with standardized high-energy ESWT and UGN in patients with symptomatic calcific tendinitis of the rotator cuff who were nonresponsive to conservative treatment. Our hypothesis was that UGN is superior in terms of clinical and radiographic outcome after 1-year follow-up.

MATERIAL AND METHOD

The study was designed as a single centre randomized controlled trial with parallel groups. Patients were included between May 2014 and December 2017. The study was registered in the Dutch clinical trial registration (NL4304/NTR4448) and approved by both the medical ethics review committee (METC, number NL44205.094.13) and the

institutional review board (IRB Spaarne Gasthuis, Hoofddorp, the Netherlands). Informed consent forms were signed by all participating patients.

STUDY POPULATION

The population consisted of patients referred to the outpatient orthopaedic clinic with clinical signs of non-traumatic anterograde-lateral shoulder pain when the arm was elevated. The medical history was taken and a clinical examination of the shoulder was performed. Standardized shoulder radiographs (anteroposterior, outlet-, axial-, and acromioclavicular view) and an ultrasound examination of the rotator cuff were obtained.

Inclusion criteria for participation in this study were: age > 18 years, clinical sign of subacromial pain syndrome, standardized radiographs showing a calcific deposit with a diameter of at least 5 mm in size, morphological type-I and type-II deposits corresponding to the classification of Gärtner[17] (type-I, sharply outlined and densely structured; type-II, sharply outlined and inhomogeneous or homogenous with no defined border), symptoms for more than four months, a completed and unsuccessful nonsurgical treatment program including non-steroidal anti-inflammatory drugs, physiotherapy (concentric and eccentric rotator cuff strengthening exercises in combination with scapular stabilization) and at least 1 SAI with a corticosteroid. Exclusion criteria were the following: ultrasonic signs of a partial or full rotator cuff tendon, clinical or radiographic signs of a resorption phase as defined as a recent period of increased pain in combination with a morphological type III deposit (cloudy and transparent in structure) on radiographs, calcific deposits in multiple tendons of the rotator cuff, osteoarthritis of the glenohumeral or acromioclavicular joint, adhesive capsulitis, previous shoulder surgery , ESWT or UGN to the affected shoulder, instability of the shoulder, rheumatoid arthritis, neurological disorders or dysfunction of the upper limb and the inability to give informed consent.

INCLUSION AND RANDOMIZATION

Eligible patients were provided with written and oral information about the trial and had at least 1 week to consider participation. Patients who were willing to participate were referred to the coordinating investigator (J.L.) for further evaluation and inclusion. A research nurse allocated the patients to 1 of the 2 treatment groups using the computer generated block randomization function (ten patients per block) in Research Manager (Nova Business Software, Zwolle, the Netherlands). Treatment was scheduled within 4 weeks.

ESWT: TECHNIQUE AND STUDY PROTOCOL

High-energy shockwave therapy is a technique where monophasic pressure pulsus with high peak pressure are distributed to the calcific deposit and the surrounding soft tissues through, in this study, a piezoelectric mechanisms. The shockwave group was treated with 4 sessions of high-energy extracorporeal shockwave therapy with a 1 week interval. Each session consisted of 2000 piezoelectric pressure pulses, focussed on the calcific deposit, at a frequency of 4 Hz with a total energy flux density of 0.351 mJ/mm^2 resulting in a total energy amount of 2808 mJ. Two identical extracorporeal shockwave sources were used in this study, the Piezowave2 system (Richard Wolf GmbH, Knittlingen, Germany). The calcific deposit was localized by ultrasound with the patient positioned in a supine position. Patients initially received a small amount of low-energy pulses to get used to the sensation after which the actual therapeutic dose was administered. After treatment the visual analogue score for pain was registered and when necessary the shoulder was cooled with ice-packs. The high-energy ESWT treatment was performed at 2 nearby physiotherapy clinics by 2 specialized shoulder physiotherapist (R.B. and E.V.) with extensive experience in shockwave treatment.

US-GUIDED NEEDLING: TECHNIQUE AND STUDY PROTOCOL

In UGN, ultrasound is used to allow a radiation free, 3-dimensional localization and assessment of the calcific deposit. Assisted by real-time ultrasonic guidance the deposit is then punctured and irrigated with a needle to break it down. This procedure effectively removes part of the calcific deposit and promotes further reabsorption of the calcific material. In this study a double-needle technique was used with repeated perforation of the deposit and subsequent aspiration and lavage. Patients were treated with a single UGN procedure, performed in an outpatient clinical setting by one orthopaedic shoulder surgeon (A.v.N.) assisted by an experienced ultrasonographer. The patient was positioned in a supine position and the size and location of the calcific deposit was confirmed and marked by ultrasound imaging. After sterile preparation, patients received a local anaesthetic injection of the skin and subcutanial tissue with 5cc lidocaine HCL 10mg/ml (Braun, Melsungen, Germany). The ultrasound transducer was kept focused on the calcific deposit and the deposit was punctured multiple times with a 40-mm 17-gauged needle. A second 40-mm 17-gauged needle was introduced from a different angle and lavage and aspiration of the deposit with a saline solution was performed. After the UGN procedure one of the needles was introduced in the subacromial bursa under ultrasonic guidance and a mixture of 4 cc bupivacaine HCL 0.5% (Pfizer Inc., NY, USA) and 1 cc depomedrol 40mg/ml (Pfizer Inc.) was injected. The sterile drapes were removed and the puncture site was sealed with an island dressing. The visual analogue score for pain during treatment was registered after treatment.

POST-PROCEDURE CARE

After treatment both groups followed a standardized physical therapy program including active and passive exercise mobilization techniques. Oral analgesics were administered for a maximum of 7 days post-intervention when necessary. The medication was only prescribed once. We have not systematically monitored the use of additional over the counter analgesics. In case of persistent or refractory symptoms within the 1-year follow-up period, additional treatment options were discussed with the patients. In case of full resorption but persistent pain despite analgesics, a subacromial bursa infiltration was considered. In case of no- or partial resorption, (redo) UGN or an arthroscopic bursectomy with intra-operative needling was considered.

CLINICAL AND RADIOGRAPHIC EVALUATIONS

Both treatment groups had regular follow-up visits with the coordinating investigator before the intervention and at 6 weeks, 3 months, 6 months and 1 year after treatment. At each visit, the Constant Murley score (CMS)[18], the Disabilities of the Arm, Shoulder and Hand questionnaire (DASH)[19] were used for clinical assessment. A visual analogue scale (VAS) for average pain during the last week and VAS for satisfaction was registered at each follow-up visit. At 6 months and 1 year the patients' reported change in symptoms were screened using a seven-point Likert scale. The size, morphology and amount of resorption of the calcific deposit (complete, less than 50%, more than 50%, none) were assessed using standard shoulder radiographs obtained at baseline and after 6 weeks and 6 months. The length of the deposit was measured in terms of the maximum size of the longest axis in any direction. The radiographs were analysed by an independent physician, blinded for the allocated treatment.

SAMPLE SIZE

In this superiority study the 0-100 points Constant score was used as primary outcome measure. A difference of 12 points was defined as the minimal clinical important difference between the treatment groups. With an assumed standard deviation of 20 points we computed that a sample size of 44 participants randomized in each treatment group, would achieve a power of 80% to detect a 12 point difference. The statistical level of significance was set at .05.

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS version 24.0 (IBM Corp. Armonk, NY, USA). Continuous data are presented as means with standard deviations (SD) or 95% confidence intervals (CI), and categorical variables as frequencies with accompanying proportions. Primary analysis was performed according to the intention to treat (ITT) principle. Change from baseline (CFB) was calculated for the CMS, DASH and VAS.

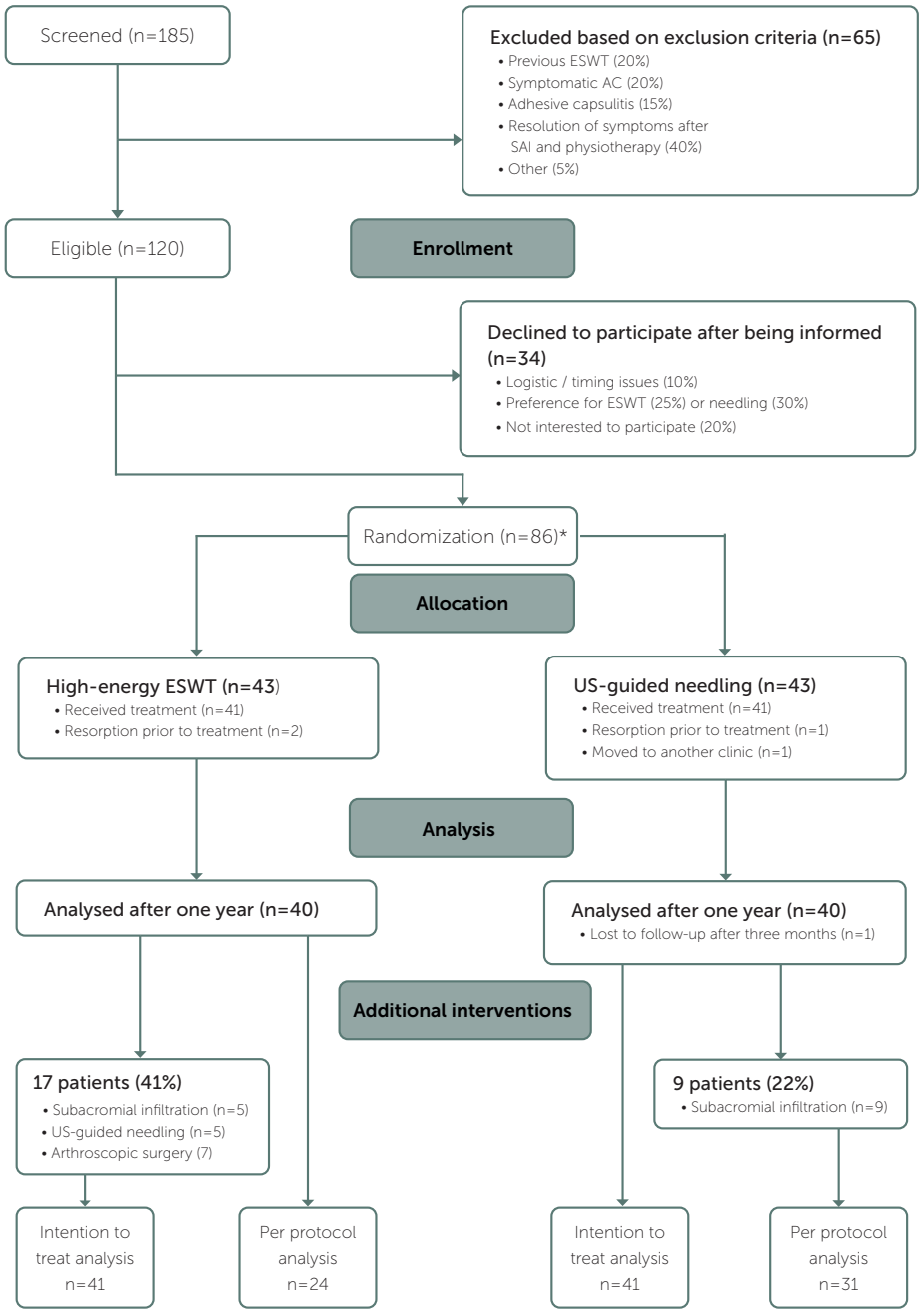

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flowchart. (*) The a priori sample size calculation computed that 44 participants randomized in each treatment group, was required to achieve a power of 80%. (AC, Acromioclavicular joint; ESWT, Extracorporeal shockwave therapy; SAI, Subacromial infiltration; US, ultrasound.)

Differences between the treatment groups were analysed by use of Student's T-tests as well as multivariate linear regression analyses, adjusted for potential confounders (gender**,** age, BMI, duration of complaints, baseline, Gärtner) at all follow-up moments. In addition, a mixed-model repeated-measures analysis of covariance was used to assess treatment effect during the follow-up period of 12 months. Adjustment for potential confounders (gender**,** age, BMI, duration of complaints, baseline, Gärtner) was performed and interaction between treatment and follow-up was assessed. Secondary ordinal variables were analysed by use of Mann-Whitney U-tests, for categorical variables Chi^2 -tests were used. The level of statistical significance was set at $P < .05$ for all tests. Due to an imbalance of the occurrence of additional treatments between the two groups (22% vs 41%), two sensitivity analyses were performed: a per protocol and last observation carried forward protocol. In the last observation carried forward protocol[20], additional treatment was considered an endpoint, and results of the last follow-up before initiation of the additional treatment were carried forward to avoid overestimation of the treatment effect.

RESULTS

BASELINE CHARACTERISTICS

Between May 2014 and December 2017, a total of 185 patients were screened for participation in the study. A CONSORT study flowchart is provided in figure I. Sixty-five patients were not found to be eligible for participation because they did not meet the inclusion criteria and 120 patients were invited for the study. After being invited 34 patients (28%) were not willing to participate and 86 patients were randomized. Prior to treatment 1 patient switched to another clinic for treatment and 3 patients improved in such a manner that no further treatment was indicated. The final study group consisted of 82 patients of which 56 (65%) were female with a mean age of 52.1 ± 9.1 years. The mean duration of symptoms was 3.2 ± 3.0 years and the supraspinatus was the most frequently (85%) affected tendon. Demographics and baseline clinical characteristics were similar for both groups except for the distribution of the Gärtner types as is shown in table 1.

INTERVENTIONS

During intervention the mean VAS scores were 6.2 ± 1.2 in the ESWT group and 4.5 ± 2.4 in the UGN group. This score was significantly lower in the UGN group ($p < .001$). The consistency of the calcific deposits during UGN was categorized as solid in 54%, soft in 20% and mixed in 26% of the cases.

Table 1. Demographics and baseline data

	ESWT (n=41)	UGN (n=41)
	Mean (SD)	Mean (SD)
Gender, n (%)		
Male	14 (34)	15 (37)
Female	27 (66)	26 (63)
Age, mean (SD)	51.6 (9.4)	52.7 (8.7)
BMI, mean (SD)	25.6 (4.3)	25.6 (3.4)
Duration complaints (years), mean (SD)	3.4 (3.0)	3.0 (3.0)
Location, n (%)		
Supraspinatus	35 (85)	36 (88)
Infraspinatus	4 (10)	3 (7)
Subscapularis	2 (5)	2 (5)
Size deposit (mm), mean (SD)	15.5 (5.8)	15.8 (4.5)
Gärtner, n (%)		
Type I	13 (32)	21 (68)
Type II	28 (51)	20 (49)
CMS, mean (SD)	67.7 (12.2)	66.4 (12.7)
DASH, mean (SD)	38.7 (16.0)	35.2 (15.8)
VAS pain, mean (SD)	5.8 (1.8)	6.0 (1.5)

ESWT = high-energy extracorporeal shockwave therapy, UGN = ultrasound guided needling, BMI = body mass index, SD = standard deviation, CMS = Constant Murley score, DASH = disability of the arm, shoulder and hand score, VAS = visual analogue score

CLINICAL OUTCOME MEASURES

Table 2 shows the change from baseline scores and total scores for the 3 clinical outcome measures. A significant interaction between follow-up and treatment was observed for the change from baseline scores from the CMS ($P < .01$), DASH ($P = .03$) and VAS ($P < .01$). For both the CMS (figure 2a) and the DASH (figure 2b) a statistically significant and clinical relevant improvement was observed after 1 year, without significant differences between the treatment groups. Six weeks after treatment, the DASH score for the UGN group was significantly worse than the ESWT group ($P = .046$). When looking at the average pain over the week, measured on a 0- to 10-point VAS score, the UGN group improved by 3.9 points and the ESWT group improved by 2.6 points, which was not significantly different after adjusting for confounding factors ($P = .12$) (table 2 & figure 2c). The mean satisfaction scores after one-year were 7.6 ± 2.2 for the ESWT group and 7.0 ± 2.8 for the UGN group ($P = .30$). Patient reported change in symptoms is reported in table 3. Sixty-seven percent of the ESWT patients and 78% of the UGN patients reported either an improvement or strong improvement in symptoms after 1-year follow-up.

Results of both types of sensitivity analyses (PP and LOCF) of the CMS, DASH and VAS at all follow-up moments were similar to those of the primary analyses (supplementary table 1 and 2).

RADIOGRAPHIC OUTCOME

The radiographic results were superior in the UGN group ($P < .001$) as shown in figure 3 and table 4. UGN resulted in full resorption of the calcific deposit in 27 cases (68%) with a mean size of 1.8 ± 3.4mm after 6 months, implying a mean reduction of 14.2 ± 4.1 mm. In the ESWT group full resorption was observed in 14 cases (34%). With a mean size of 8.6 ± 8.3 mm after 6 months, a reduction in size of 7.1 ± 8.7 mm was measured.

Table 2. Change from Baseline (CFB) scores for the CMS, DASH and VAS pain (ITT)

	ESWT	UGN	Crude	Multivariate	
	Mean (95%CI)	Mean (95%CI)	*P*-value	B-coefficient* (95%CI)	*P*-value
CMS (CFB)					
6 weeks	7.6 (3.5; 11.7)	5.1 (0.8; 9.4)	0.40	4.1 (-1.8; 10.0)	0.17
3 months	9.9 (5.4; 14.4)	7.0 (2.4; 11.7)	0.37	3.3 (-3.1; 9.8)	0.31
6 months	13.3 (7.8; 18.8)	12.4 (7.1; 17.6)	0.80	1.9 (-5.6; 9.3)	0.62
1 year	15.7 (10.1; 21.3)	20.9 (16.9; 24.8)	0.13	-3.6 (-9.5; 2.3)	0.23
DASH (CFB)					
6 weeks	-12.3 (-17.2; -7.4)	-5.0 (-9.9; -0.2)	**0.04**	-6.8 (-13.4; -0.14)	**0.046**
3 months	-13.2 (-19.3; -7.1)	-6.4 (-12.4; -0.4)	0.11	-6.2 (-14.0; 1.5)	0.11
6 months	-17.6 (-24.1; -11.1)	-13.6 (-18.5; -8.7)	0.32	-3.2 (-10.8; 4.4)	0.41
1 year	-20.7 (-27.2; -14.2)	-20.1 (-25.4; -14.8)	0.87	1.1 (-6.5; 8.6)	0.78
VAS pain (CFB)					
6 weeks	-1.6 (-2.3; -0.9)	-0.9 (-1.7; 0.03)	0.19	-1.1 (-2.1; -0.1)	0.03
3 months	-1.7 (-2.6; -0.7)	-1.1 (-2.1; -0.1)	0.41	-1.0 (-2.2; 0.1)	0.08
6 months	-2.3 (-3.3; -1.3)	-2.9 (-3.6; -2.2)	0.28	0.3 (-0.8; 1.4)	0.62
1 year	-2.6 (-3.7; -1.6)	-3.9 (-4.6; -3.1)	**0.05**	0.9 (-0.2, 2.0)	0.12

Mean difference between treatment groups, adjusted for potential confounders where required (gender, age, BMI, duration of complaints, baseline, Gärtner). CFB = change from baseline, CI = confidence interval, CMS = Constant Murley score, DASH = disability of arm, shoulder and hand score, ESWT = high-energy extracorporeal shockwave therapy, UGN = ultrasound guided needling, VAS = visual analogue score.

