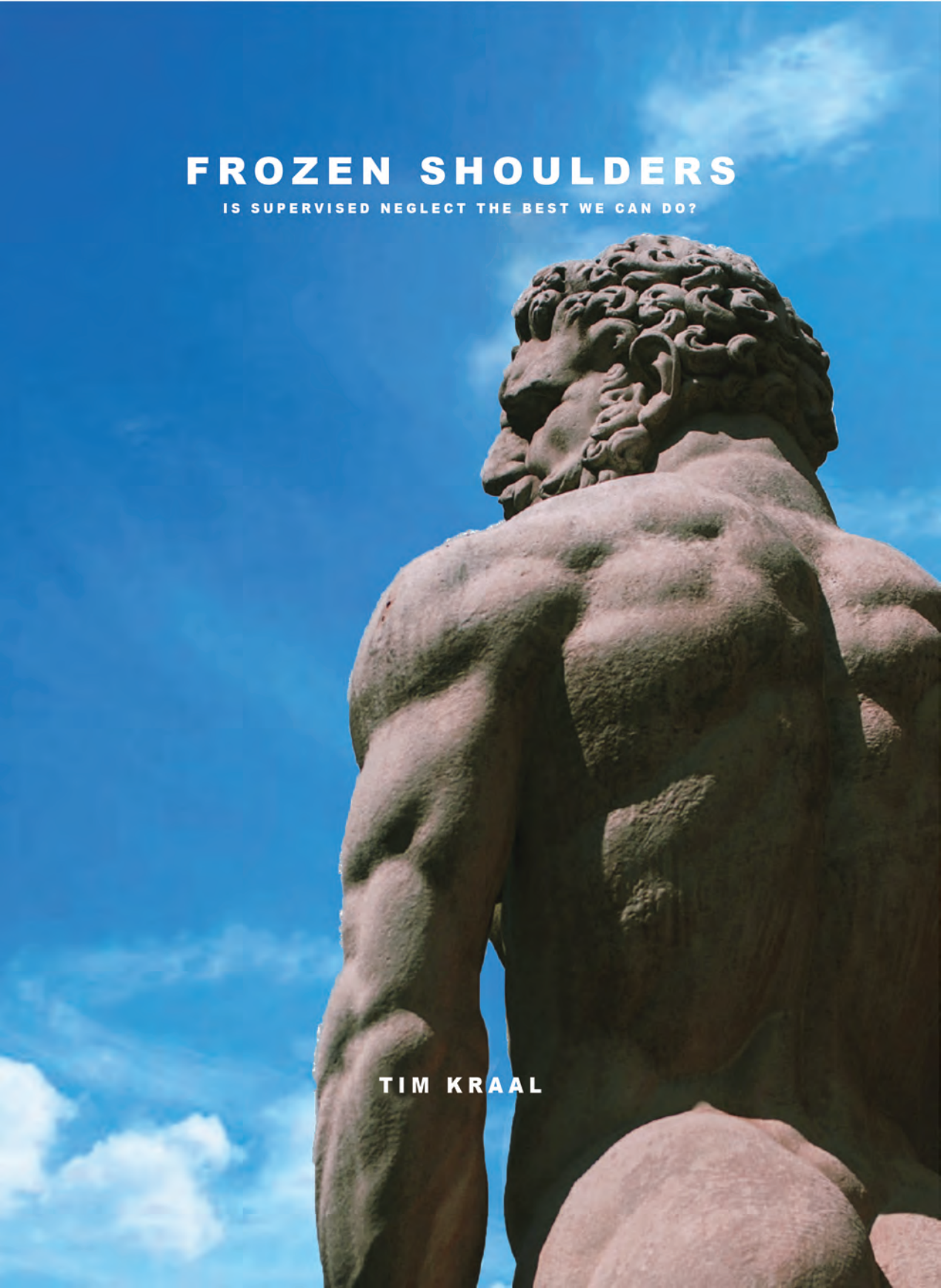
# FROZEN SHOULDERS

## IS SUPERVISED NEGLECT THE BEST WE CAN DO?



TIM KRAAL

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Colofon

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aan de Universiteit van Amsterdam
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# PART ONE

## INTRODUCTION AND PATHOPHYSIOLOGY

# CHAPTER ONE

## Introduction and aim of this thesis

# INTRODUCTION

The idea for this thesis originates from my first experiences as a non-training resident in orthopedics when I attended outpatient clinics with several shoulder specialists. It soon became clear to me that frozen shoulder (FS) was a common condition in our orthopedic practice. To diagnose a frozen shoulder did not seem to be the issue. All surgeons were very confident about the diagnosis, based on history and physical examination, in a relatively short amount of time. However, as a young doctor, I was surprised to see what a variety of different recommendations and treatment strategies I heard from each individual surgeon. There was no local protocol in our hospital, and the recommendations how to deal with a frozen shoulder ranged from supervised neglect, injections, physiotherapy, manipulation under anesthesia to arthroscopic capsular release. The general aim of this thesis is to aid clinical decision making for orthopedic surgeons in the treatment of FS patients, guiding orthopedic surgeons when to do more than just 'supervised neglect'.

# THE SHOULDER JOINT

The human shoulder joint has a remarkably wide range of motion, and it's most important function is to position the forearm and hand in space around our body. Elevation of the arm is a combined process of four joints around the shoulder. The scapulothoracic joint, not a true synovial joint because it lacks a surrounding capsule, but a unique articulating surface wherein the scapula slides upward over the thorax with elevation of the arm. The glenohumeral joint itself, with a rather large humeral head compared to a small and shallow glenoid socket. The acromio-clavicular joint and the sterno-clavicular joint are important for range of motion of the upper limb and transmission of compressive forces of the arm to the sternum and axial skeleton. The clavicle works like a strut that keeps the shoulder lateral to the trunk. It rotates backwards around it's longitudinal axis with elevation of the arm, and the midshaft S-shaped curvature is there to clear the top of the ribcage upon elevation of the arm.

The shoulder is important to evolutionary scientists because it is believed that morphology follows function throughout human evolution. As a result of reduction of overhead activities and climbing during daily life, the scapula is positioned low and dorsal on the thorax, the scapular spine became longer, and the glenoid fossa faces more laterally compared to superiorly in primates.[1] Compared to quadrupedal primates, humans have a more spherical shape of the humeral head and the position of the tubercles is lower, which results in a higher degree of mobility, with increased external rotation of the shoulder joint.[2] This is important from an evolutionary point of view, to

facilitate tool use, but also because humans acquired the ability to throw forceful and accurate, approximately two million years ago.[3] This is a skill unique to humans and has made humans efficient and successful predators.[4] The coraco-acromial ligament for example, is only present in hominoids, and is thought to resist shear forces in the anterosuperior direction with throwing.[5] Although throwing is no longer critical for survival in our modern society, the shoulder is the most mobile joint in our body, allowing a wide range of motion. This comes at the expense of stability, since the shoulder is also the most frequently dislocated joint. However, instability is on the opposite side of the spectrum compared to frozen shoulders, the topic of this thesis.

Nowadays, the unique function of our shoulder is indefinitely demonstrated in sports: Grabbing on to the high bar after a flight element in gymnastics, throwing a javelin over a distance of 90m, swimming 100m butterfly in less than 50 seconds, or pitching a fastball over 160 km/h. Although these are examples of the extremes that we can accomplish, we all need the range of motion of the shoulder for our normal daily activities, more than we often realize. Around 100 degrees of elevation is needed to wash your armpit and applying deodorant, 70 degrees of internal rotation is needed to wash your lower back and combined abduction with 50 degrees of external rotation is required to wash and comb your hair.[6,7] A frozen shoulder can lead to functional restrictions in these normal daily life activities for a prolonged period of time.



## ANATOMY

The glenohumeral joint is a synovial “ball and socket” type joint. The articulating surface of the humeral head is on average three times larger than the surface of the glenoid, in other words, only one third of the articular surface of the humeral head is in contact with the glenoid at any given time. Both surfaces are covered by cartilage, with thicker cartilage on the glenoid side compared to the humeral side.[8] The shoulder is not a constrained joint, with a slight mismatch between the radius of curvature of the humeral head compared to the glenoid. The articulating cartilaginous surface is more congruent compared to the osseous anatomy and the central and inferior part of the glenoid has the best congruency with the humeral head.[9] The labrum is a fibrocartilaginous structure, attached to the glenoid rim, and it increases the depth of the glenoid socket. The humeral head is dynamically compressed into glenoid by the combined forces of the rotator cuff muscles: subscapularis anteriorly, supraspinatus superiorly, infraspinatus posterosuperiorly and teres minor posteriorly. The rotator interval is a triangular shaped gap, at the anterosuperior portion of the glenohumeral joint, in between the subscapularis and supraspinatus. (Figure 1) This is a complex anatomic region, containing capsuloligamentous structures and the long head of the biceps with both its medial and

lateral pulley structures. All these structures are covered by the deltoideus muscle. The deltoid is a strong, superficially located muscle, which forms the rounded contour of the shoulder.

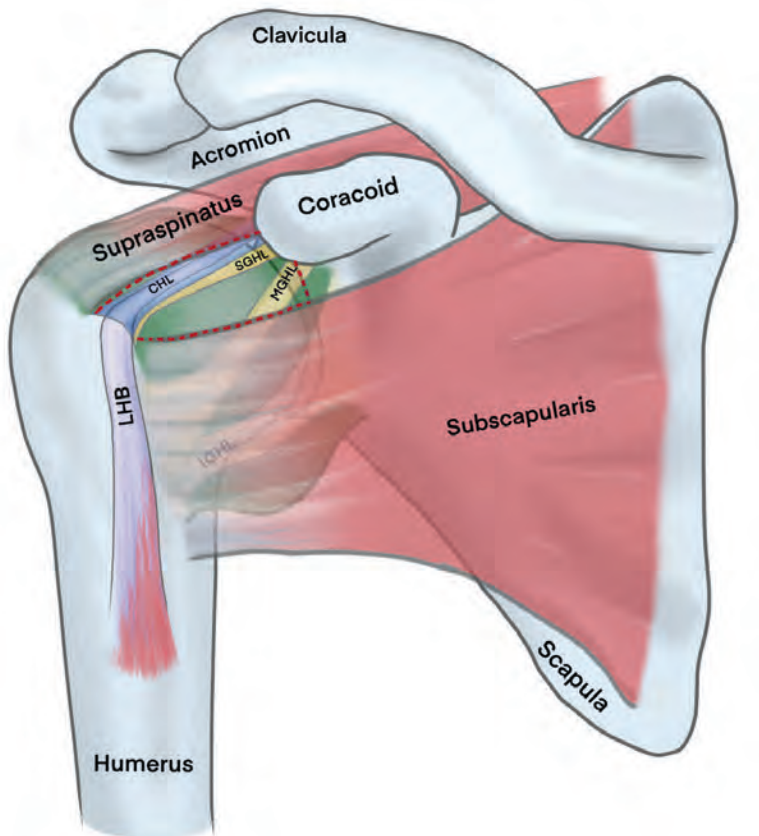


**Figure 1** Illustration of the shoulder joint, frontal view, with the rotator cuff muscles (subscapularis and supraspinatus) and the rotator interval highlighted with the red dotted line. (LHB = long head of biceps)