Table 3. Patient reported change in symptoms after one-year follow-up

	(strong) decline	neutral	(strong) improvement
ESWT, n (%)	3 (8)	10 (26)	26 (67)
UGN , n (%)	1 (3)	8 (20)	31 (78)

P = .25 (Mann Whitney U-test), ESWT = high-energy extracorporeal shockwave therapy, UGN = ultrasound-guided needling

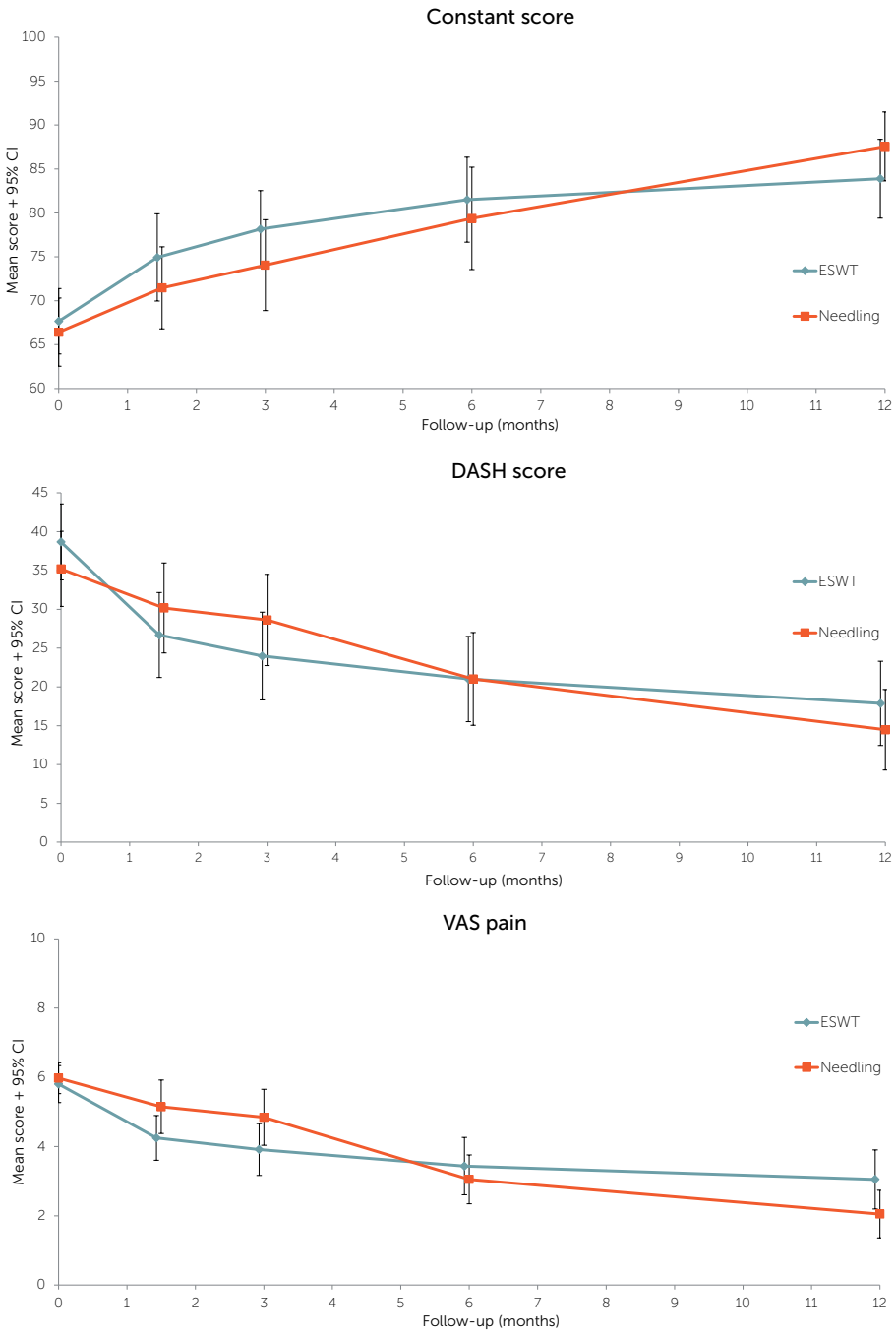

Fig 2. Development of the mean Constant Murley Score (A), DASH (B), and VAS pain score (C) after treatment with ESWT and UGN. (CI, confidence interval; DASH, Disability of Arm, Shoulder, and Hand Score; ESWT, Extracorporeal shockwave therapy; UGN, ultrasound-guided needling; VAS, visual analog scale.)

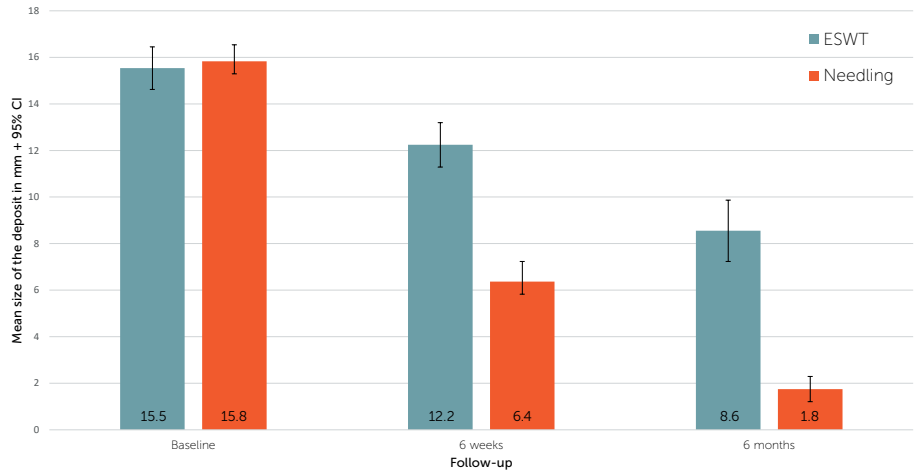

Fig 3. Change in size of calcific deposits. (CI, confidence interval; Extracorporeal shockwave therapy.)

Table 4. Resorption of calcific deposits after six months follow-up

	No change	<50%	>50%	Full resorption
ESWT patients (%)	17 (42)	6 (15)	4 (10)	14 (34)
UGN patients (%)	0 (-)	1 (3)	12 (30)	27 (68)

P <.001 (Mann Whitney U-test), ESWT = high energy extracorporeal shockwave therapy, UGN = ultrasound-guided needling

COMPLICATIONS AND ADDITIONAL INTERVENTIONS

Overall, there were no serious adverse events. Respectively 1 (ESWT) and 2 (UGN) patients developed a frozen shoulder. Symptoms resolved during the study follow-up. One (ESWT) versus 5 (UGN) patients returned to the outpatient clinic in the first 2 months with severe symptoms of subacromial bursitis which resolved after a SAI. One patient was lost to follow-up after the 12 weeks visit. In total, 26 patients received an additional treatment due to persistent pain and symptoms (figure 1). 9 patients (22%) in the UGN group and 17 (41%) in the ESWT group (*P* = .058). In the UGN group the additional interventions primarily consisted of a SAI to treat an acute bursitis in the first few weeks after treatment (5 patients) or persistent pain after 6 months despite full resorption on radiographs. In the ESWT group 5 patients received an additional SAI (full resorption), 5 a UGN procedure and 7 an arthroscopic bursectomy and intra-operative

needling procedure. The secondary UGN and surgical procedures were performed after a minimal follow-up of 6 months (range 6 – 15 months).

POST-HOC SAMPLE SIZE ANALYSIS

A post-hoc power-analyses with the actual standard deviation found in this study after 1 year (SD = 13.4) showed that 21 patients per group would have been sufficient to show a statistically significant and clinically relevant difference of 12 points in the CMS score. With 82 treated patients a 97% power with a β error of 3% was achieved.

DISCUSSION

The most important finding of this study is that both treatment techniques show clinically relevant improvements in terms of shoulder function and pain after 1-year follow-up. UGN was more effective in eradicating the calcific deposit and there were more requests for additional interventions in the high-energy ESWT group. This study therefore only provides partial evidence to support our hypothesis.

The effectiveness of UGN has been studied in 2 previous randomized controlled trials. de Witte et al.[13] compared UGN with an US-guided SAI in their RCT containing 48 patients. They concluded that UGN is superior to a SAI in terms of functional and radiographic results after 1-year follow-up without between-group differences after 5-year follow-up . Kim et al.[12] analysed 54 patients in their RCT comparing UGN with high-energy ESWT. Although both treatment techniques improved clinical outcomes, the results for UGN were superior in terms of functional outcome, pain and resorption. However, in this study the ESWT protocol consisted of high-energy shockwaves focused, without ultrasound guidance, at the point of maximum tenderness. In a single blinded RCT, Sabeti-Aschraf et al. already showed that the outcome of ESWT is superior when focussing on the calcific deposit as opposed to the point of maximum tenderness.[21] We therefore believe that this was not a best-level of evidence shockwave protocol.[22] The ESWT protocol in the present study consisted of ultrasound guided shockwaves focussed on the calcific deposit. The energy flux density was based on data from a meta-analysis containing 15 high-energy ESWT RCT's.[9]

The clinical results show that both treatment options provide a clinical relevant improvement in functional outcome and pain. A minimal clinically important difference (MCID) for the CMS was not known when the study protocol was conducted. In 2013, Kukkonen et al.[23] concluded that the MCID for patient undergoing rotator cuff surgery is 10.4 and a recent systematic review estimated the MCID for the CMS to be 8.3 based on 10 studies.[24] Accounting for this, it took patients between 3 and 5 months to reach

this MCID level. For the UGN group the pain and DASH scores stabilized at 6 to 12 weeks follow-up after which further improvement was seen between 3-months and 1-year follow-up. This might be attributed to the temporary treatment effect of the subacromial corticosteroids, which declines after 6 weeks while the natural healing response of the tendon has not been completed yet.[13,25]

The radiographic results are in favour of UGN with near full resorption in most of the patients. Despite the fact that the radiographic results of the ESWT group were less successful this did not result in a statistical significant difference in clinical outcome. Previous studies have reported good clinical outcome without full removal of the calcific deposit and the beneficial inflammatory response after ESWT might also contribute.[21,26] However, Chou et al. concluded that there is a strong relationship between subsidence of symptoms and remission of the calcification.[27] It must be noted that most additional interventions were in patients with none or only partial (<50%) resorption of the calcific deposit. No differences in clinical outcome were found between Gärtner type I and II calcifications. Previous authors suggested that UGN might be more efficient in the more ill-defined Gärtner type II and type III deposits.[13,28] In this study, Gärtner type III deposits were excluded since they have the highest chance of resorption and natural resolution of symptoms without (minimally) invasive therapies.[3,6,17] Long-term data on the natural history of calcific tendinitis varies greatly. Gärtner et al.[17] reported a 85% chance of natural resolution after three years for type III deposits, as opposed to 33% for type I and II deposits. In his classic study, Bosworth[3] reported that 6.4% off calcific lesions showed spontaneous resorption.

The effectiveness and safety of high-energy shockwave therapy has been studied extensively in previous randomized controlled trials and has been shown to be superior when compared to low-energy[14,21,29], sham treatment and placebo.[14,30,31] In both treatment groups a percentage of patients experienced persistent pain and prolonged symptoms with or without radiographic change in size of the calcific deposit. Although not statistically significant the absolute amount of patients was higher in the ESWT group and the applied treatment techniques more invasive. It must be noted that the study protocol did not contain an objective cut-off point, in terms of CMS, DASH or pain scores, indicating when the treatment was considered unsuccessful, and an additional intervention would be required. There were no re-needling procedures or conversions to surgery in the UGN group. Previous studies reported a re-needling rate of between 10% to 45% and a conversion to arthroscopy in 6% to 17% of the cases.[13,32] The incidence of acute bursitis, necessitating a corticosteroid subacromial bursa injection, was slightly higher than previously reported.[10,15] Despite the fact that aspiration and lavage of the calcific material was performed these bursitis symptoms are probably caused by a

reactive inflammatory response due to residual calcific minerals in the bursal tissue. The necessity of a corticosteroid SAI following UGN was questioned in a recent RCT comparing steroids with saline. However, pain and function were significantly lower in the corticosteroid group in the short term without long term disadvantageous effects.[33] A double-needle technique was used in our UGN protocol and although a single needle technique is also known to be effective,[13] two needles can create a continuous in- and outflow of saline to remove calcific minerals and control the pressure inside the calcification during injection.

LIMITATIONS

The results of this study must be interpreted in light of several limitations. First, the presence of a third, observational, control group would have made the study results stronger. We attempted to compensate for this fact by including only patients with prolonged symptoms (mean period of 3 years) who did not respond to a strict nonoperative treatment protocol and exclude patients that had a high chance of natural resolution of symptoms. Our opinion was that patients would not have been willing to participate if there was a one-third chance they would have to continue with their conservative therapy. A second limitation is that blinding of patients was not possible due to the differences in technique and treatment protocol. Thirdly, the substantial amount of additional interventions and variety in techniques might have caused a source of bias on the part of the provider. However, when correcting for this confounder in the sensitivity analysis, no differences in outcome were found. Fourthly, the study population was slightly smaller than anticipated in the sample size analysis. However, due to a more homogeneous study population (with smaller standard deviation), the post-hoc sample size analysis revealed that the study was adequately powered (97%) with a minimal beta-error (3%) to show a significant clinically relevant difference. Finally, the follow-up of 1 year might have been short since recovery from calcific tendinitis sometimes takes longer. However, patients eventually ask for a treatment option in which their prolonged symptoms will resolve in an acceptable amount of time. The natural history of the condition will also play a more predominant role as the follow-up period exceeds the conventional 1-year period.[34–36]

CONCLUSION

This RCT compares the clinical and radiographic results of UGN and high-energy ESWT in the treatment of calcific tendinitis of the rotator cuff. Both techniques are successful in improving function and pain with high satisfaction rates after one-year follow-up. However, UGN is more effective in eliminating the calcific deposit and the amount of additional treatments was greater in the ESWT group.

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Supplementary Table 1. Sensitivity analysis **– last observation carried forward.** In this analysis, the additional treatment was considered an endpoint, and results of the last follow-up before initiation of the additional treatment were carried forward to avoid overestimation of the treatment effect.

	ESTW (n=41)	**UGN (n=41)**	Crude	Multivariate	
	Mean (95%CI)	Mean (95%CI)	*P*-value	**β**-coefficient* (95%CI)	*P*-value
CMS (CFB LOCF)					
6 weeks	7.6 (3.5; 11.7)	5.1 (0.8; 9.4)	0.40	4.1 (-1.8; 10.0)	0.17
3 months	9.0 (4.2; 13.7)	7.0 (2.4; 11.6)	0.56	2.3 (-4.4; 9.0)	0.50
6 months	11.1 (5.4; 16.8)	11.0 (5.6; 16.3)	0.97	1.2 (-6.7; 9.1)	0.76
1 year	11.6 (5.9; 17.3)	14.7 (9.0; 14.3)	0.44	-1.6 (-9.6; 6.3)	0.68
DASH (CFB LOCF)					
6 weeks	-12.3 (-17.2; -7.4)	-5.0 (-9.9; -0.2)	**0.04**	-11.3(-20.2; -2.4)	**0.01**
3 months	-12.8 (-18.8; -6.9)	-6.4 (-12.4; -0.4)	0.13	-6.1 (-15.7; 3.4)	0.20
6 months	-16.1 (-22.7; -9.5)	-11.8 (-16.8; -6.8)	0.30	0.3 (-7.6; 8.2)	0.94
1 year	-17.8 (-24.0; -11.6)	-14.9 (-20.4; -9.4)	0.49	1.9 (-5.9; 9.8)	0.62
VAS pain (CFB LOCF)					
6 weeks	-1.7 (-2.4; -0.9)	-0.8 (-1.7; -0.1)	0.13	-1.2 (-6.1; 2.4)	**0.02**
3 months	-1.7 (-2.7; -0.8)	-1.1 (-2.0; -0.1)	0.34	-0.9 (-2.0; 0.3)	0.13
6 months	-2.2 (-3.2; -2.2)	-2.4 (-3.2; -1.5)	0.80	-0.04 (-1.3; 1.2)	0.95
1 year	-2.4 (-3.4; -1.3)	-3.1 (-4.1; -2.2)	0.26	0.6 (-0.8; 1.9)	0.40

Mean difference between treatment groups, adjusted for potential confounders where required (gender**,** age, BMI, duration of complaints, baseline and/or Gärtner). CFB = change from baseline, CI = confidence interval, CMS = Constant Murley score, DASH = disability of arm, shoulder and hand score, ESWT = high-energy extracorporeal shockwave therapy, UGN = ultrasound guided needling, VAS = visual analogue score.

Supplementary Table 2. Sensitivity analysis **– per protocol analysis.** In this analysis only the cases were included who were compliant with the study protocol and did not receive additional treatments.

	ESTW (n=24)	**UGN (n=31)**	Crude	Multivariate	
	Mean (95%CI)	Mean (95%CI)	*P*-value	**β**-coefficient* (95%CI)	*P*-value
CMS (CFB PP)					
6 weeks	10.9 (5.1; 16.7)	6.3 (1.0; 11.5)	0.23	5.6 (-1.6; 12.8)	0.13
3 months	13.1 (7.2; 19.1)	11.0 (6.0; 16.0)	0.57	0.4 (-6.1; 6.9)	0.91
6 months	18.3 (10.9; 25.8)	17.1 (12.2; 21.9)	0.77	0.0 (-7.0; 7.1)	0.99
1 year	19.9 (11.8; 26.3)	22.0 (17.6; 26.4)	0.46	-3.8 (-10.2; 2.5)	0.23
DASH (CFB PP)					
6 weeks	-16.1 (-23.4; -8.7)	-4.4 (-10.0; 1.1)	**0.01**	-11.3 (-20.2; -2.4)	**0.01**
3 months	-19.5 (-27.8; -11.2)	-8.4 (-15.5; -1.2)	**0.04**	-6.1 (-15.7; 3.4)	0.20
6 months	-24.1 (-33.2; -15.0)	-16.8 (-21.9; -11.6)	0.16	-0.3 (-7.6; 8.1)	0.94
1 year	-26.2 (-34.5; -17.9)	-20.9 (-26.3; -15.5)	0.28	1.9 (-5.9; 9.8)	0.62
VAS pain (CFB PP)					
6 weeks	-2.1 (-3.1; -1.1)	-1.1 (-2.2; 0.1)	0.18	-1.3 (-2.6; -0.03)	**0.046**
3 months	-2.5 (-3.9; -1.1)	-1.6 (-2.6; -0.5)	0.29	-1.0 (-2.3; 0.4)	0.15
6 months	-3.3 (-5.6; -1.9)	-3.4 (-4.1; -2.8)	0.79	0.1 (-0.9; 1.3)	0.70
1 year	-3.5 (-4.8; -2.2)	-4.1 (-5.0; -3.3)	0.38	0.6 (-0.5; 1.8)	0.28

Mean difference between treatment groups, adjusted for potential confounders where required (gender**,** age, BMI, duration of complaints, baseline and/or Gärtner). CFB = change from baseline, CI = confidence interval, CMS = Constant Murley score, DASH = disability of arm, shoulder and hand score, ESWT = high-energy extracorporeal shockwave therapy, UGN = ultrasound guided needling, VAS = visual analogue score.