A frozen shoulder is a condition in which the glenohumeral capsule is the affected structure. The glenohumeral capsule, is a contained bag of fibrocollagenous tissue around the joint. An intact capsule preserves the negative pressure in the joint, and the joint is filled with synovial fluid, produced by the synovium, the inner layer of the capsule. The capsule is normally a thin layer of connective tissue and compliant enough to allow the remarkable wide range of motion of the shoulder. The capsule is reinforced by several bandlike structures, the glenohumeral ligaments, and together this provides passive stability at the end range of motion. (Figure 2) The superior glenohumeral ligament (SGHL) is a reinforcement of the anterosuperior capsule located on the articular side, or inner side of the rotator interval. It originates from the supraglenoid tubercle, just anterior to the long head of the biceps anchor, and inserts on the humerus, above the lesser tuberosity, at the medial aspect of the bicipital groove, just where the long head of the biceps enters the joint.[10] The coracohumeral ligament (CHL) is located on the extra-articular side, or the outer side of the rotator interval. It originates from the dorsolateral base of the coracoid, spans the rotator interval and is divided in two bundles. The medial bundle attaches to the rolled upper border of subscapularis and the lesser tuberosity. The lateral bundle inserts on to the anterior border the leading edge of supraspinatus and greater tuberosity. The medial bundle together with the superior glenohumeral ligament forms the medial biceps pulley complex and the lateral bundle is part of the lateral biceps pulley complex.[11] The middle glenohumeral ligament (MGHL) originates from the anterosuperior labrum, or the glenoid neck just medial to the labrum.[10] It runs obliquely across the intra-articular subscapularis tendon and attaches together with the upper subscapularis tendon on to the lesser tuberosity. The inferior glenohumeral ligament (IGHL) is divided in an anterior band and an inferior band, with the axillary pouch in between those two bands. The IGHL is the most important capsular stabilizer to prevent anterior dislocations in the abducted position.[12,13] It runs from the inferior half of the anterior labrum to the humeral neck, just inferior to the articular cartilage.[10]



## WHAT IS A FROZEN SHOULDER?

Frozen shoulder is a common cause of shoulder pain and restricted range of motion, with an estimated prevalence of 2-4% in the general population.[14] It affects mainly middle aged people in their fifth or sixth decade of life, occurring slightly more frequent in women than in men, with a slight predilection for the non-dominant arm.[15] Patients who have had a FS on one side have an increased risk, up to 20%, to develop a FS on the contralateral shoulder, but recurrence of a frozen shoulder in the same shoulder is rare.[16] The French physician S. Duplay first named the condition as 'peri-arthritis scapulo-humerale' in 1872.[17] Codman was the first to use the term 'frozen shoulder' in 1934, and described the condition as "difficult to define, difficult to treat, and difficult to explain".[18]

In 1945 Neviaser suggested the term adhesive capsulitis, because of his observation that the axillary fold became adherent to the humeral head, although the existence of true adhesions could not be confirmed in other studies.[19] Frozen shoulder and adhesive capsulitis are now interchangeably used in the literature for the same condition. The term frozen shoulder is chosen for this thesis.

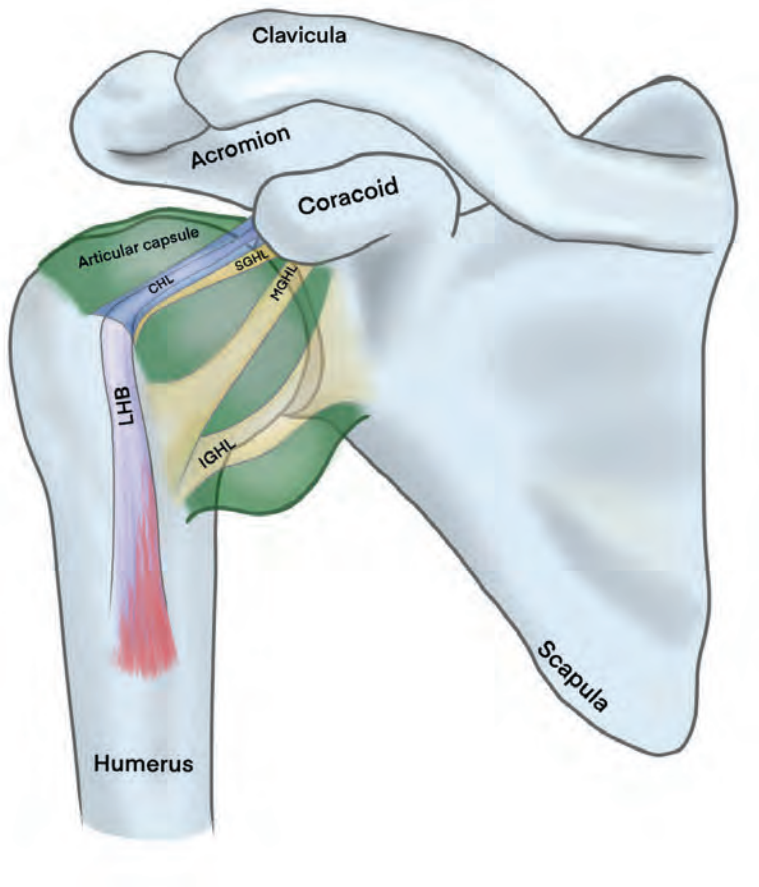


**Figure 2** Illustration of the articular capsule and the ligaments. (CHL = coracohumeral ligament, SGHL = superior glenohumeral ligament, MGHL = middle glenohumeral ligament, IGHL = inferior glenohumeral ligament, LHB = long head of biceps)

FS is typically a clinical diagnosis, made on the basis of history and physical examination. Loss of passive external rotation is the most characteristic finding at physical examination. There is no clear cut off for the restriction in passive range of motion for the diagnosis of FS. A decrease of 30 degrees in two planes of motion, or 50% or less of external rotation compared the contralateral side is frequently used. There is often pain on palpation over the coracoid area.[20] Pain can also be felt in the upper arm, over the scapula and around the acromioclavicular joint. Selective loss of passive external rotation is only associated with two other conditions; advanced glenohumeral osteoarthritis or a locked posterior shoulder dislocation, which can both be ruled out with conventional x-rays.[16] Shoulder kinematics are altered, with increased elevation and upward rotation of the scapula to compensate for the lack of range in in the glenohumeral joint. FS can be classified into idiopathic, or primary FS and secondary FS. Idiopathic FS is most common, when no underlying cause can be identified. There are some systemic metabolic conditions which are considerable risk factors to develop a FS, of which diabetes mellitus is the most important. The life time risk to develop a FS is 10-30% for patients with diabetes.[21] And more, FS tends to be prolonged and more refractory in diabetic patients.[22,23] This is probably due to impaired remodelling capacity of the connective tissue caused by crosslinking between the collagen fibers under influence of hyperglycaemia.[24] Thyroid disorders, hyperlipidemia and cardiovascular disease are other systemic predisposing factors.[25]



In secondary frozen shoulders, there is a known condition correlated to stiffness, such as a fracture to the upper limb treated with immobilization, a surgical procedure to the shoulder, surgery or radiation to the chest wall for example in breast cancer. The term secondary frozen shoulder is rather confusing because the underlying pathophysiology is most likely different from idiopathic frozen shoulders. Therefore, it might be better to use the term ‘secondary shoulder stiffness’ if an underlying cause is known, and to use the term frozen shoulder exclusively for idiopathic frozen shoulders.[26,27]

## NATURAL HISTORY

The natural history of FS is most commonly divided in three stages, originally described by Reeves.[28] Stage 1 is called the freezing stage with severe pain, and increasing stiffness. Patients usually report an insidious onset of pain before they notice a loss in their range of motion.[29] It starts with a general shoulder pain which can be achy at rest and sharper with every motion. Early on in the development of a FS, it is not that easy to diagnose a FS because pain prevails and symptoms are non-specific. In stage 2, the frozen stage, the general pain at rest settles down, and pain is typically present at the end range of motion. Restriction of range of motion is evident with a firm endpoint on passive examination.[30]

Stage 3 is the thawing stage, which is characterized by gradual recovery of range of motion and decreasing pain. The duration of different stages can vary, and there are no cut off values for each stage. In fact, the stages represent a continuous spectrum of disease rather than clearly separated stages. A simplification was suggested by Lewis with a 'pain greater than stiffness' stage and a 'stiffness greater than pain' stage.[19] A more comprehensive classification with 4 stages is described by Hannafin.[31] This classification is based on duration of symptoms, physical examination including the range of motion under anesthesia, arthroscopic and histologic findings. A short first stage, preceding the freezing stage is defined, in which the majority of motion loss is caused by painful synovitis but not by capsular contraction yet. It's impossible to fully use this classification in clinical practice, since the majority of FS patients do not require examination under anesthesia and a surgical procedure to objectify arthroscopic and histologic findings, but it is certainly helpful to increase our understanding of the condition.

FS is often considered a self-limiting condition, with spontaneous resolution of symptoms within one to three years.[16,32] However, complete resolution of symptoms is slightly disputable. Vastamäki et al showed a good recovery with pain less than 3 out of 10 in 94% of their patients treated non-operatively at long term.[33] And more, Diercks et al found a Constant score of over 80 (a near normal shoulder function) in 89% of their patients treated with supervised neglect.[34] On the contrary, multiple studies have shown that residual pain and restricted range of motion can occur after non-operative treatment, even at long term. Hand et al showed in a natural history study with more than 4 years follow up that 35% of their patients still had mild to moderate symptoms. Six percent had severe symptoms of pain and a decreased shoulder function.[35] Griggs et al showed that range of motion does not fully recover to normal after conservative treatment, although a satisfactory result was met in 90% of patients with conservative treatment.[36] In the study of Shaffer et al, 35% of patients had mild pain after a mean follow up of 7 years, and 30% of their patients had a measurable restriction in range of motion.[37] So, most authors agree that there is a small minority of patients with a refractory frozen shoulder that do not reach a satisfactory outcome after conservative treatment, and mild residual symptoms do occur at long term. Since there is a lack of long term follow up studies after surgical treatment of FS, it is not known whether surgical treatment leads to better results at long term compared to conservative treatment. However, even if the condition is self-limiting, patients with a FS will have an extensive period of pain and marked disability, affecting their quality of life including their capacity to work.[38] Therefore, it should be our goal as orthopedic surgeons, together with other healthcare professionals, to reverse the process of joint contracture early on in the disease or to shorten the duration of symptoms.

## PATHOPHYSIOLOGY

The pathophysiology of FS is not completely understood yet. The restriction in passive range of motion in frozen shoulders is caused by tissue fibrosis, resulting in a thickened contracted glenohumeral capsule. (Figure 3) The normal shoulder joint (without distension) has a volume of at least 15ml, and on average 20ml.[39,40] Old fashioned arthrography studies have shown that in FS the joint volume is often less then 5ml.[39] Capsular stiffness is demonstrated in studies measuring the intra-articular pressure while distending the capsule by infusing a solution. Pressure volume curves show a much steeper rise in FS compared to controls, indicating greater capsular stiffness. Maximal intra-articular joint pressure rises over 400mmHg in FS patients compared to 75mmHg in healthy controls, and capsular rupture occurs in FS at a much lower volume compared to normal shoulders.[41–43] Tissue fibrosis in FS is resembling to Dupuytren's contracture in the hand, but it is unique for FS that spontaneous resolution can occur.[44] It has long been recognized that anterior structures, as the anteroinferior capsule, the coracohumeral ligament and the rotator interval are involved in the pathophysiologic process of frozen shoulders. This explains the characteristic finding of loss of passive external rotation.[45]

The main histologic finding in capsular tissue biopsies are a high number of fibroblast, differentiated into myofibroblasts, within an extracellular matrix (ECM) of densely packed type III collagen.[31] More recent publications have shown that one of the first steps in the development of a FS, preceding the cascade of tissue fibrosis, is an immune response with increased expression of inflammatory cytokines.[46,47] In **Chapter 2** a detailed overview with all the currently known relevant aspects of the complex pathophysiology of FS is summarized. We do understand the process of tissue fibrosis quite well, however, the key is to find the trigger how this process is started. Ideally, this should lead eventually to early identification of a frozen shoulder together with an intervention to stop and reverse the cascade of tissue fibrosis.

## IMAGING

In clinical practice, imaging is mainly used to rule out other pathology before the diagnosis of a frozen shoulder is stated. Conventional radiographs in two directions are usually sufficient, and these are typically without any abnormalities in FS patients, except for disuse osteopenia or cuff calcifications.[48] Cuff calcifications can be a coincidental finding without clinical relevance in FS patients, but there is some evidence that shows that calcifications seem to increase the risk of developing a FS.[49,50] Ultrasound and MRI are not routinely used for the diagnosis of FS. However, both ultrasound and MRI can be used to rule out rotator cuff tears in case of a traumatic origin of shoulder stiffness.

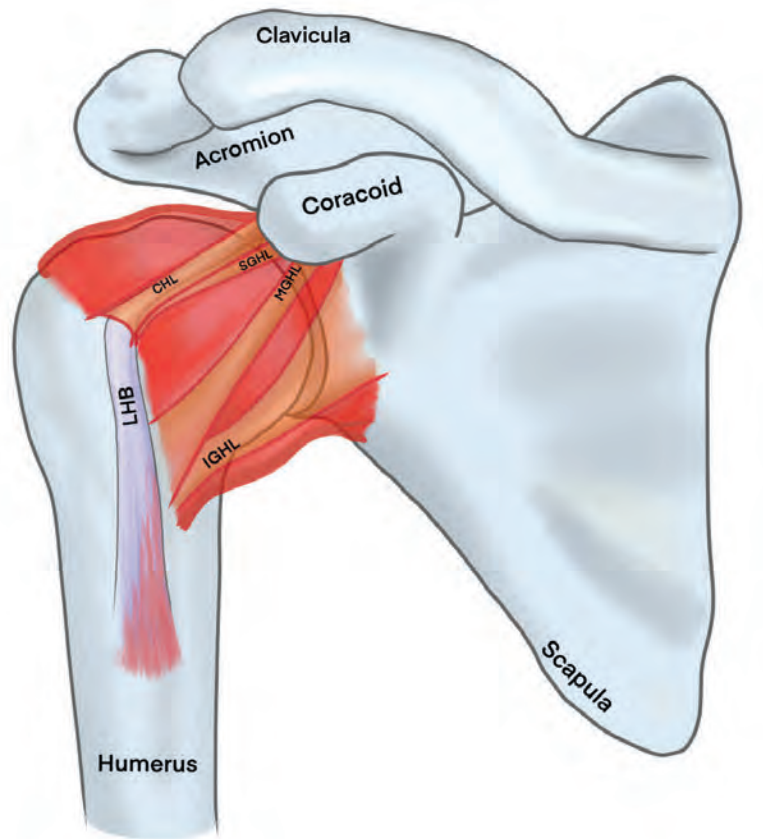


**Figure 3** Illustration of a frozen shoulder. The glenohumeral capsule is thickened and contracted with a reduced volume of the axillary pouch

The characteristic MRI findings in frozen shoulders are well described. Thickening of the joint capsule and synovial membrane can be appreciated, especially in the rotator interval with thickening of the CHL and SGHL.[51,52] Synovitis can be seen around the long head of the biceps tendon.[53] Thickening of the capsular tissue in the axillary pouch, with obliteration of the axillary recess is another characteristic MRI finding in FS. Obliteration of fat in the subcoracoid triangle on the sagittal views occurs in the later stage of the condition.[54]

## TREATMENT OPTIONS

There is a wide variety of treatment options available for the treatment of frozen shoulders. These can be divided in conservative measurements and more invasive or surgical interventions. **Chapter 3** entails the first exploratory survey of this thesis in order to gain insight into the preferred treatment strategies of frozen shoulders among shoulder specialists in the Netherlands and Belgium.

It is believed that there is currently enough evidence to state that conservative treatment with non-steroidal anti-inflammatory medication (NSAIDs), intra-articular corticosteroid injections with or without physiotherapy, is sufficient for the majority of patients.[33,55] Intra-articular corticosteroid injections have an established role in the treatment of frozen shoulders.[56–58] It is thought that corticosteroids are most effective in stage 1, with the ability to modulate the fibroblast differentiation and reduce inflammation.[59] A decrease in pain and improved function with corticosteroid injections compared to placebo injections has been shown repetitively, at least at short term.[60]



The role of physiotherapy in the treatment of FS is somewhat controversial. Patients often report worsening symptoms after attempted physiotherapy treatment. This is especially true for the initial stage of the condition, and might even represent the worsening natural history of the condition in the first stage. On the other hand, it seems to be quite evident that physiotherapy can have a supportive role and enhance recovery of shoulder range of motion. It is important that the intensity of exercises, stretching and mobilization techniques should be guided by pain. In other words, 'tissue irritability' must be taken into account.[30,61] Furthermore, there is some evidence that physiotherapy is more effective in conjunction with intra-articular corticosteroid injections compared to physiotherapy alone.[62] In **Chapter 4** the additional value of physiotherapy after an intra-articular corticosteroid infiltration for the treatment of FS is investigated in a randomized controlled trial.

However, when NSAID's, corticosteroid infiltrations and physiotherapy are not sufficient, the question is whether a more invasive intervention is justified. Arthrographic distension injection, manipulation under anesthesia (MUA) and arthroscopic capsular release (ACR) are the most commonly used procedures.

Arthrographic distension (also known as hydrodilatation, or hydraulic distension) is a technique wherein a fluid, usually containing saline and corticosteroids, is injected in to the joint under image guidance. A relatively high volume of fluid (30-90ml) is injected with pressure to distend the joint until a tolerable level of pain, or until rupture or impending rupture of the capsule.[63] Although this can be performed as quite a simple

outpatient clinic procedure, the additional value of distension over a regular intra-articular corticosteroid injection is questioned.[58,64]

Traditionally, MUA was a well-established treatment if conservative measures had failed. The tight shoulder capsule can be stretched and torn with manipulation, and is usually followed by intensive physiotherapy. MUA is relatively easy to perform and can restore range of motion rapidly.[65]

However, with the rise of shoulder arthroscopy, the arthroscopic capsular release has gained popularity at the expense of the reputation of MUA. Opponents of MUA argue that it cannot be seen or felt what structures other than the joint capsule are damaged during manipulation. With arthroscopy, the contracted capsule can be visualised and cautiously released circumferentially. However, there is no evidence that shows superiority of one of these procedures over the other.[66] In fact, there is no randomized trial comparing the efficacy of these procedures yet. In **Chapter 5** it is aimed to compare these two most common interventions, ACR and MUA, in the treatment of FS. Both interventions have their own advantages and disadvantages and this is presented based on the current relevant literature.

Furthermore, it is difficult to define a clear indication for a surgical procedure as MUA or ACR. Failure of conservative treatment is only a descriptive term which can be interpreted freely. In other words, the threshold for orthopedic surgeons to proceed with an intervention will vary, and choosing the right timing is important. If a wait and see policy is maintained too long, some patients will probably suffer longer than necessary. But a low threshold to proceed with a surgical intervention will most likely lead to a considerable amount of needless procedures, given the natural course of this condition with spontaneous resolution of symptoms in the majority of patients.[33] An important paper for both general practitioners and orthopedic surgeons in the Netherlands was published in 2004 by prof dr. R. Diercks et al.[34] In their study, a cohort of patients was treated with supportive therapy and exercises within pain limits (supervised neglect), and compared to a successive cohort treated with intensive physical rehabilitation, beyond the pain threshold, including passive stretching and manual mobilization, in a quasi-experimental design. Both groups improved over time but the supervised neglect group had significantly better Constant scores after two years follow up. This study has perhaps reinforced our cautious and conservative attitude towards the treatment of FS patients, and this fits what is probably ingrained in our Dutch tradition to be very sound and careful to select patients for invasive interventions. However, this does not imply that the best we can do is to inform patients about their condition, reassure them that “it will get better in time” and further neglect them.