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7

The impact of minimally invasive treatment for rotator cuff calcific tendinitis on self-reported work ability and sick leave

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ABSTRACT

PURPOSE

The aim of this prospective study among rotator cuff calcific tendinitis (RCCT) patients was: (1) to examine the impact of RCCT on patients' self-reported work ability and sick leave, (2) to compare work ability and sick leave with shoulder function after minimally invasive treatment and (3) to assess which prognostic factors influence the change in work ability.

METHODS

A prospective cohort was analysed in this study. The primary outcome measure was the single question work ability score (0-10 points). Secondary outcome measures were quality and quantity of work, sick leave, functional outcome and radiographic resorption. Potential predictive factors (treatment method, age, sex, resorption of the calcific deposit, physical work load and work status) were tested in a statistical model. Follow-up was at six months and one year.

RESULTS

The study cohort consisted of 67 patients. The mean age was 49.6±6.4 years and 45 (67%) were females. Physical workload was categorized as light (58%), medium (24%) and heavy (18%). Work ability score improved from a mean of 6.1 ± 2.8 to 8.5 ± 2.0 points after 1 year. Treatment with minimal invasive treatment techniques was associated with a reduction in partial or full-time sick leave from 28% to 6%. The mean days of sick leave a month declined from 3.3 to 0.8 days. Functional disability was greater in patients with partial or full-time sick leave. The physical workload turned out to be the most important patient associated factor predicting change in work ability.

CONCLUSION

This study supports the hypothesis that RCCT has a significant impact on work ability and sick leave. Minimally invasive treatment resulted in a clinical relevant improvement in work ability score and decline in sick leave. Especially patients with medium and high physically demanding work for the shoulder benefit from minimally invasive treatment to improve their work ability.

LEVEL OF EVIDENCE: II, prospective cohort

INTRODUCTION

Shoulder problems are common in the Netherlands with an incidence in the primary care of around 19 per 1000 person-years.[1] Shoulder disorders represent various clinical diagnoses, varying from ICD (International Classification of Disease) code M75.0 – M75.5. Rotator cuff calcific tendinitis (RCCT) (M75.3) represents a specific subgroup of shoulder patients with calcific deposits in the tendons. The prevalence of RCCT is between 2.7% and 10% in patients without shoulder pain and up to 40% in symptomatic patients. Clinical symptoms are generally described as activity related pain similar to subacromial pain syndrome (SAPS).[2] The condition most frequently affects females (2:1 ratio) who are of working age.[3] The treatment initially consists of physiotherapy, analgesics and a subacromial infiltration with corticosteroids.[4,5] When primary treatment fails minimally invasive therapies like high-energy extracorporeal shockwave therapy (ESWT) and ultrasound guided needling (UGN) can be considered as an alternative for a surgical intervention. Multiple prospective studies and reviews have analysed the functional outcome after treatment for patients with RCCT.[6,7] However, little is known about the patients' work ability and sick leave before and after minimal invasive treatment for RCCT. Since this condition primarily affects people in their working age it is of importance to know what the treatment effect is on work ability and sick leave. These are questions that too often remain unanswered in clinical studies. Therefore the aim of this prospective study among RCCT patients was: (1) to examine the impact of RCCT on patients' self-reported work ability and sick leave, (2) to compare work ability and sick leave with shoulder function after minimally invasive treatment and (3) to assess which prognostic factors influence the change in work ability.

We hypothesize that RCCT has a significant impact on work ability and sick leave and that this is correlated with a greater functional disability. . With regard to the prognostic factors we hypothesize that work status (salaried or self-employed), work load and successful resorption of the deposit are the most important predictors for change in work ability.

MATERIAL AND METHODS

The study was designed as a prospective cohort study. The patients were included in a clinical randomized controlled trial comparing high-energy ESWT with UGN in patient with RCCT with the Constant score as main outcome measure.[8] For this study, both groups were analysed as a cohort to answer our research questions concerning work ability and sick leave. Patients were included between May 2014 and December 2017. The study was registered in the Dutch clinical trial registration (NL4304/NTR4448) and approved by both the medical ethics review committee (METC, number

NL44205.094.13) and the institutional review board (IRB number 2013.26, Spaarne Gasthuis, Hoofddorp, the Netherlands). Informed consent forms were signed by all participating patients.

STUDY POPULATION

Sixty-seven consecutive patients referred to the outpatient orthopaedic clinic, with clinical signs of non-traumatic anterograde-lateral sided shoulder pain when the arm was elevated, were included. Patients were eligible for inclusion when they reported to perform self-employed or salaried work. The medical history was taken and a clinical examination of the shoulder was performed. Standardized shoulder radiographs (anteroposterior, outlet-, axial-, and acromioclavicular view) and an ultrasound examination of the rotator cuff were obtained.

Inclusion criteria for participation in this study were: age > 18 years, clinical sign of subacromial pain syndrome, standardized radiographs showing a calcific deposit in the rotator cuff tendons with a diameter of at least 5mm in size, morphological type-I and type-II deposits corresponding to the classification of Gärtner[9] (type-I, sharply outlined and densely structured; type-II, sharply outlined and inhomogeneous or homogenous with no defined border), symptoms for more than four months, a completed and unsuccessful nonsurgical treatment program including non-steroidal anti-inflammatory drugs, physiotherapy, and a subacromial infiltration with a corticosteroid. Exclusion criteria were the following: unemployment, ultrasonic signs of a partial or full rotator cuff tendon, clinical or radiographic signs of a resorption phase, calcific deposits in multiple tendons of the rotator cuff, osteoarthritis of the glenohumeral or acromioclavicular joint, adhesive capsulitis, previous shoulder surgery, ESWT or UGN to the affected shoulder, instability of the shoulder, rheumatoid arthritis, neurological disorders or dysfunction of the upper limb and the inability to give informed consent.

INCLUSION

Eligible patients were provided with written and oral information about the trial and had at least one week to consider participation. Patients who were willing to participate were contacted by the coordinating investigator (J.L.) for further evaluation and inclusion.

TREATMENT PROCEDURES

The ESWT group was treated with 4 sessions of high-energy extracorporeal shockwave therapy with a 1 week interval between sessions. Each session consisted of 2000 piezoelectric pressure pulses at a frequency of 4 Hz with a total energy flux density of 0.351 mJ/mm^2 resulting in a total energy amount of 2808 mJ. The Piezowave2 system (Richard Wolf GmbH, Knittlingen, Germany) was used as ESWT device. The UGN group

was treated with a single procedure, performed in an outpatient clinical setting by 1 orthopaedic shoulder surgeon (A.v.N.) assisted by an experienced ultra-sonographer. A double-needle UGN technique with aspiration and lavage of the calcific deposit was used. After the UGN procedure one of the needles was placed in the subacromial bursa under ultrasound guidance and a mixture of 4cc bupivacaine 0.5% (Pfizer Inc., NY, USA) and 1cc depomedrol 40mg/ml (Pfizer Inc., NY, USA) was injected.

After treatment both groups followed a standardized physical therapy program including active and passive exercise mobilization techniques (concentric and eccentric rotator cuff strengthening exercises in combination with scapular stabilization) to increase power and range-of-motion and prevent muscular deficit or imbalance. Oral analgesics were administered for a maximum of 7 days postintervention when necessary. The use of additional over the counter analgesics was not systematically monitored.

WORK ABILITY AND SICK LEAVE

At baseline, all patients were asked if they were self-employed or had a salaried job. Subsequently, to assess the self-reported work ability, the single-item work ability score (WAS) question concerning the "current work ability compared with the lifetime best", with a score of 0 ("completely unable to work") to 10 ("work ability at its lifetime best") was used as the primary outcome of this study.[10–12] The designers of the method suggested the following categorization: poor (0-6 points), moderate (6-7), good (8-9), excellent (10).[13,14] The WAS is part of the Work Ability Index, a 7-part self-assessment questionnaire. The following aspects of the patients' working situation were also self-reported using the Work Ability Index: number of working hours per week; absenteeism from work in the last month due to shoulder complaints (yes/no; number of days) and whether the patient thought their shoulder complaints were work-related. Secondary work questions were related to: the amount of work (quantity), the quality of work and the experienced limitations during work due to their shoulder disorder. The participants' jobs were classified as light, medium or heavy, corresponding with the physical demands of their work for the shoulder. These physical demands were based on the evidence-based exposure criteria for the work-relatedness of SAPS by the Dutch Center for Occupational Diseases.[15] Two occupational health experts independently scored all jobs, and disagreements were resolved by discussion.

Six months and 1 year after treatment patients were asked to answer the same Work Ability Index. Based on the difference in pre- and posttreatment employment, working hours and work-ability scores, sick leave was classified as: full return to work (no experienced limitations), partial return to work (partial improvement of work-ability and working hours) and full-time sick leave.

CLINICAL AND RADIOGRAPHIC EVALUATIONS

The following patient characteristics were collected: gender, age (years), body mass index (BMI; kg/m^2), co-morbidities, duration of symptoms and hand dominance. At baseline and after 6 months and 1 year, the Constant Murley score (CMS)[16], the Disabilities of the Arm, Shoulder and Hand questionnaire (DASH)[17] and a visual analogue score, for average pain over a one week period, were used for the clinical assessment. The minimal clinical important difference (MCID) for the CMS (8.3 points), DASH (10.2 points) and VAS pain (2.1 points) were determined based on available literature.[18] The size, morphology and amount of resorption (full, more than 50%, less than 50%, no change) of the calcific deposit were analysed by standard shoulder radiographs at baseline and after 6 months. The length of the deposit was measured in terms of the maximum size of the longest axis in any direction. The radiographs were graded by another physician who was blinded for the allocated treatment.

STATISTICAL ANALYSIS

Statistical analyses were performed by using SPSS version 26.0 (IBM Corp. Armonk, NY, USA). Continuous data are presented as means with standard deviations (SD) or 95% confidence intervals (CI), and categorical variables as frequencies with accompanying proportions. Change of work related and clinical outcome between follow up moments was assessed with paired t-tests or McNemar tests or Wilcoxons Signed Ranks tests where appropriate. To identify predictive factors for change in WAS, all potential predictive factors (treatment method (ESWT vs UGN), age, sex, resorption (less or more than 50%), physical work lead (light vs medium/heavy) and work status (salaried vs self-employed) were initially tested by univariate linear regression analyses. In case of significant association (adjusted significance level of 0.10), these factors were entered in a multivariate regression model.

RESULTS

BASELINE CHARACTERISTICS

Between May 2014 and December 2017, a total of 67 patients were included (Table 1). One patient was lost to follow-up after 6 months. The mean age was 49.6±6.4 years and 45 (67%) were females. The mean duration of symptoms was 3.2±3.0 years and the supraspinatus was the most frequently (87%) affected tendon. Most patients were employees (78%). Physical workload was categorized as light (58%), medium (24%) and heavy (18%). Nineteen patients reported sick leave (28%) of which 9 patients (13%) were on permanent sick leave prior to treatment. Twenty-one percent of the patients stated that their shoulder symptoms were work-related.

Table 1. Demographics and baseline characteristics (n=67)

Sex, female, n (%)	45 (67)
Age, mean (SD)	49.6 (6.4)
BMI, mean (SD)	25.3 (3.7)
Nonmusculoskeletal comorbidities, n (%)	25 (37)
Duration complaints (years), mean (SD) Dominant side affected, n (%)	3.2 (3) 43 (64)
Size calcific deposit (mm), mean (SD)	15.7 (6.2)
Location, n (%)	
Supraspinatus	58 (87)
Infraspinatus	5 (8)
Subscapularis	4 (6)
Work status, n (%)	
Salaried	52 (78)
Self-employed	15 (22)
Physical workload, n (%)	
Light work Medium work Heavy work	39 (58) 16 (24) 12 (18)
Working hours a week (mean)	31.0 (10.7)
Self-reported work-relatedness of symptoms, n (%)	
Related Not related Don't know	14 (21) 17 (25) 36 (54)
CMS, mean (SD)	66.9 (12.1)
DASH, mean (SD)	37.4 (15.4)
VAS pain, mean (SD)	5.9 (1.6)

BMI = body mass index, CMS = Constant Murley Score, DASH = Disabilities of Arm, Shoulder and Hand score, SD = standard deviation, VAS = visual analogue score.

WORK RELATED AND CLINICAL OUTCOMES

Table 2 presents the work related outcomes of this study. Between 6 months and 1 year two patients lost their job because of non-shoulder related reasons. WAS improved from a mean score of 6.1 ± 2.8 to 8.5 ± 2.0 after one year. The change from baseline scores for work related factors improved significantly for all 4 subcategories: work ability, quality of work, quantity of work and functional limitations. Out of the 9 patients who reported to be on full time sick leave, 5 patient were still on full time sick leave after 6 months and 2 after 1 year follow-up. The percentage of patients reporting sick leave was reduced from 19 patients (28%) to 4 patient (6%) with a decline in sick leave from a mean of 3.3 days a month to 0.7 days a month.

Table 2. Work-related and clinical outcome

	Baseline (n=67)	6 months (n=66)	1 year (n=64)	*P*-value
Sick leave, n (%)				
None	48 (71.6)	54 (81.8)	60 (93.8)	-
Partial	10 (14.9)	7 (10.6)	2 (3.1)	-
Full time	9 (13.4)	5 (7.6)	2 (3.1)	-
Days of sick leave a month, mean (95%CI)	3.3 (1.8-4.8)	2.2 (0.9-3.6)	0.7 (0.0-1.5)	-
Self-reported work-ability questionnaire, mean (95%CI)				
Quality	7.7 (7.0-8.4)	8.3 (7.6-9.0)	9.2 (8.7-9.6)	<0.001
Quantity	7.7 (7.0-8.4)	8.3 (7.6-9.0)	9.1 (8.7-9.6)	<0.001
Work-ability	6.1 (5.5-6.8)	7.8 (7.1-8.4)	8.5 (8.0-9.0)	<0.001
Functional limitations	4.7 (3.9-4.4)	7.4 (6.7-8.1)	8.0 (7.3-8.6)	<0.001
Clinical outcome measures, mean (95%CI)				
CMS	66.9 (63.9-69.8)	81.3 (77.1-85.5)	87.2 (84.2-90.1)	<0.001
DASH	37.4 (33.6-41.1)	20.1 (15.7-24.4)	14.1 (10.5-17.6)	<0.001
VAS (pain)	5.9 (5.5-6.3)	3.6 (2.9-4.2)	3.0 (2.3-3.7)	<0.001

CMS = Constant Murley Score, DASH = Disabilities of Arm, Shoulder and Hand score, SD = standard deviation, VAS = visual analogue score.

Overall the Constant, DASH and VAS pain scores at final follow-up improved with clinical relevant differences in comparison to the baseline scores (Table 2). Radiographic resorption was complete in 53%, almost complete in 18%, minimally changed in 9% and unchanged in 20%. Patients that were with partial- or fulltime sick leave at baseline had significantly lower Constant (58.5 ± 9.4 vs 70.2 ± 11.4 p=<0.001) and DASH scores (48.5 ± 15.3 vs 32.9 ± 13.2 p=<0.001) when compared to the group without sick leave. After six months (p=0.05) and one year (p=0.006) this difference remained significant for the DASH score.

PROGNOSTIC VARIABLES FOR THE WORK ABILITY SCORE

Table 3 presents the results of the univariate analyses of each potentially prognostic factor for the change in WAS, as well as the final model. After 6 months and 1 year follow-up, only the physical work load, defined as light versus medium and heavy combined, was a predictive factor for a significant change in WAS (p=0.01) with a β-coefficient of 1.43 (95% CI 0.08; 2.79) in favour of the high workload group. All other factors were not significantly associated with the change in WAS. Figure 1 graphically shows, that the change from baseline scores for WAS in the light workload group (1.0 after 6 months and 1.8 after 1 year), were significantly lower than the scores in the medium physical workload group (2.1 after 6 months and 3.2 after 1 year) and high physical workload group (2.9 after 6 months and 3.5 after 1 year).

Table 3. Prognostic variables for work ability

	6 months		1 year	
	β-coefficient (95%CI)	*P*-value	β-coefficient (95%CI)	*P*-value
Univariate				
Age	-0.07 (-0.17; 0.04)	0.20	-0.04 (-0.14; 0.06)	0.41
Gender	0.43 (-1.02; 1.89)	0.56	0.53 (-0.79; 1.84)	0.43
ESWT versus UGN	0.09 (-1.28; 1.47)	0.90	0.74 (-0.50; 1.99)	0.24
Resorption of the calcific deposit	0.64 (-0.87; 2.15)	0.40	1.08 (-0.27; 2.43)	0.11
Workload (light versus medium/heavy)	1.43 (0.08; 2.79)	**0.04**	1.55 (0.33; 2.76)	**0.01**
Workstatus (self-employed versus salaried)	0.31 (-1.53; 2.15)	0.74	0.54 (-0.92; 2.00)	0.46
Final model				
Workload (light versus medium/heavy)	1.43 (0.08; 2.79)	**0.04**	1.55 (0.33; 2.76)	**0.01**

ESWT = high-energy extracorporeal shockwave therapy, UGN = ultrasound-guided needling

DISCUSSION

The principal finding of this study is that RCCT has a significant impact on patients' work ability and sick leave. Treatment with minimally invasive treatment techniques was associated with a reduction in partial or full-time sick leave from 28% to 6%. The mean days of sick leave a month declined from 3.3 to 0.8 days. WAS improved from a mean score of 6.1 ± 2.8 to 8.5 ± 2.0 after 1 year. The physical workload turned out to be the most important patient associated factor predicting change in WAS. Especially the patients with medium to high physically demanding work improved the most. This is important information for the clinicians when discussing treatment options with their patients and it might encourage patients with high physical demanding work to choose for minimal invasive therapies.