The survey in Chapter 3, showed that the highest volume of manipulations in the Netherlands were done in the Amphia hospital. This was the rationale to progress with research on the effectiveness of MUA. A systematic review is presented in **Chapter 6** including all articles reporting clinical results of MUA with a pooled analysis of pain scores and range of motion. The different indications for MUA, the technical variety in the procedure itself and the rehabilitation protocols are discussed in this review. The next step was to have a closer look at our own results of MUA. In **Chapter 7** the results of MUA performed in the Amphia hospital between 2012 and 2014 are presented in a retrospective cohort study. Although the results from the retrospective cohort study were encouraging, the two shoulder surgeons in this hospital still had a different threshold whether to proceed with MUA in the treatment of a FS. It was felt that a well-designed randomized controlled trial comparing MUA with conservative treatment was justified and desired. The study protocol for this RCT is presented in **Chapter 8**



The general aim of this thesis is to aid clinical decision making for orthopedic surgeons in the treatment of FS patients, guiding orthopedic surgeons when to do more than just 'supervised neglect'. This starts with a better understanding of the complex pathophysiology of frozen shoulders. Next, optimizing conservative treatment with physiotherapy and injections is addressed. The objective of the final part of this thesis is to give insight in the effectiveness and the role of manipulation under anesthesia in the treatment of frozen shoulders.

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# CHAPTER TWO

## The puzzling pathophysiology of frozen shoulders – a scoping review

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# ABSTRACT

**Background** The pathophysiology of frozen shoulders is a complex and multifactorial process. The purpose of this review is to scope the currently available knowledge of the pathophysiology of frozen shoulders.

**Methods** A systematic search was conducted in Medline, Embase and the Cochrane library. Original articles published between 1994 and October 2020 with a substantial focus on the pathophysiology of frozen shoulders were included.

**Results** Out of 827 records, 48 original articles were included for the qualitative synthesis of this review. Glenohumeral capsular biopsies were investigated in 30 studies. Fifteen studies were classified as association studies. Three studies investigated the pathophysiology in an animal studies. A state of low grade inflammation, as is associated with diabetes, cardiovascular disease and thyroid disorders, predisposes for the development of frozen shoulder. An early immune response with elevated levels of alarmins and binding to the receptor of advance glycation end products is present at the start of the cascade. Inflammatory cytokines, of which transforming growth factor-β1 has a prominent role, together with mechanical stress stimulates fibroblast proliferation and differentiation into myofibroblasts. This leads to an imbalance of extracellular matrix turnover resulting in a stiff and thickened glenohumeral capsule with abundance of type III collagen.

**Conclusions** This scoping review outlines the complexity of the pathophysiology of frozen shoulder. A comprehensive overview with background information on pathophysiologic mechanisms is given. Leads are provided to progress with research for clinically important prognostic markers and in search for future interventions.

## BACKGROUND

Frozen Shoulder (FS) is a common cause of shoulder pain associated with restricted active and passive range of motion. Although this condition has been recognized as a clinical disease entity for about 150 years, we still have not unraveled the pathophysiology yet. FS has often been described as a self-limiting condition, with recovery within two to three years for the majority of patients.[1] However, symptoms of mild to moderate pain and stiffness are reported in 27-50% of patients at long term.[2–4] Even in patients with a favorable natural course of the condition, there is still an extensive period to deal with pain, and functional limitations.

Current surgical interventions, such as manipulation under anesthesia or arthroscopic capsular release, are aimed at the advanced stage of the disease, when the fibrotic cascade has already had its effect. To optimize treatment the treatment of FS, it is of fundamental importance to get a better understanding of the pathophysiology. With advancing knowledge, it might become possible to intervene early on in the disease process.



The aim of this scoping review is to systematically collate the currently available knowledge that we have about the pathophysiology of FS. The histologic findings and the mechanism of tissue fibrosis on a cellular level are addressed. The purpose is to give and apprehensible overview which aids clinicians in the understanding of the pathophysiology and to translate this to clinical implications.

## METHODS

A systematic search in Medline, Embase and the Cochrane library was conducted in all three databases on the fifth of October 2020. The search was build including the following terms; “frozen shoulder”, or (“shoulder” AND “adhesive capsulitis”), “pathophysiology”, (“etiology” or “aetiology”) and (“histology” or “anatomy and histology”). Publications had to be original papers published in English after the first of January 1994. The limit of 1994 was chosen since the techniques to analyze tissue samples of more than 25 years ago are most likely outdated and therefore not relevant anymore. Articles were eligible for inclusion if the there was a substantial focus on the pathophysiology of FS. All studies on tissue samples from FS patients were eligible for inclusion. Association studies between medical co-morbidities and FS were only eligible if the pathophysiologic mechanism between the investigated condition and FS was discussed. Basic science studies (in vitro or animal model studies) were eligible for inclusion if the aim of the article was to clarify the pathophysiology of FS. Reviews, case reports and imaging studies were excluded.

# RESULTS

A number of 1088 potential relevant studies were identified in the searches. After removal of duplicates, titles and abstracts were screened from a total of 827 studies. A low threshold was used to verify if the full text articles included unique or relevant information on the pathophysiology of FS. This resulted in 48 original studies eligible for inclusion in the qualitative synthesis of this review. A PRISMA flow chart of the review process is presented in figure 1. (Figure 1)

The 48 included articles are categorized by study design in three tables, in a chronological order. The most relevant finding for each article is given. Table one shows all 30 original articles wherein tissue samples from the glenohumeral joint were analyzed. These are mostly case control studies with a small number of patients. The controls were usually patients undergoing arthroscopy for different shoulder pathology like instability or rotator cuff surgery. The number of FS patients, controls, biopsy location and used method for tissue analysis is described for each study. (Table I) Table two shows 15 association studies wherein the pathologic mechanism between a certain co-morbidity (e.g. diabetes, thyroid disorder) and FS is discussed. This includes studies investigating the association between FS and serum levels in peripheral blood, for example hormones, lipids or gene polymorphism. (Table II) Table three displays three animal (rats) studies investigating the pathophysiologic pathways in FS in detail. (Table III)

Table I, II, and III are displayed at the end of this chapter.

## PATHO-ANATOMY

The restriction in passive range of motion in FS is caused by a contracted glenohumeral capsule. The normal shoulder joint has a volume of at least 15ml, and on average 20ml.[5] In FS, the joint volume can be less then 5ml.[6] Capsular stiffness is demonstrated in studies measuring intra-articular pressure while distending the capsule. Pressure volume curves show a much steeper rise in FS compared to controls and capsular rupture occurs in FS at a much lower volume with higher pressures compared to normal shoulders.[7–9] It has long been hypothesized that the rotator interval with the coracohumeral ligament (CHL) is involved in the pathophysiologic process of FS, and might have a pivotal role in the development of FS, and the rest of the joint capsule is involved later on in the process.[10–13] The CHL spans the extra-articular side of the rotator interval, is strained in external rotation, and release of the CHL is an important part of the surgical release of a FS.[14,15] Several other findings are reported in the literature that support a prominent role in the etiology of FS for the rotator interval. Ultrasound guided corticosteroid injections in the rotator interval and around the CHL had greater effect on pain and range of motion compared to intra-articular corticosteroid injections directed from

posterior.[13] Fluorodeoxyglucose (FDG)-PET CT scans in FS demonstrate that FDG uptake is predominantly located in the rotator interval, anterior joint capsule and axillary recess.[16] Angiography studies identified neovascularization, branching of the thoracoacromial artery, in the rotator interval of FS patients.[17] Upregulation of proteins involved in collagen metabolism, cell adhesion and the immune response were identified in the rotator interval of FS patients.[18] The gliding mechanism of the biceps tendon sheat, the lateral border of the rotator interval, was involved to a variable degree.[19]

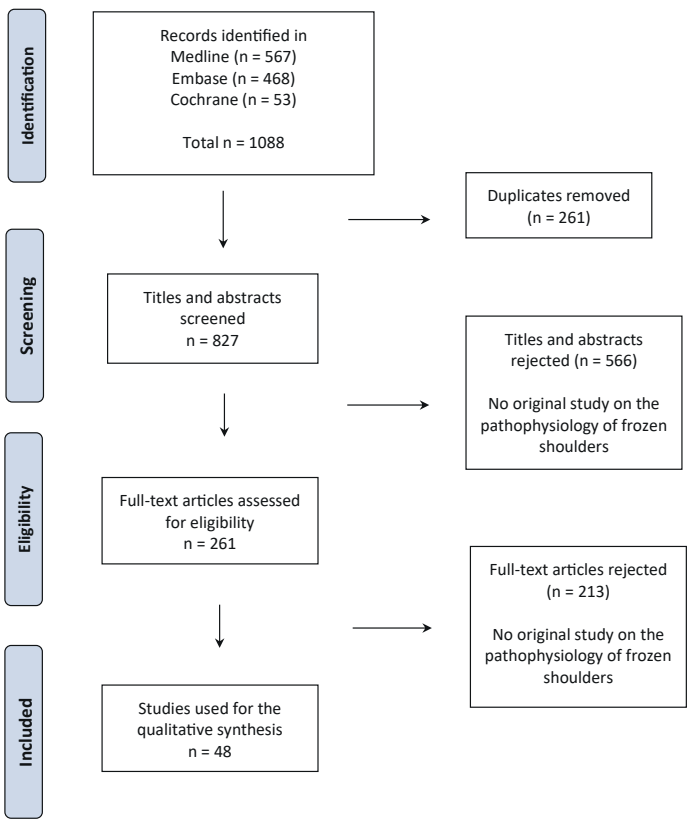


**Figure 1** PRISMA flow chart of the systematic search and review process

## HISTOLOGIC FINDINGS

Several authors have studied biopsies of the rotator interval and glenohumeral capsule. Early in the disease process, inflammatory changes with subsynovial hypervascularity, synovial hyperplasia, and fibroblastic proliferation with an increased number of

fibroblasts (fibroplasia) is found.[20] This is accompanied by the formation of new nerve fibers around small blood vessels. Neogangionesis is demonstrated by overexpression of hematopoietic cell marker, CD34, and vascular endothelial growth factor (VEGF).[21] Neurogenesis is driven by an increased expression of nerve growth factor receptor p75.[22] Besides nerve ingrowth, pro-inflammatory mediators upregulate the acid sensing ion channels that contribute to hyperalgesia.[23] Later on in the disease process, when stiffness is established, the signs of inflammation can disappear gradually.[24] In this stage, an increased number of differentiated fibroblasts into myofibroblasts are seen within an extracellular matrix (ECM) of densely packed disorganized type III collagen.[25] The increased number of contractile myofibroblasts can be picked up with alfa smooth muscle actin (α-SMA) staining, a marker for the differentiation of fibroblasts in myofibroblasts. It has been demonstrated that α-SMA staining is not that prominent yet in the early stage of the disease compared to a more mature FS.[26] To summarize, in the early stage of FS, inflammatory changes can be seen with synovial hyperplasia and subsynovial hypervascularity and neurogenesis. Whereas in the later stage inflammation usually disappears gradually and tissue fibrosis occurs with a high number of fibroblasts within an ECM of densely packed type III collagen. (Figure 2)

## FIBROBLAST CONTRACTILITY: THE ROLE OF TGF-β1 AND MECHANICAL STRESS

Not only the abundancy of collagen, but also the contractility of fibroblasts in the ECM is a prerequisite to stiffening of the tissue. Myofibroblasts can contract by using a smooth muscle type actin/myosin complex. Vimentin, a cytocontractile protein and marker for contractility, has been shown to be overexpressed in capsular biopsies of FS patients.[30] Interestingly, although fibroplasia has been shown to occur in the entire joint capsule in FS, capsular contracture measured by vimentin staining was more pronounced anteriorly compared to posteriorly.[31]

Transforming growth factor-β one (TGF-β1), and mechanical stress are two important factors contributing to contractility of fibroblasts.[32] TGF-β1, an inflammatory cytokine, is present in a lot of tissues throughout the human body, and can be secreted by parenchymal cells, epithelial cells, fibroblasts and by influxing immune cells.[33] The TGF-β1 signaling pathway is believed to have a central role in fibrotic diseases.[34,35] TGF-β1 has been shown to stimulate contractility of fibroblasts *in-vitro* collagen gels and can be seen as a potent activator of myofibroblasts.[36,37] The expression of TGF-β1 and its receptor is increased in biopsies of the joint capsule in FS patients.[38] Besides stimulating myofibroblast differentiation, TGF-β1 also influences ECM turnover by promoting collagen synthesis. Certain genetic variants of genes for the TGF-β pathway and MMPs could be identified as risk factors for the susceptibility of FS.[39]

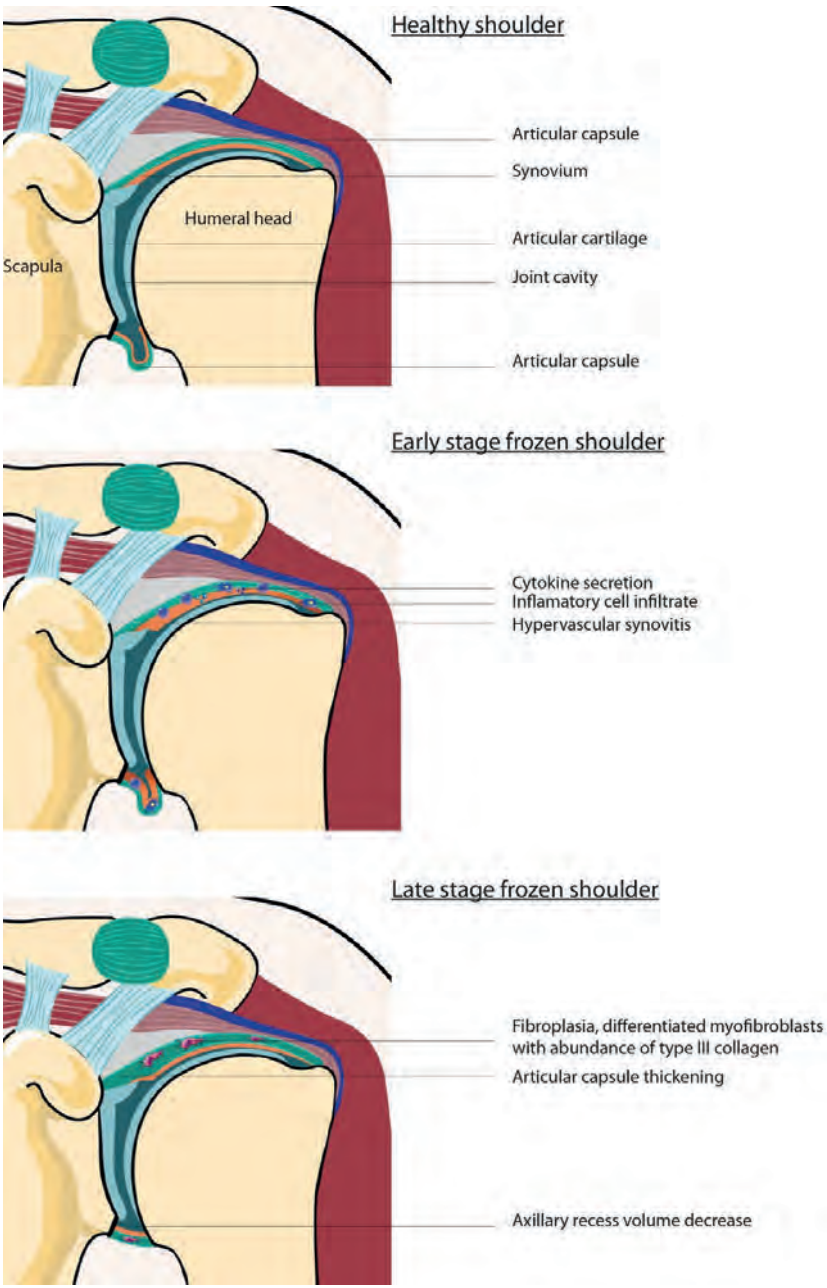


**Figure 2** (a) schematic drawing of a healthy shoulder, (b) the early stage, and (c) late stage frozen shoulder. Synovial inflammation precedes capsular fibroplasia, differentiation of myofibroblasts resulting in capsular thickening with reduction of compliance and capsular volume

Besides chemical stimulation by cytokines like TGF-β1, mechanical stress is also an important factor in tissue fibrosis. Fibroblasts are mechano-responsive cells, which means that they can 'sense' mechanical stress in the ECM with their intracellular cytoskeleton, and their differentiation in to myofibroblasts is stress dependent. *In-vitro* studies showed that fibroblasts seem to have a threshold for mechanical stress which needs to be reached before they differentiate in to myofibroblasts.[40] Furthermore, mechanical stress has the ability to activate latent TGF-β1, hereby upregulating the process of tissue fibrosis. So, both mechanical stress and TGF-β1 are two important closely interrelated factors in the process of tissue fibrosis.[41] This process is actually a self-reinforcing process. When the tissue gets stiffer, tissue compliance decreases and the mechanical stress recorded by the fibroblasts increases inherently.

## CHRONIC LOW-GRADE INFLAMMATION MIGHT PREDISPOSE TO THE DEVELOPMENT OF FROZEN SHOULDER

Several authors have hypothesized an association with a chronic state of low grade inflammation which might predispose to the development of FS.[42] Several association studies support this theory.[43–45] Fasting serum cholesterol, triglycerides and plasma glucose levels are often elevated in FS.[25,46] Inflammatory lipoproteins such as LDL and non-HDL, associated with vascular inflammation and immune reactions, are known risk factors for atherosclerosis. However, these inflammatory lipoproteins have also been identified as independent risk factors for FS.[45,47] Vascular endothelial cell activation is accompanied by increased expression of intercellular adhesion molecule-1 (ICAM-1), a well-established marker of chronic inflammation. It has also been shown that ICAM-1 levels are elevated in the joint capsule and synovial fluid of FS patients compared to controls.[48] Similar to ICAM-1, is TIMP associated with chronic inflammation. Diabetes mellitus (DM), cardiovascular disorders and thyroid disorders are conditions associated with chronic inflammation and increased levels of similar pro-inflammatory cytokines as are found in FS. This is, at least partially, an explanation why DM and thyroid disorders are strong risk factors for the development of FS, and supports the theory of a chronic state of low-grade inflammation as a predisposing factor in the etiology of FS.[49]

## AN EARLY INFLAMMATORY RESPONSE AT THE ONSET OF FROZEN SHOULDER

Traditionally, fibroblasts are known for their structural role in the synthesis and remodeling of ECM in connective tissue. However, fibroblast can also act like sentinel cells involved in immune responses, and thereby modulate the recruitment of immune cells and regulate their behavior.[50,51] A chronic inflammatory cell infiltrate with mast cells, macrophages, B- and T-cells has been shown to be present in rotator interval biopsies from FS patients.[52] Recent publications suggest that an immune response with an overexpression of inflammatory cytokines is one of the first steps in the development

of a FS, preceding the cascade of tissue fibrosis.[53,54] Cytokines can regulate proliferation, activation and differentiation of fibroblasts, hereby dysregulating collagen synthesis.[55] Multiple studies have shown increased levels of pro-inflammatory cytokines such as TGF-β1, tumor necrosis factor-α (TNF- α ), Interleukin-1 and -6 (IL-1, IL-6) and platelet derived growth factor (PDGF) in joint fluid and capsular tissue in FS.[53,54,56] Interestingly, increased levels of cytokines were also found in the subacromial bursa in FS patients.[53] When *in-vitro* cultured fibroblasts are stimulated with joint aspirates of FS patients, fibroblast proliferation was markedly elevated.[57] Furthermore, when fibroblasts were being activated, the inflammatory response was enhanced.[58] A recent study confirmed an elevated level of fibroblast activation markers in capsular tissue biopsies of FS patients compared to controls.[50] Persistent fibroblast activation is a potential cellular mechanism of symptoms of a prolonged frozen stage in FS.

Cytokine release and fibroblast activation is not the first step in the inflammatory response. Capsular biopsies of FS patients have shown elevated levels of several alarmins including High Mobility Group Box 1 (HMGB1) proteins, compared with controls.[59] Alarmins, or Damage-Associated Molecular Pattern (DAMP) molecules, are signal molecules released when cells are distressed, injured or 'in danger'. Alarmins are the early activators of the immune system and have a role in amplifying the inflammatory response in many inflammatory conditions.[60] HMGB1 can be released into the ECM upon cell death or stress where it mediates an inflammatory reaction. *In-vitro* cultured human dermal fibroblast and lung fibroblasts stimulated by HMGB1 have been shown to produce more TGF-β1, thereby activating the TGF-β signaling pathway and subsequently significantly upregulate myofibroblast differentiation. And more, HMGB1 has the ability to bind to the receptor of AGE (Advanced Glycation End products) and to activate a pro-inflammatory response through the Nuclear Factor κB (NF-κB) pathway inducing TGF-β1 release.[61,62] Although an elevated level of alarmins in frozen shoulder capsular biopsies might be quite an aspecific finding, this is an indication that an inflammatory response has an important role at the onset of the pathophysiologic process of FS, triggering the inflammatory cascade leading to tissue fibrosis.