Not much is known about the impact of RCCT on work ability and sick leave. Since this condition primarily affects patients of working age, information regarding these outcome measures is of great importance for both clinicians and patients. However, none of the 16 randomized controlled clinical trials analysed in a previous meta-analysis[7], discussed work related outcome measures. While data on RCCT is scarce, multiple studies have been published on work related risk factors for SAPS.[15,19–21] For work-related specific shoulder disorders, the biomechanical factor seems to be the most important but psychosocial factor might also contribute. Van Rijn et al. concluded in their systematic review that forceful exertion in work, highly repetitive work, awkward postures and high psychosocial job demand are associated with the occurrence of shoulder disorders.[19] This was confirmed by a more recent meta-analysis by van der Molen et. al. stating that there is moderate GRADE level evidence for a two-fold chance of developing SAPS when being exposed to arm elevation and shoulder load during work.[15]

In this study the physical demands were classified based on the evidence-based exposure criteria for the work-relatedness of SAPS by the Dutch Center for Occupational Diseases. We found that a higher percentage of patients in medium and high physical demand jobs were on (partial) sick leave at baseline and reported a significant lower WAS with low functional performance scores. The present data supports the hypothesis that especially patient with medium or high physically demanding work for the shoulder might benefit from minimally invasive treatment. The other factors that were tested in our predictive model were not significantly associated with the change in WAS. Engebretsen et al. found, in their RCT comparing radial ESWT and supervised exercise in SAPS patients, that 12 or fewer years of education is the most consistent predicting factor for absenteeism and low functional outcome scores after one year.[20] While they

did not report the workload of these patients, there is probably a strong relationship between a lower education level and performance of higher physically demanding work. Seil et al. reported no difference in return to work between difference physical work load categories in a retrospective cohort study analysing surgical outcomes for RCCT.[22] They concluded that the only difference in time to return to work was due to the presence of disability claims.

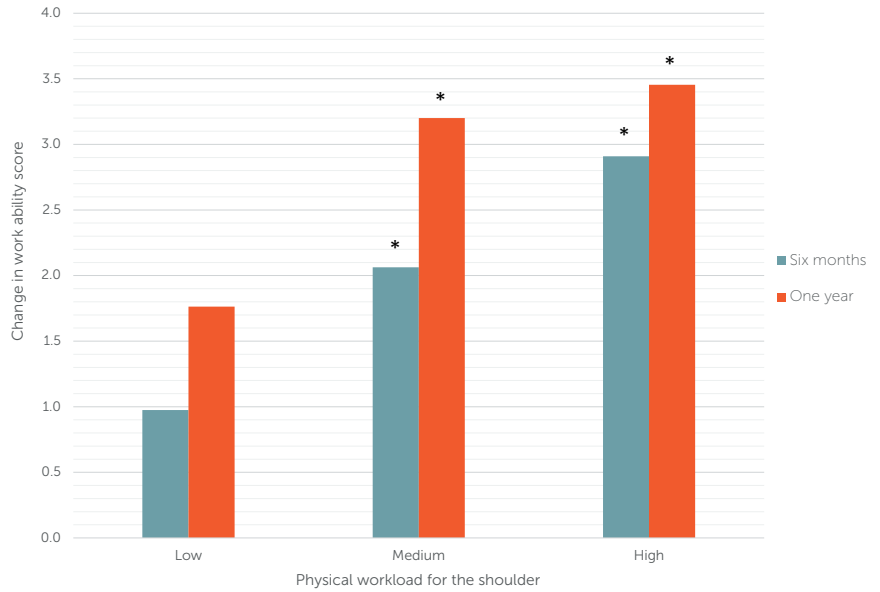

Figure 1. Difference in change from baseline work ability score after 6 months and 1 year, categorized in three physical workload categories. * = *P*-value <.001 in comparison to category 'low'.

A strength of this study is that it contains 1 year follow-up data on both validated work-related outcome measures and clinical outcome measures. Moreover, the patients worked in a wide variety of occupational settings, which makes the results more generalisable than a selective sample of workers. While the numbers in this study were relatively small, data from 95% of the patients were available at one year follow-up and differences statistically tested.

Work related outcome measures should be included more frequently in orthopaedic surgery research, as these parameters are relevant in the treatment of working-age patients and are frequently not reported in clinical trials. The use of a single-item

measure has been validated in previous studies and has numerous advantages: it is short in length, requires less time to complete and is more likely to be completed by the employee in comparison to multiple-item questionnaires.[23–25] Furthermore it has been shown not to decrease the validity of the work ability information collected in comparison to multiple-item questionnaires.[25]

Self-reported variables such as self-reported likelihood of the work-relatedness of the musculoskeletal disease, rating of the expected effectiveness of work-related interventions, presence of support from supervisors, and presence of modifiable job duties can play an important role in the assessment of work related outcome measures. Furthermore, it would be interesting to validate if patient with high physical demanding jobs for the shoulder benefit more from minimal invasive treatment options than patients with low physical demanding jobs.

LIMITATIONS

One of the limitations of this study is that it did not include a control group and therefore cannot compare the outcome with patients receiving no treatment. Furthermore, since the study was primarily powered to look for a difference in the clinical Constant score, it might have been underpowered for the outcome measure work ability and sick leave. Finally, since this study focused specifically on RCCT, statements made in this study are not generalizable to other conditions that cause subacromial pain syndrome.

CONCLUSION

This study supports the hypothesis that rotator cuff calcific tendinitis has a significant impact on work ability and sick leave. Minimally invasive treatment resulted in a clinical relevant improvement in work ability score and decline in sick leave. Especially patients with medium and high physically demanding work for the shoulder benefit from minimal invasive treatment to improve their work ability.

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Quantifying the minimal and substantial clinical benefit of the Constant-Murley score and the Disabilities of the Arm, Shoulder and Hand score in patients with calcific tendinitis of the rotator cuff

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ABSTRACT

BACKGROUND

To aid the interpretation of clinical outcome scores it is important to determine the measurement properties. The aim of this study was to establish the minimal clinical important difference (MCID) and substantial clinical benefit (SCB) for the Constant-Murley score (CMS) and the Disabilities of the Arm, Shoulder and Hand score in patients with long-lasting rotator cuff calcific tendinitis treated with high-energy extracorporeal shockwave therapy and ultrasound guided needling. The secondary purpose was to assess the responsiveness of both questionnaires and to identify variables associated with achieving the MCID and SCB.

METHODS

A prospective cohort of 80 patients with rotator cuff calcific tendinitis was analyzed. Two anchor-based methods were used to calculate the MCID and SCB. Effect sizes and standardized response means were calculated to assess the responsiveness. Additional univariate logistic regression analyses were performed to identify factors associated with the achievement of the MCID and SCB.

RESULTS

For the Constant-Murley score, we found an MCID and SCB of 9.8 and 19.9, respectively, based on the mean change method and 5.5 and 10.5, respectively, based on receiver operating characteristic analysis. For the Disabilities of the Arm, Shoulder and Hand score, we found a MCID and SCB of - 8.2 and - 19.6, with the former and - 11.7 and - 12.5, respectively, with the latter. The responsiveness of both outcome measures was good, with large effect sizes and standardized response means. The radiographic resorption after 6 weeks and 6 months appeared to be the most important positive predictor for achieving the MCID and SCB after 6 months.

CONCLUSION

This study established the MCID, SCB and responsiveness for patients with long-lasting rotator cuff calcific tendinitis who were treated with minimal invasive treatment options. With this information, physicians can distinguish between a statistically significant difference and a clinical relevant benefit. Successful radiographic resorption after 6 weeks and 6 months was associated with achieving clinically significant improvement after treatment.

INTRODUCTION

Calcific tendinitis of the rotator cuff is a painful condition characterized by the deposition of hydroxyapatite crystals in the rotator cuff.[1] It is a frequent cause of subacromial pain, and patients experience overhead activity-related pain.[2] Although the condition might be self-limiting in the majority of cases, symptoms can be severe and prolonged. In the past few years, numerous clinical trials and reviews have been published on the minimally invasive treatment of this condition.[3,4] In general, these studies have drawn their conclusion based on changes in function, pain, and general health, measured by clinical outcome scores or patient-reported outcome measures. The term 'statistical significance' is frequently used to describe a change in outcome of these clinical scores, which does not necessarily mean a relevant benefit for the patient. For example, even small changes can be statistically significant in large clinical trials while the real question is whether these changes are clinically relevant for the patient. Therefore, there is an increased need to establish clinical relevance within these outcome measures. The outcome measures should have clearly defined measurement properties such as the validity, reliability and responsiveness. Responsiveness is defined as the ability of an instrument to detect change over time in the construct to be measured.[5,6] To aid the interpretation of clinical outcome score findings, researchers developed the concept of minimal clinical important difference (MCID), defined as the smallest change in score in the domain of interest which the patients perceive as important.[7] The MCID can help interpret the magnitude of effects of interventions as well as help researchers to determine a more accurate sample size in future studies. An alternative clinically significant measure is the substantial clinical benefit (SCB), defined as the change in outcome associated with patient perception of a large meaningful improvement.[8]

The distribution- and anchor-based methods are 2 common approaches to calculate the MCID.[9] The distribution-based method uses statistical analysis to determine minimal clinically important changes that occur beyond expected measurement error or variance. The anchor-based approach uses 'anchor' questions that aim to evaluate domains such as pain and function to classify changes in clinical outcome scores.

Although systematic reviews addressing the MCID in shoulder outcome scores are available, they report a wide range of MCIDs and are investigated in a wide range of shoulder pathology.[10,11] Even fewer data is available on the SCB values for frequently used shoulder outcome scores.

The main purpose of this study was therefore to establish the MCID and SCB for the Constant-Murley score (CMS) and the Disabilities of the Arm, Shoulder and Hand (DASH)

score in patients with long-lasting calcific tendinitis of the rotator cuff treated with high-energy extracorporeal shockwave therapy or ultrasound guided needling. The secondary purpose was to assess the responsiveness of both questionnaires and to identify variables associated with achieving the MCID and SCB.

MATERIALS AND METHODS

STUDY POPULATION

The study population consisted of patients included in a randomized clinical trial evaluating the effect of high-energy shockwave therapy and ultrasound-guided needling for calcific tendinitis of the rotator cuff.[12] The inclusion criteria for this study were : age ≥ 18 years; clinical signs of subacromial pain syndrome for more > 4 months; standardized radiographs showing a calcific deposit with a diameter of at ≥ 5mm in size in the rotator cuff; a completed and unsuccessful nonsurgical treatment program including nonsteroidal anti-inflammatory drugs, physiotherapy (concentric and eccentric rotator cuff strengthening exercises in combination with scapular stabilization) and a subacromial infiltration with a corticosteroid.

The study was registered in the Netherlands Trial Register (NL4304/NTR4448). and approved by both the medical ethics review committee (METC, number NL44205.094.13) and the institutional review board (IRB number 2013.26, Spaarne Gasthuis, Hoofddorp, the Netherlands). Informed consent forms were signed by all participating patients.

OUTCOME MEASURES

The CMS and a region-specific DASH score were available for all patients at baseline and after 6 months.[13,14] Outcomes at baseline and 6 months follow up were used for MCID and SCB calculation. For this purpose, an anchor question (7-point global transition rating scale) concerning shoulder complaints was added at 6 months' follow up. Additional baseline characteristics such as age, sex, workload, dominance, and treatment, as well as radiographic parameters (after 6 weeks and 6 months), were also assessed.

CONSTANT-MURLEY SCORE

The CMS score is a standardized, simple clinical method of assessing shoulder function and has a maximum score of 100 points, with both subjective (35 points) and objective (65 points) components.[13] The subjective parameters assess the degree of pain perception (15 points) and the ability to perform the normal tasks of daily living in both activity- and position-related terms (20 points). The objective parameters include

testing of active range of motion (40 points) and muscle strength (25 points). The CMS has established measurement properties.[15,16]

DASH SCORE

The Disabilities of the Arm, Shoulder and Hand (DASH) Outcome Measure is a 30-item, self-report questionnaire designed to measure physical function and symptoms in patients with various musculoskeletal disorders of the upper limb.[14] It has been validated in the Dutch language.[17] The DASH has acceptable measurement properties[18,19]. The score ranges from 0 (no disabilities) to 100 (most severe disabilities) and is considered incomplete in case more than 3 items (10%) are missing. [18]

ANCHOR QUESTION

As external anchor for this study a 7-point global rating of change scale (GRC) was used. Patients were asked a single question to indicate how their symptoms had changed since baseline:[7,20] "Since the start of the treatment, in what way would you describe the change in symptoms related to your shoulder condition?". The answer options were (1) much improved, (2) improved, (3) slightly improved, (4) unchanged, (5) slightly worse, (6) worse, and (7) much worse. The "slightly improved" and "improved" categories were used to identify patients who experienced minimally important and substantial improvement, respectively.

STATISTICAL ANALYSIS

Statistical analyses were performed by use of SPSS (version 26.0; IBM, Armonk, NY). Summary statistics were used to describe patients' clinical characteristics and score distributions of the CMS and DASH score. Continuous variables were presented as means with standard deviations. Categorical variables were presented as frequencies with accompanying percentages. To assess the suitability of the anchors, Spearman rank correlation coefficients were calculated between the change from baseline scores and the anchor. If the Spearman rank correlation coefficient was >0.50, the anchor was considered suitable.[21] Because the number of patients who reported a decline in shoulder function was small (n = 6), assessment of responsiveness and estimation of the MCID and SCB were only performed for the clinically improved patients.

RESPONSIVENESS

For each transition category of the GRC, effect sizes and standardized response means were calculated to assess the responsiveness. The effect size and standardized response mean were calculated by dividing the mean change-from-baseline score at 6 months' follow-up by the standard deviation of the baseline score and by the standard deviation of the change-from-baseline score, respectively.[22,23] Hypotheses for these variables

were formulated for both outcome measures according to the definitions of Cohen, with absolute values being at least small (0.2), medium (0.5) and large (0.8) for patients reporting slight improvement, improvement and much improvement, respectively.[24]

MCID AND SCB ESTIMATION

To calculate the SCB and MCID of the DASH score and CMS, 2 anchor-based methods were applied, using the GRC as anchor. The MCID and SCB were calculated as the mean change score (95% confidence interval [CI]) of both outcomes for those patients who reported being slightly improved and improved on the GRC scale, respectively.[25] Next, the MCID and the SCB were estimated by using the receiver operating characteristic cutoff points of DASH score and the CMS change score. The Youden index was used to assess the optimal cutoff points with the smallest number of misclassified patients for each outcome measure. Additional bootstrapping (statistical resampling) procedures (with 1000 bootstrap samples) were performed to estimate the standard error of the retrieved cutoff values and calculate the 95% 95%CI.[26]

The area under the curve was calculated as measure of accuracy. It represents the probability that patients with and without minimal or substantial improvement are correctly classified (according to the external criterion). This area ranges from 0.5 (accuracy based only on chance) to 1.0 (perfect accuracy). An area under the curve > 0.7 (with a 95% CI lower bound ≥ 0.5) was considered a good discriminator.[27] The external criterion for SCB was defined as the merged GRC categories of improved and much improved. For the minimal important change, the category of slightly improved was added.

FACTORS ASSOCIATED WITH MCID AND SCB

Additional univariate logistic regression analyses were performed to identify factors associated with the achievement of the MCID and SCB of the CMS and DASH score derived from the mean change analysis. Odds ratios and 95% CIs were calculated. $P < .05$ was considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS

Between May 2014 and December 2017, a total of 82 patients were randomized and treated with either high-energy extracorporeal shockwave therapy or ultrasound-guided needling. After 6 months, 80 patients (97.5%) were available for follow-up. The mean age was 52 ± 9 years and 51 of patients (64%) were women. Calcifications were predominantly located in the supraspinatus muscle (Table 1).

Table 1. Patient and clinical characteristics (n = 80)

Age (years), mean (SD)	52.1 (9.0)
Gender, n (%)	
Male	29 (36)
Female	51(64)
Dominant arm treated, n (%)	51 (64)
Workload, n (%)	
Light	39 (59)
Medium	16 (24)
Heavy	11 (17)
Unemployed	14
Gartner, n (%)	
I	34 (42)
II	46 (58)
Treatment, n(%)	
H-ESWT	40 (50)
UGN	40 (50)
Location	
Supraspinatus	69 (86)
Infraspinatus	7 (9)
Subscapularis	4 (5)
Magnitude at baseline (mm), mean (SD)	15.7 (5.2)
Resorption at 6 weeks, n (%)	52 (65)
Resorption at 6 months, n (%)	61 (76)

H-ESWT = high-energy extracorporeal shockwave therapy, mm = millimetre, SD = standard deviation, UGN = ultrasound-guided needling

CLINICAL OUTCOME MEASURES

The overall mean CMS score at baseline was 67.3 ± 12.1 with an improvement after 6 months to 80.5 ± 17.3. The DASH score at baseline was 36.6 ± 15.9 which declined after 6 months to 20.9 ± 18.5. The subgroup scores for each anchor category can be found in table 2.

ANCHOR

Among 82 included patients, 80 patients filled in the GRC scale after 6 months. Using the GRC scale, 6 patients (8%) reported a deterioration in function (much, n = 2; considerable, n = 1; and slight, n=3), 13 (16%) reported no changed in function, and 61 (76%) reported improvement (Table 2).

CORRELATION OF CHANGE IN CLINICAL OUTCOME WITH THE ANCHOR

Both outcomes were significantly correlated with the anchor, with values of 0.73 and -0.73, with the absolute values of both coefficients exceeding the threshold of 0.50, indicating that the GRC scale was suitable as an anchor.

RESPONSIVENESS

Effect sizes and standardized response means of subgroups formed by the transition GRC scale are presented in table 2. Both variables increased with increased reported improvement on the GRC scale.

All effect sizes and standardized response means of all transition categories met the aforementioned criteria of Cohen.[24] The effect sizes and standardized response means of patients who did not experience a clinical improvement did not exceed 0.2 (Table 3).

MCID AND SCB ESTIMATION

The MCID and SCB values of the CMS and DASH score based on both methods are presented in table 3. The mean change method generally revealed higher MCID values than the receiver operating characteristic analysis.

FACTORS ASSOCIATED WITH MCID AND SCB

Radiographic resorption of the calcific deposit after 6 weeks (CMS & DASH score) and 6 months (DASH score) was associated with the achievement of the MCID. For the SCB, resorption after 6 weeks (CMS) and 6 months (DASH score) was associated with achieving the SCB. Detailed results are reported in Table 4 & 5.

Table 2. Responsiveness of CMS and DASH score: effect sizes and standardized response means

	Baseline Mean (SD)	6 months Mean (SD)	Change Mean (95%CI)	ES	SRM
CMS					
No change (n=13)	67.1 (16.1)	66.8 (14.4)	-0.3 (-4.7; 4.0)	0.02	0.04
Slightly improved (n=19)	68.0(11.8)	77.8 (11.4)	9.8 (3.7; 15.9)	0.83	0.80
Improved (n=15)	66.0 (10.5)	85.9 (10.5)	19.9 (13.6: 26.3)	1.90	1.75
Much improved (n=27)	69.0 (11.3)	93.3 (6.4)	24.3 (19.3; 29.4)	2.15	1.91
DASH					
No change (n=13)	34.1 (19.1)	32.6 (19.4)	-1.7 (-8.0; 4.6)	-0.09	-0.17
Slightly improved (n=19)	36.1 (15.0)	27.9 (12.5)	-8.2 (-14.7; -7.5)	-0.55	-0.61
Improved (n=15)	39.0 (15.5)	19.4 (11.7)	-19.6 (-26.3; -12.8)	-1.26	-1,61
Much improved (n=27)	35.3 (14.1)	4.7 (3.9)	-30.7 (-36.2; -25.1)	-2.18	-2.19

CI = confidence interval, CMS = Constant-Murley score, DASH = Disability of the Arm Shoulder and Hand score, ES = effect sizes, SD = standard deviation, SRM = standardized response means.