## THE IMPLICATIONS OF HYPERGLYCAEMIA IN FROZEN SHOULDER

The lifetime prevalence of FS in diabetic patients is with 10-30% much higher than 2-5% in the general population.[63–65] The higher the cumulative hemoglobin $A_{1c}$ level, the higher the incidence of FS.[66] FS tends to be prolonged and more refractory to conservative treatment in diabetics.[67] The exact mechanism behind this is most likely multifactorial. Several authors have hypothesized an important role for AGEs. AGEs are formed by a process called non-enzymatic glycation when glucose forms covalent adducts with proteins, caused by oxidative stress. When AGEs bond to long-lived proteins they cannot be degraded by normal remodeling, and accumulate in connective tissue. This is a normal

process which happens progressively with aging, can be slowed down by endurance training, but is accelerated in patients with DM.[68] A particular non-enzymatic 'AGE' reaction of interest is the alteration of collagen proteins by crosslinking.[69,70] Excessive levels of AGEs can lead to pathological collagen crosslinking and structural changes in the tissue, making the tissue less compliant.[71] The level of AGEs has been shown to be significantly higher in capsular tissue samples of FS patients compared to controls.[70] AGEs have also been shown to decrease the expression of MMPs and increasing TIMP expression in diabetic nephropathy, similar to the pathogenic mechanism of imbalance in ECM turnover in FS.[72] And more, it has been shown in diabetic retinopathy and nephropathy that AGEs accumulation can lead to an increased expression of basic fibroblast growth factor and upregulation of the expression of profibrotic cytokines as TGF-β1, PDGF and connective tissue growth factors.[73] It is hypothesized that these pro-fibrotic actions of AGEs also have their role in the pathophysiology of FS, and are part of the explanation why FS in diabetic patients have a tendency to be refractory.[70]

## DISCUSSION

It is outlined in this review that the pathophysiology of frozen shoulder is a rather complex process. It involves an early inflammatory response, production of pro-inflammatory cytokines, enhanced fibroblast proliferation, activation and differentiation into myofibroblasts, and an imbalance in ECM turnover with an abundance of disorganized collagen III deposition (Figure 3). It is clear that there are a lot of factors involved, and we have most likely not identified all related factors yet. There are some important questions that remain unanswered. - A chronic state of low-grade inflammation plus an unknown trigger

**Figure 3** Diagram with important steps in the pathophysiology of frozen shoulders

- Alarmins, such as HMGB1 are released, "the early activators of the immune system"
- Inflammatory response with increased expression of several pro-inflammatory cytokines such as IL-1, IL-6, TNF-α, TGF-β and PDGF
- Alarmins bind to the receptor of AGE, activating the NF-κB pathway, inducing TGF-β release
- Mechanical stress and the TGF-β signalling pathway leads to fibroplasia, an increased number of fibroblasts
- Fibroblasts become activated and differentiate into myofibroblast, increased contractility is shown by α-SMA and Vimentin
- The balance of ECM turnover is disturbed, with reduced levels of MMPs compared to TIMPs, with collagen deposition exceeding degradation
- Abundancy of densely packed, disorganized collagen type III
- Crosslinking of the collagen fibers under influence of AGEs, further decreases capsular compliance

Trigger (unknown)
Chronic state of low-grade inflammation
- Diabetes Mellitus
- Thyroid disorders
- Inflammatory lipoproteins
Alarmins (e.g. HMGB1) "early activators of the immune response"
Pro-inflammatory immune response
Binding to the receptor of AGE
- TNF-α
- IL-1 + IL-6
- PDGF
- VEGF
- TGF-β
NF-κB pathway activation
AGEs
Cytokines and growth factors
Mechanical stress
Activation and differentiation
Fibroblasts
Myofibroblast (α-SMA, Vimentin)
+ Crosslinking of collagen
+ Increasing TIMP expression
MMP
TIMP
imbalance in ECM turnover
Collagen type III

Figure 3

## WHAT TRIGGERS THE ONSET OF A FROZEN SHOULDER?

As with many diseases, it is still unclear what triggers the onset of the disease. Microtrauma has been suggested as a trigger, although this is hard to support with evidence.[74] With the identification of predisposing factors we do get a better understanding of the etiology. An increasing amount of evidence supports a chronic state of low-grade inflammation as an important predisposing factor for the development of FS.[42,45,47,75,76] Markers of chronic inflammation (ICAM-1, TIMP) are elevated in FS patients, and pro-inflammatory lipoproteins are significant risk factors for FS, similar to patients with cardiovascular disease or metabolic syndrome.[45,48] The incidence of FS is so much higher in patients with DM and thyroid disorders, since these conditions are associated with a chronic state of inflammation.[49,77] Even depressive personality traits are sometimes linked to FS, and depression is also associated with enhanced inflammatory cytokine levels.[78] It seems plausible that female hormones might be related in this context, since the peak incidence of FS is in perimenopausal women. However, a clear explanation, or a direct relationship between female hormones and FS was not found in the current literature.

## WHY ONLY THE SHOULDER?

How is it possible that FS is a condition unique for the shoulder without similar conditions in other joints? Pietrzak et al hypothesized an evolutionary explanation.[79] The ability to throw accurately and forcefully is an important ability acquired during human evolution. Therefore, the shoulder is built for elastic energy storage and generation of maximal shoulder external rotation.[80] In our modern sedentary lifestyle without the need for throwing or overhead activities, parts of the anterior shoulder capsule and ligaments are probably not being exercised or stretched sufficiently. This makes the (anterior) shoulder capsule and ligaments probably more susceptible to oxidative stress, related to cytokine production and the formation of AGEs.[75] Although it is uncertain how much of this is true, this could potentially explain why FS is seen less frequently in manual laborers, and why the dominant side seems less likely to be involved.[2,3,74,81]

It is debatable whether FS is truly unique to shoulders. Is the capsule of the shoulder so much different to that of other joints? The joint capsule has to be compliant and allows the widest range of motion of all our joints. Is this why shoulder fibroblasts are more ‘sensitive’ to inflammation or mechanical stress? There is some literature about a similar condition in hips, ankles and also knees. However, the currently available literature are mainly case reports of conditions seldomly seen in clinical practice.[82,83] Contractures with fibrosis do occur frequently mainly in knees and elbows, but without the potential for spontaneous recovery as FS has. We did try to find clues why and how the reversibility happens in FS, but we are not able to find an answer to this question. Apoptosis of the myofibroblasts is probably what occurs in the final stage of the condition, this is how they normally disappear from granulation tissue after wound healing.[8427]

## CLINICAL IMPLICATIONS AND POTENTIAL FUTURE TREATMENT STRATEGIES

Physiotherapy and corticosteroids are the most widely used treatment modalities in FS. There is reasonable evidence for the use of intra-articular corticosteroids in the treatment of FS.[85] Corticosteroids have a general suppressive effect on the inflammatory response and hampers the differentiation of fibroblasts into myofibroblasts. Evidence of less α-SMA staining was found, indicating less myofibroblasts, in capsular biopsies in patients treated with corticosteroid injections compared to patients without corticosteroids.[84] One can also understand that the earlier in the disease process the corticosteroid injection is administered, the greater the effect on the clinical symptoms. Corticosteroids can suppress the inflammatory response, but they cannot reverse the fibrotic changes later on in the cascade. When administered in the frozen stage later on, the effect of corticosteroids is usually more temporarily.[86]



The negative effect of physiotherapy including mobilization techniques beyond the threshold of pain early on in the disease is explained by the mechanosensitive properties of the fibroblasts.[87] It is hypothesized that the inflammatory response is probably sensitizing the fibroblasts more to mechanical stress. On the other hand, stretching exercises up to a tolerable level of pain resulted in an increase in MMP/TIMP ratio, hereby favoring collagen remodeling and was found to be superior to supervised neglect in the study of Lubis et al.[29] Some mechanical stress is apparently necessary for the remodeling of ECM, especially in the later stage of the condition. This is why tissue irritability, guiding treatment intensity, is implemented in physiotherapy guidelines for the treatment of FS.[88]

More advanced treatment strategies have been suggested to intervene with the inflammation-fibrosis cascade in different ways. The TGF-β pathway was interrupted by silencing the Smad4 gene in rats with a FS induced by immobilization, through transfection with a lentivirus.[35] Smad proteins are mediators in the TGF-β signaling cascade. Silencing of this gene suppressed the TGF-β pathway, impairing the inflammatory response and myofibroblast differentiation. The rats with the silenced Smad4 gene had better shoulder range of motion and an increased joint volume compared to rats without Smad4 silencing.[35] Systemic inhibition of TGF-β might have unwanted side effects since it is also an important cytokine for connective tissue homeostasis involved in the proliferation epithelial cells, endothelial cells and immune cells.[41] However, TGF-β inhibitors with low toxicity is a field of intense research. There are now clinical trials with TGF-β inhibitors in cancer patients.[89] Glenohumeral intra-articular infiltration of a TGF-β inhibitor, hereby minimizing systemic effects, could perhaps be a promising suggestion to intervene early on in FS.

Calcitonin was more or less accidentally discovered as a treatment agent for FS when postmenopausal women with FS were treated with calcitonin for osteoporosis.[90] Their FS symptoms improved significantly after the use of a nasal calcitonin spray. Calcitonin is a hormone, secreted by the thyroid, known to inhibit osteoclast activity and lowering the kidney excretion of calcium. The presence of abundant calcitonin receptors in fibroblasts of the shoulder synovium and capsule could be confirmed with immunohistochemistry. Cultured fibroblast from FS patient stimulated with salmon calcitonin showed a significant decrease in the production of collagen type I and III. Synthesis of TGF-beta1 mRNA was suppressed by salmon calcitonin, and the adhesion ability of the fibroblasts decreased with if treated with salmon calcitonin. Apoptosis of the cultured fibroblasts could even be induced with high levels of salmon calcitonin. The efficacy of nasal calcitonin spray was demonstrated in a placebo controlled double blind randomized trial.[91] This might also explain why patients with thyroid disorders have an increased risk of FS, since hypothyroidism and auto-immune thyroiditis can be accompanied by calcitonin deficiency.[92,93]

Intra-articular injections with human recombinant relaxin-2 is suggested as a potential agent for the treatment of FS.[94] Relaxin-2 is known because it is temporarily elevated to soften the cervix during child birth. In an animal study with in vitro cultured fibroblasts Relaxin-2 has been shown to up regulate MMP production, and to down regulate collagen production and expression of TIMP and TGFB-1. This results in a net breakdown of ECM proteins. Furthermore, Relaxin-2 seems to prevent fibroblast differentiation into myofibroblasts. The safety and efficacy still has to be investigated in a human clinical trial. Lee et al suggested HMGB1 as a therapeutic target and Hinz et al suggested to target the stress sensors of the fibroblasts, hereby rendering them blind for mechanical stress.[41,61] However, to what extend these options are realistic and safe options in the near future is unclear.

## LIMITATIONS

The search strategy for this scoping review was designed to keep our scope wide to make sure that all available relevant articles are included. A limitation is that the main selection criteria for this scoping review (a substantial focus on pathophysiology of FS) is subjective. Furthermore, the pathophysiologic findings are dependent on the stage of the condition and most of the current research data comes from patients with a refractory frozen stage. To make progress in our understanding of the onset of FS, it might be necessary to include patients early on in the freezing stage in research with histological and immunological analysis.

## REMARKS FOR THE FUTURE

There are some considerable clinical challenges for healthcare professionals dealing with FS patients. Based on just history and physical examination, it is impossible to predict what the natural course of a FS in an individual patient will be. This is relevant information, not only to inform the patient, but also for shared decision making on when to intervene. Research on prognostic factors for FS is surprisingly scarce. A worse prognosis can be expected in patients with DM and with severe symptoms on presentation.[95] Age over 60 has shown to be a favourable prognostic factor and gender is not correlated with the prognosis.[67] Immunological research seems crucial to get a better understanding of the individual variety in natural history of a FS. Perhaps immune composition in biopsies or biomarkers in synovial fluid can be used as prognostic factors to predict the natural course of FS. Collaboration of orthopedic surgeons with immunologists and rheumatologists is essential in order to move forward in this field of research.



## CONCLUSIONS

The complexity of the pathophysiology of FS is outlined in this review. A state of low grade inflammation, as is associated with DM, cardiovascular disease and thyroid disorders, predisposes for the development of FS. An early immune response with elevated levels of alarmins such as HMGB1 and binding to the receptor of AGE starts the cascade of inflammation. Activation of the NF-κB pathway together with mechanical stress stimulates release of inflammatory cytokines, of which TGF-β has a prominent role. Fibroblasts proliferate, become activated and differentiate into myofibroblasts. This results in an imbalance of ECM turnover and a stiff and thickened glenohumeral capsule with abundance of type III collagen. Based on the pathophysiologic mechanism in FS it can be explained why intra-articular corticosteroid injections should be used early on in the condition and why the intensity of physiotherapy should be guided by tissue irritability. Leads are provided to progress with research for clinically important prognostic markers and in search for early interventions in FS.

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**Table 1** Biopsy studies

| Author | Year | Study design | Biopsy location | n FS | n Controls | Analysis method | Most relevant findings |
|---|---|---|---|---|---|---|---|
| Hannafin[20] | 1994 | case series | anterior, inferior and posterior | 15 | - | histology | Frozen shoulder starts with a hypervascular synovitis followed by diffuse fibroplasia with thickening and contracture of the capsule |
| Bunker[25] | 1995 | case series | CHL + RI | 12 | - | immunohistochemistry | Active fibroblastic proliferation with differentiation into myofibroblasts and the deposition of thick nodular bands of collagen |
| Rodeo[96] | 1997 | case control | anterosuperior | 19 | 21 | immunohistochemistry | Hypervascular synovial hyperplasia with fibroblasts, occasional T-cells, B-cells and newly synthesized collagen type I and III was found. TGF-β, PDGF, IL-1β and TNF-α are involved in an inflammatory and fibrotic process in frozen shoulders |
| Bunker[97] | 2000 | case serie | RI | 14 | 4 | RT-PCR | The presence of mRNA for a large number of cytokines and growth was demonstrated in frozen shoulder capsular tissue |
| Ryu[21] | 2006 | case control | RI | 11 | 5 | immunohistochemistry, western blot | Immunostaining for VEGF was stronger in frozen shoulders compared to controls |
| Hand[98] | 2007 | case series | RI | 22 | - | immunohistochemistry | Fibroblastic proliferation and an infiltrate of chronic inflammatory cells (mast cells, T cells, B cells and macrophages) was found |
| Kilian [27] | 2007 | case control | RI | 6 | 6 | immunohistochemistry, RT-PCR | Significant enhancement of α-1(I) mRNA transcription (mature collagen) was found |

**Table 1** (Continued) Biopsy studies

| Author | Year | Study design | Biopsy location | n FS | n Controls | Analysis method | Most relevant findings |
|---|---|---|---|---|---|---|---|
| Uhthoff[99] | 2007 | case series | 5 different locations | 4 | - | immunohistochemistry | Fibroplasia together with type III collagen was present in the entire joint capsule. Contracture, (vimentin expression), was found only in the anterior joint capsule (rotator interval and CHL) |
| DePalma[100] | 2008 | case series | capsule | 32 | - | histology | Evidence of a low grade chronic inflammatory process with variable involvement of the biceps tendon sheath was found |
| Kanbe[101] | 2009 | case series | RI | 10 | - | immunohistochemistry | NF-κB, IL-6, MMP3, β1-integrin and VEGF were expressed in the synovial tissue of frozen shoulders |
| Li[102] | 2009 | case control | RI | 12 | 12 | RT-PCR | A higher expression of mRNA for TGF-β and several MMPs was found |
| Kabbabe[103] | 2010 | case control | 4 different locations | 13 | 10 | qPCR | Inflammatory ( IL-6 and IL-8) and fibrogenic (MMP3) cytokines were expressed at a higher level in frozen shoulders compared to controls |
| Nago[104] | 2010 | case series + in vitro cell culture | RI | 7 | - | histology, RT-PCR | Treatment of cultured glenohumeral/synovial fibroblast from frozen shoulder patients with hyaluronan inhibited cell proliferation and expression of adhesion related procollagens and cytokines. |
| Hagiwara[105] | 2012 | case control | RI + MGHL + IGHL | 12 | 18 | immunohistochemistry, qPCR, scanning acoustic microscopy | A higher number of cells, stiffer capsular tissue and increased gene expression related to fibrosis (COL1A1, PDGF-B) inflammation (IL-1β) and chondrogenesis was found |

**Table 1** (Continued) Biopsy studies

| Author | Year | Study design | Biopsy location | n FS | n Controls | Analysis method | Most relevant findings |
|---|---|---|---|---|---|---|---|
| Xu[106] | 2012 | case control | RI | 8 | 10 | immunohistochemistry | Increased expression of nerve growth factor receptor and new nerve fibers were found in frozen shoulder capsular tissue compared to controls |
| Kim[77] | 2013 | case series | RI | 17 | 9 | immunohistochemistry, RT-PCR | ICAM-1 was increased in capsular tissue, synovial fluid, and serum of frozen shoulder patients compared to controls |
| Lho[107] | 2013 | case control | RI + subacromial bursa | 14 | 7 | immunohistochemistry, RT-PCR, ELISA | IL-1α, IL-1β, TNF-α, COX-1 and COX-2 were expressed at higher levels in joint capsule of frozen shoulder patients compared to controls. In the subacromial bursa, IL-1α, TNF-α and COX-2 were expressed at higher levels |
| Raykha [108] | 2014 | case control + in vitro cell culture | RI | ? | ? | western blot, RT-PCR | β-catenin and IGF-2 expression were found to be elevated in frozen shoulders compared to controls |
| Cho[23] | 2015 | case control | capsule | 18 | 18 | immunohistochemistry, RT-PCR | Upregulation of acid sensing ion channels (ACICs)was found in capsular tissue and synovial fluid of frozen shoulder patients |
| Cohen[109] | 2016 | case control | anteroinferior capsule | 9 | 8 | RT-PCR | Elevated expression of Tenascin C and Fibronectin 1 mRNA was found in capsular tissue of frozen shoulder patients. |
| Hettrich[84] | 2016 | case control | anterior and posterior | 20 | 14 | immunohistochemistry | Intra articular corticosteroid injection reduces fibrosis, vascular hyperplasia and myofibroblast differentiation |

**Table 1** (Continued) Biopsy studies

| Author | Year | Study design | Biopsy location | n FS | n Controls | Analysis method | Most relevant findings |
|---|---|---|---|---|---|---|---|
| Hwang[70] | 2016 | case control | RI | 8 | 14 | immunohistochemistry | Immunoreactivity of AGEs was stronger in frozen shoulder capsules compared to controls |
| Cui[110] | 2017 | case control | capsule + bursa + synovium | 5 | 2 | RNA sequencing | 147 genes were upregulated and 24 downregulated in capsular tissue of frozen shoulder patients compared to controls |
| Cher[111] | 2018 | case control | RI | 10 | 10 | immunohistochemistry | Immunoreactivity of alarmins was stronger in frozen shoulder patients. The expression of the alarmin HMGB1 correlated with the severity of pain |
| Hagiwara[18] | 2018 | case control | RI + MGHL + IGHL | 12 | 7 | shotgun proteome analysis | The pathophysiology might differ between the upper and lower parts of the joint capsule. In the RI and MGHL samples, different proteins were higher expressed compared to the IGHL samples |
| Akbar[50] | 2019 | case control + in vitro cell culture | RI | 10 | 10 | immunohistochemistry, qPCR, ELISA | Fibroblasts in FS have activated phenotype with an increased expression of fibroblast activation markers. Cultured FS fibroblasts produced elevated levels of inflammatory proteins (IL-6, IL-8, CCL-20) |
| Cho[112] | 2019 | case control + animal (rat) study | capsule | 21 | 13 | immunohistochemistry | Overexpression of IL-6, MMP-2 and MMP-9 may be associated with frozen shoulder |

**Table 1** (Continued) Biopsy studies

| Author | Year | Study design | Biopsy location | n FS | n Controls | Analysis method | Most relevant findings |
|---|---|---|---|---|---|---|---|
| Kamal[113] | 2020 | case control | anterior | 22 | 26 | RT-PCR | Inflammation and ECM remodelling were the most signifant and highly enriched processes in frozen shoulder. MMP13 expression was increased and TNF-α expression was reduced in frozen shoulders |
| Yang[90] | 2020 | case control + in vitro cell culture | RI | 9 | 10 | immunohistochemistry, RT-PCR, flow cytometry | COL1A1, COL3A1, TGF-β1, and IL-6 were expressed at increased levels in the frozen shoulder group compared to controls. The presence of calcitonin receptors in shoulder capsular tissue was confirmed. Treatment with salmon calcitonin decreased the expression of COL1A1, COL3A1, fibronectin 1, laminin 1, TGF-β1 and IL-1α |
| Yano[114] | 2020 | case control | CHL + IGHL | 33 | 25 | immunohistochemistry, RT-PCR, high performance liquid chromatography | AGEs and HMGB1 might play important roles in the pathogenesis of frozen shoulder. Gene expression levels of RAGE, HMGB1, TLR2, TLR4 and NF-κB were significantly greater in frozen shoulders compared to controls |