Table 3. Results of MCID and SCB calculations based on mean change method and cutoff point of the receiver operating characteristic (ROC) curve.

		Mean change	ROC (95% CI)	AUC (95% CI)	TP (%)	TN (%)
CMS						
	MCID	9.8 (3.7; 15.9)	5.5 (1.1; 9.9)	0.94 (0.89; 0.99)	87%	89%
	SCB	19.9 (13.6: 26.3)	10.5 (7.8; 13.2)	0.89 (0.81; 0.97)	86%	87%
DASH						
	MCID	-8.2 (-14.7; -7.5)	-11.7 (-19.1; -4.4)	0.88 (0.80; 0.96)	74%	94%
	SCB	-19.6 (-26.3; -12.8)	-12.5 (-18,8; -6,2)	0.89 (0.81; 0.96)	88%	78%

AUC = area under the curve, CI = confidence interval, CMS = Constant-Murley score, DASH = Disability of the Arm Shoulder and Hand score, MCID = minimal clinical important difference, SCB = substantial clinical benefit, TN = true negative, TP = true positive.

Table 4. Constant-Murley score: univariate factors associated with minimal improvement/substantial improvement; factors associated with achievement of MCID/SCB based on the mean change.

	OR_{MCID}	*P*-value	OR_{SCB}	*P*-value
Age	0.96 (0.91; 1.01)	0.12	1.00 (0.95; 1.06)	0.95
Gender				
female	ref		ref	
male	0.65 (0.26; 1.64)	0.36	0.54 (0.19; 1.49)	0.23
Workload				
Light	ref		ref	
Middle	1.50 (0.45; 4.99)	0.51	1.68 (0.49; 5.82)	0.41
Heavy	2.40 (0.55; 10.46)	0.24	3.36 (0.84; 13.48)	0.09
Resorption 6 weeks	3.40 (1.30.; 8.89)	**0.01**	3.12 (1.02; 9.50)	**0.046**
Resorption 6 months	2.64 (0.91; 7.66)	0.07	3.23 (0.85; 12.30)	0.09
Gärtner classification				
I	ref		ref	
II	0.76 (0.31; 1.87)	0.56	0.64 (0.25; 1.64)	0.35
Treatment				
H-ESWT	ref		ref	
UGN	1.00 (0.41; 2.41)	1.00	1.00 (0.39; 2.55)	1.00
Size of calcific deposit at baseline	0.99 (0.91; 1.08)	0.79	0.96 (0.87; 1.06)	0.34
Dominant arm treated	0.79 (0.32; 2.00)	0.62	1.43 (0.53; 3.88)	0.48

CMS = Constant-Murley score, H-ESWT = high-energy extracorporeal shockwave therapy, MCID = minimal clinical important difference, OR = odds ratio, ref = reference value, SCB = substantial clinical benefit. UGN = ultrasound-guided needling

Table 5. DASH: univariate factors associated with minimal improvement/substantial improvement; factors associated with achievement of MCID/SCB based on the mean change

	OR_{MCID}	*P*-value	OR_{SCB}	*P*-value
Age	0.99 (0.94; 1.04)	0.66	0.96 (0.91; 1.01)	0.11
Gender				
female	ref		ref	
male	0.44 (0.17; 1.18)	0.10	0.70 (0.27; 1.84)	0.47
Workload				
Light	ref		ref	
Middle	4.87 (0.97; 24.44)	0.05	1.20 (0.36; 4.03)	0.41
Heavy	6.26 (0.72; 54.41)	0.10	8.00 (1.48; 43.2)	**0.02**

Table 5. Continued.

	OR_{MCID}	*P*-value	OR_{SCB}	*P*-value
Resorption 6 weeks	3.39 (1.26.; 9.11)	**0.02**	2.58 (0.94; 7.11)	0.07
Resorption 6 months	5.42 (1.83; 16.05)	**0.002**	4.64 (1.23; 17.51)	**0.02**
Gärtner classification				
I	Ref		ref	
II	0.68 (0.26; 1.79)	0.43	1.18 (0.47; 1.96)	0.73
Treatment				
H-ESWT	ref		ref	
UGN	1.32 (0.51; 3.41)	0.57	0.46 (0.18; 1.15)	0.10
Size of calcific deposits at baseline	0.98 (0.88; 1.05)	0.34	1.01 (0.93; 1.11)	0.75
Dominant arm treated	0.91 (0.34; 2.43)	0.85	1.06 (0.42; 2.70)	0.91

DASH = Disability of the Arm Shoulder and Hand score, H-ESWT = high-energy extracorporeal shockwave therapy, MCID = minimal clinical important difference, OR = odds ratio, ref = reference value, SCB = substantial clinical benefit. UGN = ultrasound-guided needling

DISCUSSION

The primary purpose of this study was to assess the MCID and SCB of 2 frequently used shoulder metrics in a population of patients with rotator cuff calcific tendinitis. For the CMS, we found a MCID and SCB of 9.8 and 19.9, respectively, based on the mean change method and 5.5 and 10.5, respectively, based on receiver operating characteristic analysis. For the DASH score, we found a MCID and SCB of -8.2 and -19.6, respectively, with the former and -11.7 and -12.5, respectively, with the latter. The responsiveness of both outcome measures was good, with effect sizes and standardized response means that were larger than required in patients experiencing improvement and were small (<0.2) in the unresponsive group. All area-under-the curve calculations exceeded 0.70 with a lower bound of the 95% CI that was higher than 0.50, indicating adequate responsiveness (Table 3). The radiographic resorption after 6 weeks and 6 months appeared to be the most important positive predictor for achieving the MCID and SCB after 6 months. Assessment of the MCID and SCB is of value to determine whether a statistically significant clinical outcome is also clinically relevant for a specific patient category. It can also help researchers when calculating the sample size for future clinical studies.

An explanation for why the responsiveness was so high could be that the study population was very homogeneous, with small standard deviations across all

outcome measurements. The large treatment effect in both groups could also have contributed.

In the past 5 years, numerous articles have been published on the clinical relevance of shoulder outcome scores.[28–32] Recent reviews have discussed that the MCID often varies widely.[10,11,33] The range of reported MCID was broad: 3 to 36 (median estimate, 8.3) for the CMS and -4.5 to 25.4 (median estimate, 10.2) for the DASH score. The patient categories, treatment techniques and methodological protocols differed substantially among the included studies.

It is important to realize that the MCID and SCB do not have fixed values. They are influenced by numerous variables such as the baseline score, patient category, treatment effect, anchor question and definition of minimal clinical difference.[34,35] It is therefore important to calculate the MCID for different patient categories and for different shoulder metrics. Previous attempts to establish a clear relationship between these variables and the MCID values were not successful.[10] In this study, an anchor based approach was chosen with 2 different statistical methods to calculate the MCID and SCB. The most accurate way to calculate the MCID remains unclear.[35,36]

This study found that radiographic signs of resorption after 6 weeks and 6 months were the only variables that were associated with a higher chance of reaching clinical important outcomes. This finding is of great importance for physicians treating patients with rotator cuff calcific tendinitis and helps deal with the patients' expectation management after treatment.

When one is interpreting the MCID and SCB in clinical research, it is important to realize that an outcome measure also has a smallest detectable change (or measurement error), defined as the smallest change in score that one can detect with an instrument. For the purpose of individual monitoring of patients, the smallest detectable change should be smaller than the MCID to be able to distinguish a minimal clinically relevant difference from the measurement error.[37] For the DASH, the reported smallest detectable change in the literature ranges between 7.9 and 16.3, and for the CMS measurement errors as high as 17 and 23 has been reported.[19,38–40] Although these calculations were performed for different patient categories after different types of treatment, it remains important to differentiate the smallest detectable change from the MCID. In light of our own findings, the MCID values for the DASH score (8.2) and CMS (9.8) might have been clinically relevant for the patients, but it is possible that they cannot be distinguished from the measurement error. Finally, although the MCID might be exceeded by the smallest detectable change on an individual level, it could still be used in larger clinical trials.[37]

The results of this study must be interpreted in light of several limitations. Firstly, the of GRC sclaes has been questioned because such scales are seldom thoroughly investigated in terms of validity and reliability. Whether patients are able to recall their previous status has been debated. The scales have shown to be influenced by recent events and the patient's status, as well as the change over time. Owing to these factors, the GCR scale might be correlated more to the post-treatment score than the change-from-baseline score. However, this was not the case in our study. Second, there is no established external criterion for determining the MCID or SCB. In this study, a 7-point global assessment scale was used, but other authors used a 9- of 11-point GCR scale or a different scale, such as the visual analog scale. Finally, the smallest detectable change was not determined in this study.

CONCLUSION

This study established the MCID, SCB and responsiveness for patients with long-lasting rotator cuff calcific tendinitis who were treated with minimally invasive treatment options. With this information, physicians can distinguish between a statistically significant difference and a clinically relevant benefit. Successful radiographic resorption after 6 weeks and 6 months was associated with achieving clinically significant improvement after treatment.

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9

General discussion, clinical implications, and future perspective

DISCUSSION

Rotator cuff calcific tendinitis (RCCT) is a condition that is characterized by the deposition of hydroxyapatite crystals in the rotator cuff tendons and it can have a considerable impact on a patient's everyday life. Patients experience activity-related pain with abduction that is similar to the combination of symptoms described as subacromial pain syndrome (SAPS). While it might be self-limiting in most cases, symptoms can be severe and prolonged. In **Chapter 1**, a comprehensive introduction to RCCT is provided. The most advocated pathophysiological theory divides the disease in three stages: the pre-calcific stage, the calcific stage (with a formative, resting and resorptive phase) and a post-calcific stage.[1] The objective of treating RCCT is to reduce pain, regain shoulder function, prevent stiffness and stimulate resorption by improving the condition of the affected tendon and surrounding tissues. The main objective of this thesis was to improve the care for patients with RCCT, with an emphasis on the effectiveness of extracorporeal shockwave therapy and ultrasound-guided needling. Different methodologies were used in this thesis: systematic reviews with and without meta-analysis, a retrospective cohort study, a web-based interobserver study and studies based on prospectively collected data from a randomized controlled trial. The clinical findings and implications of these studies are discussed below. Finally, a treatment algorithm to support the treatment of RCCT in daily practice is presented, and recommendations for future studies are made.

PART 1. EPIDEMIOLOGICAL AND RADIOLOGICAL EVALUATION OF CALCIFIC TENDINITIS OF THE ROTATOR CUFF

Who is at risk?

In **Chapter 2** the clinical and radiological data of 1.219 adults with, and without SAPS were retrospectively reviewed. The prevalence was 7.8% in 734 asymptomatic patients and 42.5% in 485 symptomatic patients with SAPS. The study shows that the results of epidemiological studies for RCCT are very dependent on the targeted population. In the most frequently cited historical study from Bosworth et al.[2] there was an overrepresentation of young female clerks and typists (90% aged < 40), when compared to a population with more equal gender distribution, and a mean age of 55 years in our study. As the age, and the percentage of females in the targeted population increases, the prevalence of calcific deposits seems to increase. This was supported by the statistical findings in this study; age between 30-60 years, subacromial pain, and female gender, were three variables significantly associated with the presence of calcific deposits. Endocrine factors, such as diabetes and thyroid diseases, have also been identified as risk factors for RCCT.[3] Finally, occupational health factors are known to be

a risk factor for the development of shoulder complaints. This topic will be discussed in an upcoming paragraph titled 'occupational health factors'.

With regard to the radiographic characteristics, there was a significant difference in size of the calcific deposit between patients with, and without shoulder pain. The smaller calcifications, with a mean size of <0.5 cm, were most frequently found in the asymptomatic group. This may validate a more conservative approach towards these smaller calcifications. At the same time, all larger calcifications with a mean size of >1.5 cm, were found in the symptomatic group. So while not all calcifications are known to cause symptoms, larger calcifications are more likely to result in a painful shoulder than smaller calcifications. However, no reliable prediction can be made when, and which, calcific deposit will cause symptoms in the future. Bosworth[2] estimated that 30% of patients will eventually experience symptoms and that the likelihood of experiencing symptoms increases according to the size of the deposit.

CLINICAL IMPLICATIONS

- Women aged 30 to 60 years, with clinical signs of subacromial pain and a calcific deposit of >1.5 cm, have the highest prevalence of symptomatic rotator cuff calcific tendinitis.
- Calcific deposits in the rotator cuff frequently develop in asymptomatic patients. The presence of calcific deposits does not require immediate treatment whena patient does not have clinical symptoms.

Imaging and classifications

All common imaging techniques can be used to analyse calcific deposits in the rotator cuff, but radiographs and ultrasound are usually sufficient to diagnose and characterize calcific deposits. In **Chapter 2**, it was shown that ultrasound was able to more accurately localize the deposits and detect additional small, segmented calcifications in comparison to radiography. However, the clinical relevance of these small and dystrophic calcifications is likely to be small. The majority of calcifications are reported to be localized in the supraspinatus tendon, followed by the infraspinatus and the subscapularis tendon. Mochizuki et al. showed in their anatomical study that the supraspinatus insertion on the greater tuberosity is much smaller than previously believed[4], it could therefore be that the prevalence of infraspinatus deposits is underestimated.

The sonographic and radiographic appearance of a calcific deposit can vary according to the stage of the condition. Different treatment options are advised depending on the

stage of the disease. Classifying the radiographic appearance could guide treatment by combining this information with clinical parameters. Since the reliability of radiographic classification is known to be limited, an attempt was made in **Chapter 3** to improve the interobserver reliability of two frequently used radiographic classifications by reducing the measurement error. Unfortunately, this did not improve the outcome of the interobserver analysis. It appeared that observers couldn't agree on vague terms such as 'ill-defined, cloudy, inhomogeneous and localised or diffuse'. The intraobserver agreement was acceptable, and observers could agree on the radiographic location of the deposits in the rotator cuff. This study confirmed that the radiographic classification systems as developed by Gärtner and Molé lack interobserver agreement, and are not reliable enough to classify RCCT.

So, are there other classification that can serve this purpose? Maier et al.[5] tried to improve the reliability of the Gartner classification, by combining it with computed tomography, but concluded it did not make a difference. Another CT study stated that the attenuation level was correlated with the density of the deposit, which may have clinical implications for further needling or arthroscopic treatment.[6] Farin et al.[7,8] developed a widely used classification based on ultrasound characteristics. The calcifications were categorized according to their acoustic shadow. Remarkably, they state that this classification was not suitable to identify the resorption phase and that plain radiographs should be used for this purpose. However, Ogon et al.[9] did find the absence of sonographic sound extinction to be a positive prognostic factor in a more recent study. Finally, le Goff and Chiou[10,11] assessed the role of power Doppler findings. They stated that a color/power Doppler signal was significantly associated with symptoms and that none of the patients in the asymptomatic group showed a Doppler signal. So, while it is stated in this thesis that it is important to distinguish the resorption phase from the acute and chronic phase, there does not seem to be a validated individual radiographic or sonographic classification that can accurately serve this purpose. Physicians remain largely dependent on the development of symptoms over time and a combination of screening examinations to determine what phase of the disease a patient is in. Imaging techniques however are developing rapidly, and it might well be that further improvement in sonographic imaging techniques, doppler signal resolution or even the application of artificial intelligence will result in a more reliable prediction tool for RCCT.

The combination of rotator cuff tears and calcific deposits was seldomly encountered in our studies. Two recent MRI studies looked at the relationship between the prevalence of RCCT and rotator cuff tears.[12,13] They reported conflicting results. We believe that

most studies confirm that calcific tendinitis and rotator cuff tears are expressions of the age-related continuum of rotator cuff tendinopathy.[14]

CLINICAL IMPLICATIONS

- Standard radiographs and ultrasound are sufficient to diagnose and characterize calcific deposits in the rotator cuff.
- The radiographic classification systems as developed by Gärtner and Molé lack interobserver agreement.
- Absence of an acoustic shadow on sonographic examination is correlated with the resorption phase, and is considered a positive prognostic factor for the clinical outcome.
- Physicians remain largely dependent on the development of symptoms over time and a combination of screening examinations to determine which stage of the disease a patient is in.

PART 2. EXPLORING MINIMALLY INVASIVE TREATMENT OPTIONS

Most patients can be treated conservatively with pain medication, physiotherapy and prudent use of subacromial corticosteroid injections. But approximately twenty percent of patients do not sufficiently benefit from these treatment options. In **Chapter 4** a systematic review and meta-analysis was presented to provide an evidence-based overview of the short-term and mid-term effectiveness of various minimally invasive treatments in terms of pain reduction and functional outcome. As surgery has long been the treatment of choice for patients with RCCT, the most promising minimally invasive techniques were compared with the surgical outcome in **Chapter 5.** Based on these comprehensive reviews it was concluded that high-energy ESWT and ultrasound-guided needling are the most extensively investigated minimally invasive treatment options. Both modalities proved to be safe and effective in the treatment of RCCT, with a clinical outcome that is comparable to a more invasive surgical treatment. The most important concern in the ESWT studies was the heterogeneity of the treatment protocols. No consensus exists on important parameters such as: the energy flux density, number of pulses, number of sessions, interval between sessions, energy sources and focus of the shockwaves. Owing to the wide variety of these parameters, a clear guidance for the dose-effect cannot be provided. Nevertheless, the meta-analysis has been able to show that high-energy ESWT (>0.20 mJ/mm^2) has a greater chance of improving shoulder function and pain than low-energy ESWT (<0.08 mJ/mm^2), placebo or sham treatment. The energy level, generally described as the energy flux density, is likely to be the primary parameter for the physical and biological effects.[15] Finally, ESWT was

found to be more effective when focussed directly on the deposit, in comparison to focussing on the greater tubercle, or the point of maximum tenderness.

With regard to ultrasound-guided needling there were only 2 RCTs available at the time the two reviews were conducted. de Witte et al.[16] looked at ultrasound-guided needling in combination with a subacromial infiltration and compared it with a single subacromial infiltration. They found a clinically relevant difference after one year in favour of the needling group. A difference that was not yet seen after 3 or 6 months follow-up. Forty-five percent of patients in the control group were eventually treated with ultrasound-guided needling or surgery. Kim et al.[17] compared ultrasound-guided needling with a single session of high-energy ESWT focused on the point of maximum tenderness. They concluded that ultrasound-guided needling was superior to ESWT. However, compared to the trial conducted in this thesis, an inferior ESWT protocol was used. We shared our opinion on this subject in a letter to the editor.[18]

Since 2015 numerous authors made an effort to review nonsurgical therapies for RCCT and their conclusions are comparable to our findings.[19,20] While there is primarily low-level evidence that supports the clinical efficacy of ultrasound-guided needling and all of its variances, the trials differ substantially in treatment protocols, outcome measures, patient characteristics and duration of follow-up.

All treatment options proved to be safe without the occurrence of any serious adverse events in the reported trials. Complications were limited to adverse event such as: post-treatment pain, vasovagal collapse, acute bursitis and adhesive capsulitis. It must be noted that there have been (unpublished) reports of septic infections after US-guided needling in the Netherlands, which is not unimaginable since a potential porte d'entrée for bacteria is created.

Up until approximately 10 to 15 years ago, surgery was the most important treatment option when conservative therapies failed. With the upcoming success of new nonsurgical treatment options, surgery is now generally reserved for the most refractory cases. As is frequently encountered in surgical trials, techniques differ substantially. In **Chapter 5** eight surgical trials were reviewed, containing 332 patients. Most of which were low-level evidence studies. Seven out of eight trials started with a subacromial bursectomy, but from that point the techniques differed substantially. There was no consensus with regard to calcific deposit removal, the extent of the removal, application of an acromioplasty or rotator cuff repair. However, the clinical outcome after surgery was excellent in most cases. Our conclusion was confirmed by a more recent review by Verstraelen et al.[21]

Given the different techniques, further research is needed to evaluate the optimal surgical protocol. A future trial would need a large sample size to be able to detect a clinically relevant difference between the groups, because the outcome after any of the surgical techniques is likely to be good. Since the application of surgical procedures in RCCT, and for subacromial pain syndrome in general, has declined rapidly in the last decade it is unlikely that such a large trial will be conducted in the near future.

CLINICAL IMPLICATIONS

- High-energy ESWT (energy flux densitiy >0.2 mJ/mm^2) is the most thoroughly investigated nonsurgical technique and has proven to be more effective in the treatment of RCCT when compared to low-energy ESWT, sham ESWT treatment and placebo.
- ESWT is more effective when focused on the calcific deposit in comparison to focusing on the greater tubercle or the point of maximum tenderness.
- A large heterogeneity exists between the various ESWT treatment protocols. The energy level, generally described as the energy flux density, is likely to be the primary parameter for the physical and biological effects.
- Primarily low-level evidence was found that supports the clinical efficacy of ultrasound-guided percutaneous needling.
- Arthroscopy can safely be used as an effective but more invasive 'last resort' option. With regard to the operative technique, the extent of deposit removal, and the additional benefit of a subacromial decompression remains under debate.

PART 3. EVALUATING OUTCOME AFTER TREATMENT WITH ULTRA-SOUND-GUIDED NEEDLING AND HIGH-ENERGY ESWT

Both systematic reviews concluded that future research should focus on a direct best-evidence comparison between a high-energy ESWT treatment protocol and US-guided needling. A randomized controlled trial was therefore conducted, with the purpose of comparing the functional outcome, pain, patient reported outcome and radiographic resorption after treatment with high-energy ESWT and US-guided needling. The results of this RCT were presented in **Chapter 6**. Only RCCT patients with long-lasting symptoms who were nonresponsive to a conservative treatment were included. Patients with clinical and/or radiographic signs of resorption were excluded. Based on the outcome of this randomized controlled trial it is clear that both high-energy ESWT and US-guided needling show clinically relevant improvements in terms of shoulder

function and pain after 1-year follow-up. No statistical clinical differences were found between the two groups.

The ESWT protocol was based on an extensive literature review and consisted of four sessions high-energy ESWT focussed on the calcific deposit[22] This best level of evidence protocol is likely to be the reason that the ESWT group in this study outperformed the ESWT group in the comparable study from Kim et al.[17] For the ultrasound-guided needling procedure, a double needle technique was used including aspiration and lavage, in combination with an US-guided subacromial bursal corticosteroid injection. Despite a number of comparative trials, there is no consensus in the literature on the most optimal technique.[20,23,24] It seems that the purpose of ultrasound-guided needling; fragmentation and decompression of the calcific deposit, and wash-out of the minerals, can be achieved through different techniques. The necessity of a corticosteroid subacromial injection following ultrasound-guided needling has been questioned. One RCT compared a subacromial corticosteroid injection with a saline injection and reported significantly lower short-term functional outcome in the saline group, without long-term disadvantageous effects of the corticosteroid.[25] Two other studies however, state that a subacromial xylocaine injection works just as effective, or even better, compared to the combination of xylocaine and a corticosteroid.[26,27]

The radiographic results were in favour of the ultrasound-guided needling treatment with near full resorption in nearly all cases. The debate on the relationship between calcific removal, resorption and long-term clinical outcome is still ongoing. But while there are studies that state otherwise[28,29], recent data confirmed that resorption after treatment is a positive predictive factor for clinical outcome.[30] It is probable that pain and other symptoms are related to the pressure a large calcification causes in the inflamed tendon, which is relieved by the decompressive effect of calcification resorption followed by ultrasound-guided needling, high-energy ESWT or arthroscopic removal. More long-term follow-up studies will hopefully help to clarify this issue.

In both treatment groups, a percentage of patients requested an additional treatment due to persistent symptoms. This percentage was higher in the ESWT group, resulting in additional subacromial infiltrations, ultrasound-guided needling procedures or an arthroscopic bursectomy without acromioplasty. It must be noted, that in the majority of the ESWT patients with persisting symptoms, no resorption occurred. The need for arthroscopic surgery was, even in these refractory cases, limited to less than ten percent and no serious adverse events were reported.

CLINICAL IMPLICATIONS

- High-level evidence is provided that both high-energy ESWT and ultrasound-guided needling in combination with a subacromial corticosteroid infiltration, are effective in treating RCCT when conservative treatment fails.
- Ultrasound-guided needling is more effective in eradicating the calcific deposit.
- Patients treated with high-energy ESWT are more likely to request an additional treatment to achieve a good clinical outcome, especially when no resorption occurs after treatment.
- ESWT and ultrasound-guided needling very effectively reduce the necessity of arthroscopic surgery.

OCCUPATIONAL HEALTH FACTORS

Not much is known about the impact of RCCT on work ability and sick leave. Since RCCT occurs in a population with a peak incidence in the 30 to 60 age group, patients with RCCT are usually relatively young, employed and high-demanding in activities of everyday life. However, occupational health factors is a topic that very little RCCT studies look into. In fact, none of the trials included in the systematic reviews, looked at work-related outcome measures. A secondary objective of the randomized controlled trial was therefore to assess the impact of RCCT on patient-reported work ability and sick leave. Improvement of these outcome measures after treatment and prognostic factors were also analysed. The work ability score was used as primary outcome measure. The results are discussed in **Chapter 7.** RCCT was found to have a big impact on work ability and sick leave, both of which improved significantly after ESWT or ultrasound-guided needling treatment. Patients with high physical demanding work were most severely impaired in terms of physical function, pain, and work ability prior to treatment. At the same time, these patients had the biggest upside potential in terms of work ability, and improved most after treatment. Physical workload therefore turned out to be the most important associated factor with change in work ability and sick leave. This is important information for caregivers when discussing treatment options with their patients and it might encourage patients with high physical demanding work to choose for more invasive therapies in an earlier phase.

Other authors looked at risk factors for the development of shoulder disorders in general and identified highly repetitive work, awkward postures, high psychosocial jobs, arm elevation, and a lower level of education as associated with subacromial pain syndrome.[31,32] Work-related outcome measures should be included more frequently in orthopaedic trials, as these variables are very relevant to most younger patients. The

single-item measurement of work ability has been validated and requires very little effort for patients to answer.

CLINICAL IMPLICATIONS

- Calcific tendinitis of the rotator cuff has a big impact on patient's work ability and sick leave.
- Treatment with high-energy ESWT or ultrasound-guided needling both resulted in a significant improvement in work ability and reduction of sick leave.
- Patients with high physical demanding work were most severely impaired in terms of physical function, pain and work ability prior to treatment. These patients also have the biggest upside potential in terms of work ability and physical function after treatment with high-energy ESWT or ultrasound-guided needling.
- Work-related outcome measures should be included more frequently in orthopaedic trials, as these variables are very relevant to most younger patients.

OUTCOME MEASURES

To evaluate which treatment options are best, adequate measurement instruments are required. The Constant Murley score (CMS) and Dutch version of the Disabilities of the Arm, Shoulder and Hand (DASH) were frequently analysed in this thesis. To interpret the outcome of these metrics, it is important to determine the measurement properties.[33] In **Chapter 8**, the metrical properties of the CMS and DASH in patients with long-lasting RCCT were investigated. The minimal clinical important difference (MCID), substantial clinical benefit (SCB), and responsiveness of both outcome measures were established. Factors that were associated with achieving the MCID and SCB were also identified. Two anchor-based approaches were used, with a 7-point global rating of change scale as anchor. This is an established method of calculating the MCID but the scale has been shown to be influenced by the so called recall bias. For the CMS, a MCID and SCB of 9.8 versus 19.9 points and 5.5 versus 10.5 points were found, based on the mean change method and receiver operating characteristic analysis respectively. For the DASH this was -8.2 versus -19.6 and -11.7 versus -12.5 respectively. The mean change method was more able to discriminate between the MCID and the SCB. The responsiveness of both outcome measures was adequate with large effect sizes and standardized response means. It appeared that radiographic resorption after 6 weeks and 6 months was the most important positive predictor for achieving a clinical relevant improvement after 6 months. It is important to realize that the MCID and SCB do not have fixed values.

They are influenced by a number of variables such as; the heterogeneity of the target population, baseline scores, the anchor question, treatment, statistical methods, and definition of MCID. That is why it is important to calculate the MCID/SCB in different patient populations and through different methods.

The final outcome metric that should be taken into account is the smallest detectable change, also known as the measurement error. Ideally the MCID is larger than the SDC in order to be able to distinguish a measurement error from a clinically relevant outcome. In many shoulder PROMs however, the SDC is equal or larger than the MCID. We did not calculate the SDC, but this is also likely the case in our study. While the MCID remains useful in clinical research where larger sample sizes are analysed, the interpretation of the MCID on an individual level should be done with caution.

CLINICAL IMPLICATIONS

- The minimal clinical important difference and substantial clinical benefit are important measurement properties to take into account when interpreting clinical outcome.
- The mean change MCID cut-off point was 9.8 points for the Constant score vs -8.2 for the DASH.
- The mean change SCB cut-off point was 19.9 points for the Constant score vs -19.6 for the DASH.
- It is important to realise that these metrics are influenced by numerous variables.
- Radiographic resorption after 6 weeks and 6 months appeared to be the most important positive predictor for achieving the MCID and SCB after 6 months.

PREDICTING OUTCOME AFTER TREATMENT

Throughout the research conducted in this thesis we attempted to identify variables that can predict treatment outcome. This is of great importance for caregivers in guiding treatment, and dealing with patient expectation management. In this section the most important factors are discussed.-

It remains debated whether complete removal of the calcific deposits is necessary to achieve a clinically relevant outcome. This question is most relevant for techniques where direct removal of the deposit is pursued, such as surgery and ultrasound-guided needling. Many authors stated that successful outcome is strongly related

to the absence of calcific deposits after treatment.[34,35] While other authors state that partial removal of the calcific deposits is already sufficient to aid the cell-mediated resorption that is initiated after surgical incision or needling of the affected tendon.[28,29] In **Chapter 6** and **8** it was found that, independent of the treatment provided, radiographic signs of resorption after 6 weeks and 6 months were positively correlated with the outcome. All ESWT patients who eventually received an additional alternative treatment, due to persistent symptoms, showed no radiographic signs of resorption. A recently published long-term follow-up study after high-energy ESWT supports these findings. In a retrospective analysis of 241 patients treated with high-energy ESWT, patients were grouped according to the level of resorption. Eighty-one percent of patients in the full resorption group were symptom-free in comparison to 24% in the incomplete resorption group.[30]

The mean size of the deposit was small in patients without shoulder pain and larger in patient with shoulder pain, as reported in **Chapter 3**. More specific, all deposits with a size of > 1.5 cm, were found in patients with shoulder pain. This could mean that a larger deposit size is more likely to cause symptoms. A statement that is supported by Bosworth.[2] But does a larger deposit size also mean that the condition is more difficult to treat? Ogon et al. [9] states that patients with deposits larger than 1.5 cm tend to be more resistant to conservative treatment. A larger size deposit was also associated with poor outcome after treatment with ESWT in the study by Chou et al. [30] However, a large calcific deposits does not seem to influence the outcome of ultrasound-guided needling, as shown by Oudelaar et al.[36] They do note that multiple needling procedures and smaller size deposits were negatively associated with the outcome and a positive short-term response was correlated with a good long-term clinical outcome.[36] It seems that focussing solely on the treatment of small calcifications has little effect in improving the rotator cuff tendinopathy. Whereas it is more important to achieve significant resorption when treating the combination of rotator cuff tendinopathy and a larger calcific deposit. In other words, the presence of a larger calcification might inhibit the self-healing ability of the tendon tissue.

Historically, the resorption phase of the condition has been associated with a good overall prognosis. This stimulated authors to classify imaging characteristics in an attempt to isolate patients in the resorption phase. Numerous classifications were developed but they all lack interobserver reliability. Nonetheless, various prospective and retrospective clinical trials stated that Gartner III radiographic deposits (cloudy, ill-defined, segmented) and Farin type C sonographic cases (segmented deposits, absence of acoustic shadowing), were correlated with a good clinical outcome. Taking all available literature in account, we believe that, while the radiographic or

ultrasound classifications lack interobserver reliability, there is sufficient evidence to state that signs of resorption on imaging (radiographic: cloudy, ill-defined, segmented; sonographic: segmented, absent sound extension) are positive prognostic values. These characteristics should be combined with clinical signs of resorption to increase the sensitivity and guide treatment.

Finally, specific baseline characteristics such as a long duration of symptoms (> 1 year), dominant arm involvement and bilateral occurrence of RCCT have been shown to negatively influence the outcome in individual studies.[9,30,36,37]

CLINICAL IMPLICATIONS

- Positive and negative prognostic factors should be taken into account when deciding which treatment is best for an individual patient.
- Positive prognostic factors: short duration of symptoms (< 6 months), unilateral occurrence, sonographic or radiological signs of resorption prior to treatment, radiographic signs of resorption after short-term follow-up.
- Negative prognostic factors: long duration of symptoms (> 1 year), bilateral occurrence, a deposit size of > 1.5 cm, dominant arm involvement, no radiographic signs of resorption after short-term follow-up.

TREATMENT FLOWCHART – A CONCISE TREATMENT GUIDELINE

In the final phase of this thesis we decided to summarize our most important conclusions in a treatment flowchart. The aim was to provide Dutch caregivers (general practitioners, physiotherapist and physicians) with a tool, to guide treatment for patients with calcific tendinitis of the rotator cuff. A concept is presented in this thesis, and can be found in the Appendix. The flowchart was developed with input from a multidisciplinary task force, including members of the Dutch society of shoulder physiotherapist (Schoudernetwerk Nederland) and the Dutch society of shockwave therapists (NVMST).

The flowchart starts with a patient who presents with nontraumatic shoulder pain. This is followed by a step-by-step decision-making process;

1. it provides information on the indication for additional imaging, and important ultrasound characteristics
2. a step-by-step treatment protocol for shoulder physiotherapy is presented
3. implications for ESWT and ultrasound-guided needling are explained

4. the most important positive and negative prognostic factors for conservative treatment, ESWT and ultrasound-guided needling are provided

This flowchart is designed based on a best-level-of-evidence protocol, but it remains a concept. It will have to be validated in future studies.

FUTURE PERSPECTIVES

The different clinical implications presented in this thesis will contribute to the ongoing debate on how to treat patients with calcific tendinitis of the rotator cuff, and how to predict a successful outcome. As is often the case in scientific research, new questions are evoked, based on the present findings. Although rotator cuff calcific tendinitis has been known for more than a century, and countless papers have been published on this topic, important questions remain to be answered. What triggers the resorption process and can we predict when it is initiated? What should we change in the ESWT-, and ultrasound-guided needling techniques to improve the clinical outcome, and can we validate these protocols? Can we identify rotator cuff problems in an early phase to prevent work-related disability? And how many patients have recurrent symptoms after treatment in the long-term? The answers to these, and other questions will no doubt lead to a future 'ideal treatment' for calcific tendinitis of the rotator cuff.

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10

Summary

SUMMARY

EVALUATING TREATMENT OPTIONS FOR CALCIFIC TENDINITIS OF THE ROTATOR CUFF

A general introduction of rotator cuff calcific tendinitis is provided in **Chapter 1**. This thesis focusses on improving the care for patients with calcific tendinitis of the rotator cuff, with an emphasis on evaluating the effectiveness of extracorporeal shockwave therapy (ESWT) and ultrasound-guided needling. First, by giving insight in the prevalence and radiographic assessment of the condition **(Chapter 2** and **3)**. Second, by providing a comprehensive literature overview exploring all minimally invasive treatment options, and to compare these results with surgical treatment **(Chapter 4** and **5)**. Finally, by evaluating the outcome of a randomized controlled trial comparing high-energy ESWT and ultrasound-guided needling in patients with refractory rotator cuff calcific tendinitis (RCCT). The clinical and work-related outcome is discussed, and the clinical metric properties of the outcome measures are analysed **(Chapter 6 - 8)**.

PART 1. EPIDEMIOLOGICAL AND RADIOLOGICAL EVALUATION OF ROTATOR CUFF CALCIFIC TENDINITIS

Calcific depositions in the rotator cuff are frequently found in patients with subacromial pain syndrome (SAPS). However, depositions have also been described in individuals without symptoms. The presence of calcific deposits therefore does not necessarily mean that a patient has concomitant tendinitis symptoms. The reported prevalence of RCCT in patients with and without symptoms varies widely and is based on research performed in the 1940s to 1960s. The purpose of **Chapter 2** was to provide a current view on the epidemiology of RCCT. The clinical and radiological data of 1.219 adults with and without SAPS were analysed to assess the prevalence of calcific deposits in the rotator cuff. A multivariate analysis was used to define risk factors associated with the presence of calcifications. The prevalence was 7.8% in 734 asymptomatic patients and 42.5% in 485 symptomatic patients with SAPS. The supraspinatus tendon was most frequently affected (83%) followed by the subscapularis (9%) and the infraspinatus (8%). The median length of the deposits was 0.42 cm in the asymptomatic group and 1.16 cm in the symptomatic group. All the calcifications larger than 1.5 cm, were found in the symptomatic group. Age between 30-60 years, subacromial pain, and female gender, were three variables significantly associated with the presence of calcific deposits. It was concluded, that women aged between 30 to 60, with subacromial pain and a calcific deposit in the rotator cuff > 1.5 cm, have the highest chance of symptomatic RCCT. At the same time, the presence of a calcific deposit in the rotator cuff does not require immediate treatment when a patient does not have clinical symptoms.

The radiographic appearance of a calcific deposit can vary according to the stage of the condition. Differences in size, location and morphology can be observed and various classification systems exist to categorize radiographic signs of RCCT. In **Chapter 3** the psychometric properties of the two most frequently used classifications, by Gärtner and Molé, were analysed. Thirty-seven orthopaedic surgeons evaluated shoulder radiographs of 25 patients and classified the stage of the RCCT on a web-based study platform. The inter- and intraobserver agreement among observers was measured using the Siegel and Castellan multirater κ. Observers were also asked to define the affected rotator cuff tendon. The results showed that the intraobserver agreement was acceptable (surgeons tend to agree with themselves, more than with each other) but the interobserver agreement for the Gärtner classification was only fair according to the criteria by Landis and Koch. The Gärtner classification showed a higher interobserver reliability (κ = .34) than the classification by Molé (κ = .24). Surgeons were able to correctly localize the deposits in the rotator cuff tendons. It appeared easier for observers to differentiate if a deposit was in the supraspinatus or the subscapularis than in the infraspinatus. To conclude, the radiographic classification systems as developed by Gärtner and Molé lack interobserver agreement. Physicians remain largely dependent on the development of symptoms over time, and a combination of screening examinations to determine which stage of the disease a patient is in.

PART 2. EXPLORING MINIMALLY INVASIVE TREATMENT OPTIONS

Most patients with RCCT can be treated conservatively with pain medication, physiotherapy and prudent use of subacromial corticosteroid injections. But approximately 20% of patients do not sufficiently benefit from conservative treatment. Traditionally, these refractory cases were treated surgically, either by an open or arthroscopic procedure. Since a surgical procedure is costly, requires intensive rehabilitation and perioperative complications may occur, nonsurgical alternatives were developed. In **Chapter 4**, a systematic review and meta-analysis was performed to present an evidence-based overview of the short-term and midterm effectiveness of various minimally invasive treatments in terms of pain reduction and functional outcome. In total, twenty trials were selected, including 1.544 patients. Nineteen studies were designed as an RCT and one as a prospective controlled trial. Seventeen trials investigated the use of ESWT, one trial concerned treatment with radial shockwave therapy and two the use of US-guided needling. The conclusion of this comprehensive review was that high-energy ESWT is the most thoroughly investigated minimally invasive treatment option for RCCT in the short-term to midterm, and has proven to be safe and effective. There is sufficient evidence to state that high-energy ESWT is more effective than low-energy ESWT, sham treatment and placebo treatment. Ultrasound-guided needling proved to be more effective than an ultrasound-guided subacromial

corticosteroid infiltration in a level 1 trial, but these results were not confirmed by other high-quality studies.

Following **Chapter 4**, the most promising evidence-based minimally invasive treatment options were selected. As surgery has long been the treatment of choice for patients with RCCT, the objective of **Chapter 5** was to investigate how the results of these minimally invasive techniques compared to arthroscopic surgery. A comprehensive quantitative review was conducted and twenty-two studies (1.258 shoulders) were included. Eight trials involved treatment with high-energy ESWT, five concerned treatment with ultrasound-guided needling, one compared high-energy ESWT with ultrasound-guided needling, and eight reported the results after arthroscopic surgery. Overall, good to excellent clinical outcome was achieved after treatment with either one of the reviewed treatment options. No severe side effects or long-term complications were encountered. It was concluded that patients with refractory RCCT can achieve good to excellent clinical outcome after either high-energy ESWT, ultrasound-guided needling and arthroscopic treatment. Since the latter is more expensive and more invasive, physicians should consider high-energy ESWT and ultrasound-guided needling as minimally invasive treatment options when primary conservative treatment fails. Arthroscopy can safely be used as a very effective but more invasive 'last resort' option. With regard to the operative technique, the extent of deposit removal and the additional benefit of a subacromial decompression remains unclear.

PART 3. EVALUATING THE EFFECT OF TREATMENT WITH HIGH-ENERGY ESWT VERSUS ULTRASOUND-GUIDED NEEDLING

Both systematic reviews, **Chapters 4** and **5**, concluded that future research should focus on a direct best-evidence comparison between a high-energy ESWT treatment protocol and ultrasound-guided needling. A randomized controlled trial was therefore conducted with the purpose of comparing the functional outcome, pain, and radiographic resorption after treatment with high-energy ESWT and ultrasound-guided needling. Only RCCT patients with long-lasting symptoms, who were nonresponsive to conservative treatment, were included. Patients with clinical and/or radiographic signs of resorption were excluded. The included patients were randomized in two groups. The ESWT group received high-energy ESWT (2000 pulses, energy flux density 0.35mJ/mm^2 per session) for four sessions with one-week intervals. In the ultrasound-guided needling group, patients were treated with a double needle technique combined with a corticosteroid ultrasound-guided subacromial bursa injection. Shoulder function was assessed at standardized follow-up intervals (6 weeks and 3, 6 and 12 months) using the Constant Murley score (CMS), the Disabilities of the Arm, Shoulder and Hand score (DASH) and VAS for pain and satisfaction. The size, location and morphology of the

deposits were evaluated on radiographs. In **Chapter 6**, the clinical and radiological outcome of the trial were reported. Eighty-two patients were treated (56 female, 65%; mean age 52.1 ± 9 years) and one patient was lost to follow-up. After one-year follow-up the ultrasound-guided needling group showed similar good clinical results as the ESWT group with regard to the change from baseline CMS (20.9 versus 15.7; P = .23), DASH (-20.1 versus -20.7; P = .78) and VAS for pain (-3.9 versus -2.6; P = .12). The mean calcification size decreased by 13 ± 3.9 mm in the ultrasound-guided needling group and 6.7 ± 8.2 mm in the ESWT group (P = .001). Because of persistent symptoms, 22% of the ultrasound-guided needling and 41% of the ESWT patients received an additional treatment during follow-up. Less than ten percent of patients were eventually treated with an arthroscopic procedure. Over 75% of patients were (very) satisfied with the outcome. The most important finding of this study is that both treatment techniques show clinically relevant improvements in terms of shoulder function and pain after one-year follow-up. Ultrasound-guided needling was more effective in eradicating the calcific deposit. There were more requests for additional interventions in the high-energy ESWT group, especially in patients where no resorption occurred after treatment.

OCCUPATIONAL HEALTH FACTORS

Not much is known about the impact of RCCT on work ability and sick leave. Since this condition primarily affects patients at working age, information regarding these outcome measures is important for both clinicians and patients. However, none of the investigated clinical trials in chapters four and five looked at work-related outcome measures. A secondary objective of the randomized controlled trial conducted in **Chapter 6**, was therefore; (1) to examine the impact of RCCT on patients' self-reported work ability and sick leave, (2) to compare work ability and sick leave with shoulder function after minimally invasive treatment and (3) to assess which prognostic factors influence the change in work ability. In **Chapter 7** we tried to answer these questions. The single-item work ability score (0 – 10 score, higher = better), assessed at baseline and after 6 and 12 months, was used as the primary outcome. Secondary outcome measures were quality and quantity of work, sick leave, the Constant score, the DASH, and radiographic resorption. The study group consisted of 67 patients performing salaried work. The mean age was 49.6 ± 6.4 years and 45 (67%) was female. The patients' physical workload was categorized as light (58%), medium (24%) or heavy (18%). To identify predictive factors for change in work ability, potential predictive factors (treatment method, age, sex, resorption of the calcific deposit, physical workload and work status) were tested in a statistical model.

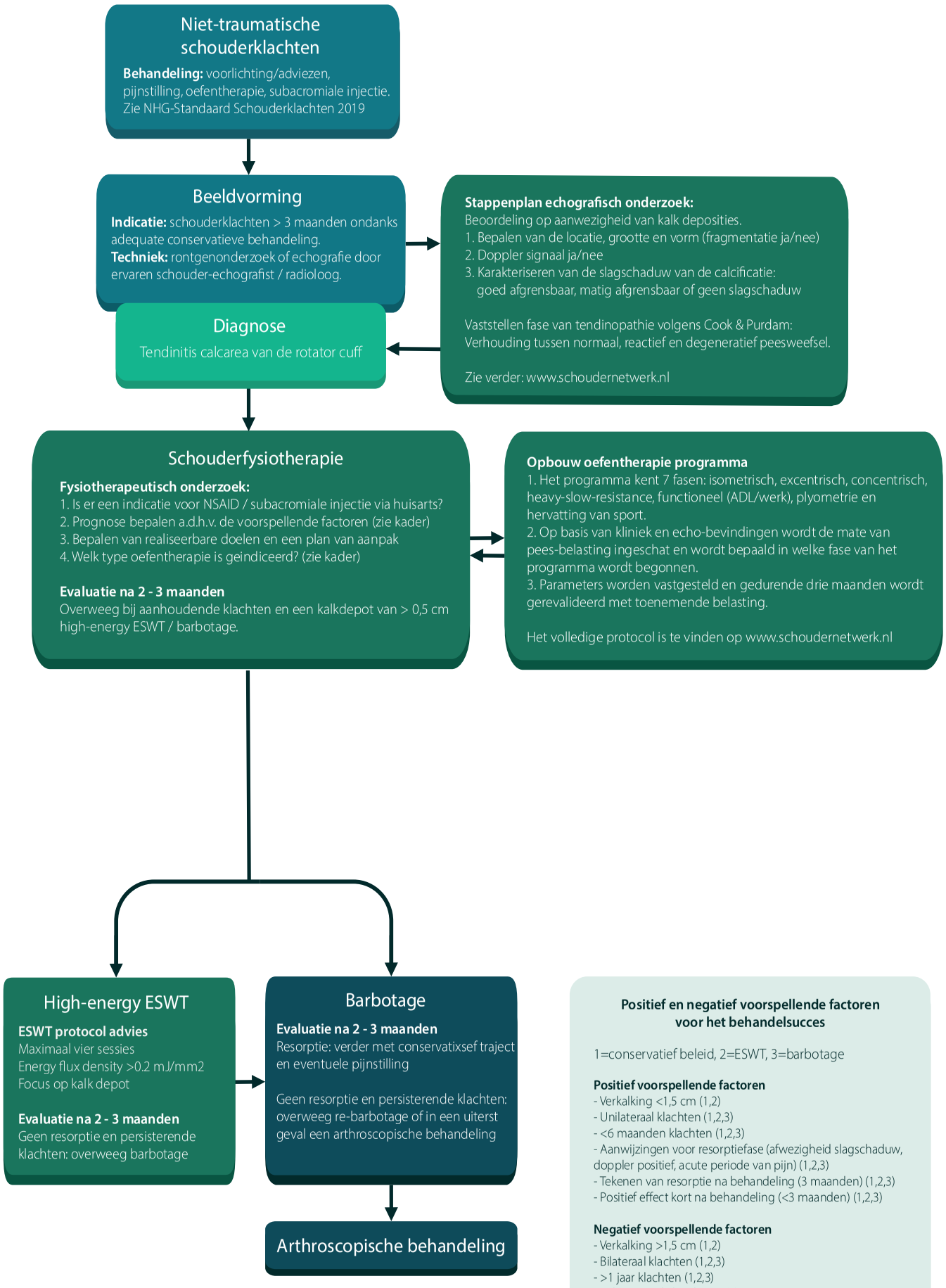
Work ability score improved from a mean of 6.1 ± 2.8 to 8.5 ± 2.0 points after 1 year. Treatment with high-energy ESWT or ultrasound-guided needling, was associated with a reduction in partial or full-time sick leave from 28% to 6% The mean days of sick leave per month declined from 3.3 to 0.8 days. The physical workload turned out to be the most important patient associated factor predicting change in work ability. Especially patients with medium and high physically demanding work for the shoulder benefited from minimally invasive treatment to improve their work ability. This study concluded that RCCT has a significant impact on work ability and sick leave. Treatment with high-energy ESWT or ultrasound-guided needling both resulted in a clinically relevant improvement in work ability and decline in sick leave.

OUTCOME MEASURES

Conclusions drawn in clinical trials are frequently based on a statistical change in clinical and/or patient reported outcome measures. The term statistically significant does not necessarily mean a clinically relevant benefit for the patient. Therefore, there is a need to establish clinical relevance for these outcome measures. To aid the interpretation of clinical outcome score findings, the concept of minimal clinical important difference (MCID) and substantial clinical benefit (SCB) was developed. The aim of **Chapter 8** was to investigate the metrical properties of the CMS score and the DASH in patient with long-lasting RCCT. The MCID and SCB were established and the responsiveness of both outcome measures was assessed. Finally, variables were identified that were associated with achieving the MCID and SCB. Two anchor-based methods were used to calculate the MCID and SCB. For the Constant-Murley score, we found a MCID and SCB of 9.8 and 19.9, respectively, based on the mean change method and 5.5 and 10.5, respectively, based on receiver operating characteristic analysis. For the Disabilities of the Arm, Shoulder and Hand score, we found a MCID and SCB of - 8.2 and - 19.6, with the former and - 11.7 and - 12.5, respectively, with the latter. The responsiveness of both outcome measures was good, with large effect sizes and standardized response means. The radiographic resorption after 6 weeks and 6 months appeared to be the most important positive predictor for achieving the MCID and SCB after 6 months. This is of great importance for physicians treating patients with RCCT and helps deal with the patients' expectation management after treatment.

Chapter 9 presents the general discussion. In this chapter the most important findings of the thesis are summarized as clinical implications, and future perspectives are discussed. A Dutch treatment flowchart is presented in the appendix.

Appendix



Multidisciplinair behandelprotocol voor tendinitis calcarea van de rotator cuff.

De volledige versie van het protocol, inclusief toelichting, zal te vinden zijn op www.schoudernetwerk.nl

NEDERLANDSE SAMENVATTING

EVALUATING TREATMENT OPTIONS FOR CALCIFIC TENDINITIS OF THE ROTATOR CUFF

Pijn in de schouder is een veel voorkomende klacht. Dit wordt vaak veroorzaakt door een pees- en slijmbeursontsteking onder het schouderdak (acromion), ook wel bekend als het subacromiale pijn syndroom (SAPS). De ontstekingen komen voor in de pezen van de rotator cuff, een viertal schouderspieren (figuur 1, hoofdstuk 1) waarvan de pezen als een manchet rondom de schouderkop zitten. Het goed functioneren van de rotator cuff is essentieel voor het bewegen en de stabiliteit van de schouder.

Een belangrijke veroorzaker van SAPS is de combinatie van een ontstoken rotator cuff pees met de aanwezigheid van kalk deposities in de aangedane pees, ook wel bekend als tendinitis calcarea. Deze verkalkingen worden aangetroffen op röntgenfoto's of tijdens een echo onderzoek. Patiënten ervaren bewegingsafhankelijke pijn in de bovenarm en kunnen ´s nachts vaak niet op de arm liggen. Alhoewel de symptomen van tendinitis calcarea na verloop van tijd spontaan kunnen verbeteren en de verkalkingen kunnen resorberen, is het beloop zeer wisselend en hebben patiënten soms langdurige en intense klachten. De eerste stap in de behandeling van tendinitis calcarea is pijnstilling, voorlichting en een oefenprogramma begeleid door een fysiotherapeut. Veel patiënten zijn hiermee al goed geholpen. Patiënten die ondanks conservatieve therapie klachten bleven houden werden voorheen altijd chirurgisch behandeld. Maar omdat er aan een chirurgische behandeling ook belangrijke nadelen kleven, zijn er minder invasieve behandelingen ontwikkeld. Voorbeelden hiervan zijn 'extracorporeal shockwave therapy', hierna ESWT genoemd, en het echogeleid fragmenteren van het kalkdepot, ook wel 'ultrasound-guided needling' of barbotage genoemd.

Een gedetailleerde introductie in het ziektebeeld tendinitis calcarea is te vinden in **hoofdstuk 1**. Het doel van dit proefschrift is om de zorg voor patiënten met tendinitis calcarea te verbeteren, waarbij de nadruk ligt op het evalueren van de effectiviteit van ESWT en echogeleide barbotage. In het eerste deel van het proefschrift wordt de prevalentie van verkalkingen in de rotator cuff geanalyseerd, en de radiografische beoordeling van het ziektebeeld besproken **(hoofdstuk 2** en **3)**. In het tweede deel wordt een literatuur overzicht gepresenteerd van alle minimaal invasieve behandelopties. Tevens worden de meest veelbelovende behandelingen vergeleken met een chirurgische behandeling **(hoofdstuk 4** en **5)**. In het laatste deel van het proefschrift worden de uitkomsten van een gerandomiseerd klinisch onderzoek gepresenteerd, waarin high-energy ESWT met barbotage wordt vergeleken als behandeling voor patiënten met langdurige klachten van tendinitis calcarea. De klinisch en werk

gerelateerde uitkomsten worden besproken en de clinimetrische eigenschappen van de uitkomstmaten worden geanalyseerd **(hoofdstuk 6 – 8)**. **Hoofdstuk 9** staat in het teken van de algemene discussie. Hierin zijn de resultaten van de verschillende studies die in dit proefschrift worden gepresenteerd in een breder perspectief geplaatst. Tevens zijn de belangrijkste bevindingen geformuleerd als klinische implicaties en wordt er een stroomdiagram gepresenteerd die ingezet kan worden bij de multidisciplinaire behandeling van patiënten met tendinitis calcarea.

DEEL 1. EPIDEMIOLOGISCHE EN RADIOLOGISCHE EVALUATIE VAN TENDINITIS CALCAREA VAN DE ROTATOR CUFF

Kalk deposities worden vaak gevonden in patiënten met SAPS. De deposities komen echter ook voor in de rotator cuff van individuen zonder klachten. De aanwezigheid van verkalkingen in de pees betekent derhalve niet dat er altijd sprake is van begeleidende tendinitis symptomen. Prevalentiecijfers van tendinitis calcarea lopen sterk uiteen en zijn gebaseerd op onderzoek uit de jaren 1940 tot 1960. Het doel van **hoofdstuk 2** is om de hedendaagse epidemiologie van tendinitis calcarea te beschrijven. De klinische en radiologische data van 1.219 volwassenen, met (symptomatisch) en zonder SAPS klachten (asymptomatisch), werden geanalyseerd op de aanwezigheid van kalk deposities. Risicofactoren voor de aanwezigheid van kalk deposities werden berekend middels een multivariate analyse. De prevalentie was 7,8% in de asymptomatische groep en 42,5% in de symptomatische groep. De supraspinatus pees was het meest frequent aangedaan (83%), gevolgd door de subscapularis (9%) en infraspinatus (8%). De mediane lengte van de deposities was 0,42 cm in de asymptomatische groep en 1,16 cm in de symptomatische groep. Verkalkingen groter dan 1,5 cm werden alleen gevonden in de symptomatisch groep. Leeftijd (30 – 60 jaar), subacromiale pijn en vrouwelijk geslacht waren de drie variabelen die significant geassocieerd waren met de aanwezigheid van kalk deposities. Er wordt geconcludeerd dat vrouwen in de leeftijd tussen 30 en 60 jaar, met subacromiale pijn en een verkalking van > 1,5 cm, de hoogste kans hebben op symptomatische tendinitis calcarea. Echter, als er een verkalking wordt gevonden maar er geen bijpassende symptomen zijn, hoeft een patiënt hier niet direct voor behandeld te worden.

Het radiologische beeld van tendinitis calcarea kan variëren afhankelijk van de fase waarin het ziektebeeld zich bevindt. Er kunnen verschillen worden geobserveerd in afmetingen, lokalisatie en morfologie. Op basis van deze eigenschappen zijn verschillende classificatie systemen ontworpen. In **hoofdstuk 3** zijn de psychometrische eigenschappen van de twee meest gebruikte classificaties, volgens Gärtner en Molé, onderzocht. Zevenendertig orthopedisch chirurgen evalueerden de röntgenfoto's van 25 patiënten op een web-based platform en classificeerden het stadium van de deposities.

De inter- en intra-beoordelaarsbetrouwbaarheid werd middels de multirater kappa berekend. De beoordelaars werd ook gevraagd om aan te geven in welke rotator cuff pees de verkalking was gelokaliseerd. Uit de resultaten bleek dat de chirurgen het over het algemeen met zichzelf eens waren (acceptabele intra-beoordelaarbetrouwbaarheid), maar dat de inter-beoordelaarbetrouwbaarheid voor beide classificaties laag was. Echter, bij de Gärtner classificatie (κ = .34) was de betrouwbaarheid iets hoger dan bij de Molé classificatie (κ = .24). De chirurgen waren in principe goed in staat om de locatie te bepalen. Het bleek alleen lastig om te differentiëren tussen de supraspinatus en de infraspinatus. Concluderend hebben de radiologische classificaties van Gartner en Molé een lage inter-beoordelaarsbetrouwbaarheid. Om te kunnen bepalen in welke fase van het ziektebeeld de verkalking zich bevindt, blijven behandelaars grotendeels afhankelijk van de ontwikkeling van symptomen door de tijd heen en een combinatie van beeldvormende technieken.

DEEL 2. EVALUATIE VAN MINIMAAL INVASIEVE BEHANDELTECHNIEKEN

De meeste patiënten met tendinitis calcarea kunnen conservatief behandeld worden met pijnstillers, fysiotherapie en zo nodig een subacromiale corticosteroïd injectie. Maar bij 1 op de 5 patiënten blijven de klachten aanhouden. Deze patiëntengroep werd voorheen chirurgisch behandeld. Er bestaan hiervoor zowel open als arthroscopische technieken. Een chirurgische behandeling heeft echter nadelen zoals een intensieve nabehandeling, het risico op perioperatieve complicaties en hogere kosten. Daarom werden niet-chirurgische alternatieven ontwikkeld. In **hoofdstuk 4** is de effectiviteit van verschillende minimaal invasieve behandelmethodes onderzocht om een evidence-based overzicht te presenteren. Door middel van een systematische review met meta-analyse werd gekeken naar de verbetering van schouder functie en reductie van pijn op de korte tot middellange termijn. In totaal werden 20 studies geselecteerd waarin 1.544 patiënten waren geïncludeerd. Negentien studies waren als gerandomiseerd prospectief onderzoek opgezet en één als prospectieve cohort studie. Zeventien studies analyseerden het effect van ESWT, in één studie werd gekeken naar radiaire shockwave therapie en in twee studies werd de effectiviteit van barbotage onderzocht. De conclusie van de systematische review is dat high-energy ESWT de best onderzochte niet-chirurgische behandeling is en dat deze behandeling veilig en effectief is als behandeling van tendinitis calcarea. High-energy ESWT bleek effectiever dan low-energy ESWT en placebo behandeling. In één gerandomiseerde studie bleek barbotage effectiever te zijn dan een subacromiale corticosteroïd injectie maar deze resultaten werden niet bevestigd door andere studies.

Na **hoofdstuk 4** zijn high-energy ESWT en barbotage als meest veelbelovende minimaal invasieve behandelingen geselecteerd. Het doel van **hoofdstuk 5** is het vergelijken

van deze behandelingen met een arthroscopisch chirurgische techniek. Na een systematische beoordeling van de literatuur werden 22 studies (1.258 behandelde schouders) geïncludeerd. De resultaten van deze studies werden op een kwalitatieve manier beschreven. In acht studies werd het effect van high-energy ESWT geanalyseerd, in vijf studies de behandeling met barbotage, één studie vergeleek high-energy ESWT met barbotage en in acht studies werden de resultaten na arthroscopische chirurgie geanalyseerd. Over het algemeen werden goede tot zeer goede klinische resultaten bereikt na elk van de beschreven behandelingen. Ook traden er geen lange termijn complicaties op. Als gekeken werd naar de operatieve technieken blijft het onduidelijk in hoeverre de depositie in zijn totaliteit verwijderd moet worden en wat de toegevoegde waarde is van een subacromiale decompressie. De conclusie van hoofdstuk 5 is dat patiënten een goede klinische uitkomst kunnen bereiken na behandeling met zowel high-energy ESWT, barbotage als arthroscopische chirurgie. Aangezien de laatste kostbaarder en meer invasief is, zouden behandelaars high-energy ESWT en barbotage kunnen overwegen als een conservatieve behandeling niet succesvol is. Arthroscopische chirurgie is een veilige optie maar zou gezien moeten worden als het laatste redmiddel.

DEEL 3. EVALUATIE VAN DE EFFECTIVITEIT VAN HIGH-ENERGY ESWT VERSUS BARBOTAGE

Op basis van de conclusies in hoofdstuk 4 en 5 bleek dat toekomstig onderzoek zich zou moeten richten op een directe vergelijking tussen high-energy ESWT en barbotage. Derhalve is een gerandomiseerd gecontroleerde studie opgezet. In **hoofdstuk 6** worden de klinische en radiologische uitkomsten van de studie beschreven. Het doel is om de functionele uitkomst, pijnbeleving en radiografische resorptie na behandeling van high-energy ESWT en barbotage te vergelijken. Alleen patiënten met langdurige symptomen die niet reageerden op een conservatief traject kwamen in aanmerking om deel te nemen. Patiënten met klinische of radiografische tekenen van resorptie werden uitgesloten. De geïncludeerde patiënten werden gerandomiseerd verdeeld in twee behandelgroepen. De ESWT-groep ontving high-energy ESWT (2000 drukgolven, energy flux density 0,35 mJ/mm^2 per sessie) gedurende vier behandelingen met een interval van één week. In de barbotage-groep werden patiënten behandeld met een twee-naalden barbotage techniek gevolgd door een echogeleide subacromiale corticosteroïd injectie. De klinische uitkomsten werden geanalyseerd op vaste controle momenten (6 weken, 3, 6, en 12 maanden) en gemeten middels de Constant Murley score (CMS), de Disabilities of the Arm, Shoulder and Hand score (DASH) en een VAS score voor pijn en tevredenheid. De grootte, locatie en morfologie van de kalkdeposities werd geëvalueerd aan de hand van röntgenfoto's.

Tweeëntachtig patiënten werden behandeld (56 vrouwen, 65%; gemiddelde leeftijd 52,1 ± 9 jaar) waarvan één patiënt uiteindelijk niet beschikbaar was voor de eindcontrole. Na één jaar lieten zowel de barbotage-groep als de ESWT groep goede resultaten zien met betrekking tot de CMS score (+20,9 vs. +15,7 punten; *P* =.23), de DASH (-20,1 vs. -20,7; *P* = .78) en VAS voor pijn (-3,9 vs -2,6; *P* = .12). De gemiddelde grootte van de kalkdepositie verminderde met 13 ± 3,9 mm in de barbotage groep en 6,7 ± 8,2 mm in de ESWT groep (*P* = .001). In verband met persisterende symptomen ontving 22% van de barbotage patiënten en 41% van de ESWT patiënten een extra behandeling binnen de controle periode van één jaar. Minder dan 10% van de patiënten ontving uiteindelijk een arthroscopische behandeling. Meer dan 75% was uiteindelijk tevreden of zeer tevreden over de behandeling. Het meest belangrijke resultaat van deze studie is dat beide behandelingen resulteren in een klinisch relevante verbetering van de schouderfunctie en pijn. Barbotage is effectiever in het laten resorberen van de verkalking. Verder waren er meer patiënten in de high-energy ESWT groep die aanvullende behandelingen ontvingen, met name in patiënten waar geen resorptie was opgetreden.

WERK GERELATEERDE FACTOREN

Er is maar weinig bekend over de invloed van tendinitis calcarea op werkvermogen en ziekteverzuim. Aangezien met name de beroepsbevolking (tussen de 30-60 jaar) geraakt wordt door deze klachten is kennis van deze uitkomstmaten van belang voor zowel de behandelaars als de patiënten. Het is dan ook opvallend dat geen enkele van de bestudeerde studies in hoofdstuk 4 en 5 werkgerelateerde factoren heeft meegenomen in de uitkomst. Een tweede doel van de gerandomiseerde studie, besproken in hoofdstuk 6, was daarom om: (1) te onderzoeken wat de impact is van tendinitis calcarea op het zelfgerapporteerde werkvermogen en verzuim; (2) te onderzoeken in hoeverre werkvermogen en verzuim samenhangen met de schouderfunctie na minimaal invasieve behandeling en, (3) te bepalen welke prognostische factoren de werkgerelateerde uitkomsten beïnvloeden. De uitkomsten van deze analyse worden beschreven in **hoofdstuk 7.** De werkvermogen score werd gebruikt als primaire uitkomstmaat en werd afgenomen voorafgaand aan de behandeling en na 6 en 12 maanden. Secundaire uitkomstmaten waren de kwaliteit en kwantiteit van het geleverde werk, verzuim, de CMS score, DASH en radiografische uitkomsten. De studiegroep bestond uit 67 patiënten met betaald werk, loondienst of zelfstandige. De gemiddelde leeftijd was 49,6 ± 6,4 jaar en 45 (67%) was vrouw. Het werk werd op basis van de fysieke belasting gecategoriseerd als licht (58%), gemiddeld (24%) en zwaar (18%). Potentieel voorspellende factoren zoals de behandeltechniek, leeftijd, geslacht, resorptie van het depot, fysieke belasting en soort werk, werden geanalyseerd in een statistisch model.

De werkvermogen score (0-10, hoger is beter) verbeterde van een gemiddelde van 6,1 ± 2,8 naar 8,5 ± 2,0 na één jaar. Na behandeling met high-energy ESWT en barbotage werd een reductie in gedeeltelijke of voltijd verzuim gezien van 28% naar 6%. Het gemiddeld aantal verzuim dagen per maand zakte van 3,3 naar 0,8. De fysieke belasting op het werk bleek de belangrijkste voorspeller te zijn voor de verandering in werkvermogen. Met name de patiënten die gemiddeld tot zwaar werk uitvoerden, profiteerden van de minimaal invasieve behandelingen. De conclusie van deze studie is dat tendinitis calcarea een significante impact heeft op werkvermogen en ziekteverzuim en dat behandeling met zowel high-energy ESWT als barbotage resulteerde in een klinisch relevante verbetering van werkvermogen en daling van het ziekteverzuim.

UITKOMSTMATEN

De conclusies die getrokken worden uit klinisch onderzoek zijn vaak gebaseerd op statistisch significante verschillen in de uitkomstmaten. Een statistisch significant verschil hoeft echter niet te betekenen dat een patiënt ook een klinisch relevant verschil bemerkt. Het is daarom belangrijk om te begrijpen wat de klinisch relevante verschillen zijn van deze uitkomstmaten. Om die verschillen te interpreteren is het concept van het minimaal klinisch relevante verschil (MCID) en de substantiële klinische verbetering (SCB) ontwikkeld. Het doel van **hoofdstuk 8** is om de klinimetrische eigenschappen van de CMS score en de DASH score te bepalen in patiënten met langdurige klachten van tendinitis calcarea. De MCID en de SCB werden berekend alsmede de responsiviteit. Tenslotte werd gekeken welke factoren het bereiken van de MCID en SCB beïnvloedden. Om de MCID en SCB te berekenen werd gebruik gemaakt van twee statische methoden gebaseerd op anker-vragen.

Voor de CMS score (0-100, hoger is beter) werd een MCID en SCB gevonden van respectievelijk 9,8 en 19,9 op basis van de 'mean-change' methode en 5,5 en 10,5 op basis van de 'receiver operating characteristic' methode. Voor de DASH score (0-100, lager is beter) werd een MCID en SCB gevonden van respectievelijk -8,2 en -19,6 op basis van de eerste methode en -11,7 en -12,5 op basis van de laatste methode. De responsiviteit van beide uitkomstmaten was goed. De resorptie van de kalkdepositie na 6 weken en/of 6 maanden bleek de belangrijkste positieve voorspeller om een klinisch relevante verbetering te behalen. Deze informatie is van belang voor behandelaars en helpt in het verwachtingsmanagement van patiënten na behandeling.

LIST OF PUBLICATIONS

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PHD PORTFOLIO

Name: Jan Karel Gerard Louwerens
PhD supervisors: prof D. Eygendaal & prof. B. van Royen
PhD co-supervisors: dr. A. van Noort & dr. M.P.J. van den Bekerom
PhD period: 2013 – 2020

1. PhD training	Year
Doctor of Medicine	2006-2013
Resident (ANIOS) orthopaedics, Spaarne Ziekenhuis, Hoofddorp	2013-2014
Clinical researcher, Spaarne Ziekenhuis, Hoofddorp	2014
Resident (AIOS) Orthopaedic Surgery at the Department of general surgery, Medical Center Alkmaar, Alkmaar	2015-2016
Resident (AIOS) Orthopaedic Surgery at the Department of orthopaedic surgery, Spaarne Ziekenhuis, Hoofddorp	2016-2017
Resident (AIOS) Orthopaedic Surgery at the Department of orthopaedic surgery, Radboud University Medical Center, Nijmegen	2017-2018
Resident (AIOS) Orthopaedic Surgery at the Department of orthopaedic surgery, Noordwest Ziekenhuisgroep, Alkmaar & Den Helder	2018-2019
Resident (AIOS) Orthopaedic Surgery at the Department of orthopaedic surgery, Spaarne Gasthuis, Hoofddorp & Haarlem	2020 - 2021
Specific courses	
Cursus Good Clinical Practice (GCP)	2014
Basic & Advanced SPSS course, Linnaeusinstituut	2013
Presentations	
Evidence for minimally invasive therapies in the management of chronic calcific tendinopathy of the rotator cuff. A systematic review and meta-analysis.	
- Poster presentation. Linnaeus wetenschapssymposium, Spaarne Ziekenhuis	2014
- Podium presentation. ESSKA congress, Amsterdam	2014
- Poster presentation. SECEC-ESSSE congress, Istanbul	2014
Prevalence of calcific deposits within the rotator cuff tendons in adults with and without subacromial pain syndrome: clinical and radiologic analysis of 1219 patients.	
- Podium presentation. SECEC-ESSSE congress, Milano	2015
- Podium presentation. NOV voorjaarscongres, Amsterdam	2015
Comparing ultrasound-guided needling combined with a subacromial corticosteroid injection versus high-energy extracorporeal shockwave therapy for calcific tendinitis of the rotator cuff: a randomized controlled trial.	
- Poster presention. STZ event, Utrecht	2018
- Oral presentation. NOV jaarcongres. Den Bosch	2019
- Oral presentation. Wetenschapssymposium Spaarne Gasthuis. Hoofddorp	2019
- Oral presentation. Jaarcongres NVA, Nieuwegein	2019
- Oral presentation. ICSES congress. Buenos Aires	2019
- Oral presentation. Nationaal shockwave congres. Zwolle	2019
- Oral presentation. European congress of shoulder & elbow rehabilitation. Den Bosch	2019
International conferences	
ESSKA congress, Amsterdam	2014
SECEC-ESSSE congress, Instanbul	2014
Voorjaarscongres NOV, Amsterdam	2015
SECEC-ESSSE congress, Milano	2015
Jaarvergaderingen NOV, Den Bosch (5x)	2015-2020
Jaarvergadering NVA, Nieuwegein	2019
ICSES meeting, Buenos Aires	2019

2. Teaching	Year
Lecturing	
Lustrumsymposium schoudernetwerk Noord-Nederland, Groningen	2018
Lustrumsymposium schoudernetwerk Amsterdam, Amsterdam	2019
Schoudernetwerk meeting Noord-Nederland, Schagen	2019
Schouderfellow meeting Spaarne Gasthuis, Hoofddorp	2019
Schoudersymposium fysiotherapie praktijk Verheul & Weerman, Nieuw-Vennep	2019
Schouderavond Noordwest Ziekenhuisgroep, Alkmaar	2019
Schoudersymposium Rijnstate ziekenhuis, Arnhem	2019

3. Parameters of esteem	Year
Grants	
Spaarne stimuleringsfonds	2014
Awards	
Linnaeus posterprijs, wetenschapssymposium Spaarne Ziekenhuis	2014

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Voor nu is het voor altijd goed.

ABOUT THE AUTHOR

Jan Karel Gerard Louwerens was born on May 2, 1988 in Rotterdam, the Netherlands. In 2006 he obtained his high school diploma at the Stedelijk Gymnasium in Nijmegen, The Netherlands. That same year he started medical school at the VU University Medical Centre in Amsterdam. After finishing his bachelor's degree in 2009 he paused his studies for a year to join the 'Lustrum' Committee of his student association to organize jubilee activities. He obtained his master's degree in August 2013.

His passion for orthopaedic surgery was inspired by his keen interest in biomechanics, endurance sports and technology, and fed by a healthy portion of orthopaedic genes in his DNA. During his junior internships he published his first orthopaedic article in collaboration with the Department of Orthopaedics of the Medical Centre Alkmaar and the Sint Maartenskliniek in Nijmegen. This was followed by a senior internship orthopaedic surgery at the Spaarne Gasthuis, Hoofddorp and the start of his PhD research project on calcific tendinitis of the rotator cuff, under supervision of Dr. Arthur van Noort, Dr. Michel van den Bekerom, Prof. Denise Eygendaal and Prof. Barend van Royen. After obtaining his medical degree he worked in the Spaarne Gasthuis as an orthopaedic resident not-in-training for six months, he travelled the world and worked on his PhD project as a clinical researcher until he started with his orthopaedic training.

In January 2015 he started his orthopaedic training as a resident in general surgery at the Noordwest Ziekenhuisgroep, Alkmaar, under supervision of Dr. Hermien Schreurs. He continued his training in orthopaedic surgery at Spaarne Gasthuis, Hoofddorp (Dr. Arthur van Noort), Radboud University Medical Centre, Nijmegen (Dr. Maarten de Waal Malefijt), Noordwest Ziekenhuisgroep, Alkmaar (Dr. Bart Burger) and returned to Spaarne Gasthuis in January 2020 where he is expected to complete his training in May 2021.

Jan lives in Amsterdam and is engaged to Nina van Hattum. In the summer of 2021 they intend to move temporarily to Adelaide, Australia, where Jan will start a one-year orthopaedic trauma fellowship at Flinders Medical Centre.