Studies investigating the pathophysiology of frozen shoulder with glenohumeral capsular tissue samples
(CHL = coracohumeral ligament; RI = rotator interval; MGHL = middle glenohumeral ligament; IGHL = inferior glenohumeral ligament; RT-PCR = real time polymerase chain reaction; ELISA = enzyme linked immune sorbent assay; TGF-β = transforming growth factor beta; AGE = advanced glycation end product; MMP = matrix metalloproteinase; TIMP = tissue Inhibitor of Metallo Proteinases; TSH = thyroid stimulating hormone; IGF = insulin like growth factor; ICAM = intercellular adhesion molecule-1; ECM = extracellular matrix; TNF-α = tumor necrosis factor alfa; VEGF = vascular endothelial growth factor)

**Table 2** Association studies

| Author | Year | Study Design | n FS | n controls | analysis method | Most relevant findings |
|---|---|---|---|---|---|---|
| Bunker[115] | 1995 | case series | 43 | 43 | peripheral blood samples | Fasting serum triglyceride and cholesterol levels were significantly elevated in frozen shoulder patients |
| Mullet[57] | 2007 | case control | 15 | 15 | glenohumeral joint aspirate, in vitro cell culture | Proliferation of cultured human fibroblast cells was significantly increased by stimulation of growth factors from joint aspirate of frozen shoulder patients |
| Lubis[116] | 2013 | case control | 50 | 50 | peripheral blood samples | MMP1 and MMP2 levels were significantly lower, while TIMP1, TIMP2 and TGF-β1 were higher in frozen shoulder patients compared to controls |
| Austin[43] | 2014 | case control | 150 | NHANES nationwide study | patient chart review | A relationship is suggested between systemic inflammation with hyperglycaemia and hypertension and frozen shoulder |
| Huang[117] | 2014 | cohort | 162 | Longitudinal health insurance database | ICD-9-CM codes | Hyperthyroid patients have a 1.22 fold higher risk to develop frozen shoulder compared to the general population in Taiwan |
| Sung[44] | 2014 | case control | 300 | 900 | peripheral blood samples | Hypercholesterolemia, and inflammatory lipoproteins have a significant association with frozen shoulder |
| Booker[118] | 2017 | case control | 20 | 26 | capsular biopsies for microbiological culture | No correlation was found between the incidence of P. Acnes and frozen shoulder |
| Chan[119] | 2017 | retrospective cohort | 197 | 24220 | peripheral blood samples | Cumulative HbA1c was (dose dependent) associated with an increased incidence adhesive capsulitis |

**Table 2** (Continued) Association studies

| Author | Year | Study Design | n FS | n controls | analysis method | Most relevant findings |
|---|---|---|---|---|---|---|
| Chen[120] | 2017 | case control | 42 | 50 | peripheral blood samples - ELISA | IL-1β was expressed at higher levels in frozen shoulder patients and is associated with susceptibility of frozen shoulder |
| Holte[121] | 2017 | case control | 100 | 73 | skin biopsies - liquid chromatography mass spectometry | Joint stiffness was associated with long term HbA1c and AGEs |
| Schiefer[122] | 2017 | case control | 93 | 151 | peripheral blood samples | Hypothyroidism was significantly more prevalent in frozen shoulder patients than in controls. A correlation between TSH levels with the severity of frozen shoulders was suggested |
| Gumina[76] | 2018 | prospective observational | 27 | genome database | peripheral blood samples - PCR | APO-A1-G75A lipoprotein polymorfism was found as a risk factor for the severity of frozen shoulder |
| Kalson[123] | 2018 | cohort | 549 | 5989 (Twins UK registry) | qPCR | Frozen shoulder patients had a significant relation with telomere length. It is suggested that telomere repair defects contribute to joint fibrosis |
| Park[45] | 2018 | case control | 37 | 222 | peripheral blood samples | Inflammatory lipoproteins are associated with adhesive capsulitis accompanied by diabetes |
| Cohen[124] | 2019 | case control | 186 | 600 | peripheral blood samples - genotyping | Certain genetic variants, SNPs of MMP13, MMP 9 and TGFβ1 were identified as independent risk factors for frozen shoulder |

Studies investigating the association between frozen shoulder and a co-morbidity, focussed on the pathophysiologic mechanism
(PCR = polymerase chain reaction; ELISA = enzyme linked immune sorbent assay; TGF-β = transforming growth factor beta; AGE = advanced glycation end product; MMP = matrix metalloproteinase; TIMP = tissue Inhibitor of Metallo Proteinases; TSH = thyroid stimulating hormone; SNP = single nucleotide polymorphism; IL-1β = Interleukin-1β)

**Table 3** Animal studies

| Author | Year | Study Design | Method used for analysis | Most relevant findings |
|---|---|---|---|---|
| Watson[125] | 2011 | animal model (rats) | RT-PCR | TGF-β1 gene transfer induced a fibrotic condition comparable to frozen shoulder patients with similar expression levels of ECM proteins, MMPs, adhesion- and collagen proteins |
| Xue[126] | 2016 | animal model (rats) + cell culture | RT-PCR and gene silencing with a lentivirus | Smad4 silencing can suppress chronic inflammation and fibrosis in joint tissue by inhibiting the TGF-β/Smad pathway |
| Blessing[94] | 2019 | animal model (rats) + cell culture | immunohistochemistry | Local delivery of Relaxin-2 downregulates type I collagen and α-SMA production |

Animal studies with the specific aim to investigate the pathophysiology of frozen shoulder (RT-PCR = real time polymerase chain reaction; TGF-β = transforming growth factor beta; ECM = extracellular matrix; MMP = matrix metalloproteinase; α-SMA = α - smooth muscle actin)

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# PART TWO

## CORTICOSTEROID INJECTIONS AND PHYSIOTHERAPY

# CHAPTER THREE

## How to treat a frozen schoulder? A survey among schoulder specialists in the Netherlands and Belgium

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# ABSTRACT

**Background** A frozen shoulder is a common cause of a painful and stiff shoulder. Many controversies still exist about the definition, the different stages and the optimal treatment regimen. It is known that most patients can be treated conservatively. However, there seems to be no consensus on the optimal strategy to treat frozen shoulders. This survey aims to give insight into the current opinions and preferences of orthopedic surgeons about the diagnosis and management of frozen shoulders.

**Methods** A web-based survey was conducted among shoulder specialized orthopedic surgeons from the Netherlands and Belgium. A questionnaire was developed with questions about physical examination, the diagnosis and preferred treatment modalities for a frozen shoulder. An email reminder was sent after two weeks and the survey was kept open for six weeks.

**Results** A response rate of 54% was reached. Fifty-two percent of the responders has more than 10 years of experience in treating shoulder pathology. External rotation was chosen as most severely restricted direction of motion by 80% of the responders. Ultrasound examination of the shoulder was recommended in the work up of shoulder pain and stiffness by 34% of the respondents. Non-steroidal anti-inflammatory drugs and intra-articular corticosteroid injections are considered appropriate in the first stage of the condition by 80% of the responders. Physiotherapy is assumed to be more important in the final stage. A wide variety of preferred treatment modalities was demonstrated in the different stages of frozen shoulder. Less than half (43%) of all surgeons used manipulation under anesthesia as an intervention for frozen shoulders. Seventy-six percent used arthroscopic capsular release as an intervention. The yearly numbers for both interventions per surgeon are low.

**Conclusions** The results of this survey indicate a wide variety of treatment strategies in the different stages of a frozen shoulder, with the highest disagreement about treatment modalities in stage two of the condition. This is most likely caused by a lack of evidence to show superiority of one strategy over others. More research is needed to compare different treatment modalities for frozen shoulder patients, ideally leading to more uniformity in their treatment. There seems to be a demand for a written guideline to aid surgeons in clinical practice in the treatment of frozen shoulders.

# BACKGROUND

A frozen shoulder (adhesive capsulitis) is a common cause of shoulder pain and affects approximately 2-4% of the general population.[1,2] An idiopathic frozen shoulder is characterised by a spontaneous onset of pain and stiffness of the shoulder, especially a loss in external rotation, without a prior traumatic event.[3] The condition is traditionally divided in three stages.[4] A freezing stage with severe pain and increasing stiffness, a frozen stage with established stiffness but reduced pain. And a third, gradual improvement of motion occurs in the thawing stage. The peak incidence is between the fifth and sixth decade, slightly more frequent in women than in men. The most important associated systemic condition is diabetes mellitus.[5,6] Although it is a condition that is described as self-limiting, restriction of shoulder movement can persist eventually.[7]

Frozen shoulder is a well-known clinical entity among orthopedic surgeons, and also frequently encountered by general practitioners and physiotherapists. There are still many controversies existing about the definition, the different stages and the optimal treatment regimen. There are many different treatments available, e.g. supervised neglect[8], non-steroidal anti-inflammatory drugs (NSAIDs), physiotherapy[9,10], corticosteroid infiltration[11], manipulation under anaesthesia[12], arthroscopic capsular release[13], arthrographic capsular distension[14] and stretching devices.[15] However, systematic reviews point to a lack of scientific evidence to recommend any specific treatment regimen.[16,17] What we do know, is that non-operative treatment is sufficient for most cases, and recovery takes place in two years on average.[3] Consequently, intra-articular corticosteroid injections and physiotherapy are among the most widely used treatment modalities described in the treatment of a frozen shoulder, in both primary and secondary healthcare settings.[16,18] However, there seems to be no general consensus on the conservative treatment of a frozen shoulder among shoulder specialists. In addition, there is no national guideline for orthopedic surgeons nor physiotherapists in the Netherlands or Belgium to guide the treatment of a frozen shoulder. This can lead to significant differences in management strategies between regions, hospitals and even between individual orthopedic surgeons within one hospital. In order to gain insight into the current opinions and preferences about the diagnosis and treatment of a frozen shoulder, a web-based questionnaire was developed for Dutch and Belgian orthopedic surgeons with a special interest in shoulder pathology.

# METHODS

A web-based questionnaire was developed by the authors, consisting of 26 questions (7 introduction questions, 3 questions about the physical examination, 4 about the diagnosis and 12 about the treatment). All orthopedic surgeons, member of the Dutch Shoulder and Elbow Society and the Belgian Elbow and Shoulder Society were invited to fill out the questionnaire. Permission was obtained from the boards of both societies to contact the members of the associations by email. A reminder email was sent after two weeks. The survey was kept open for six weeks. Data was analyzed using Statistical Package for the Social Sciences version 21.0 (IBM SPSS, Chicago, IL, USA).

# RESULTS

## GENERAL QUESTIONS

Out of the 186 invitations sent, a number of 100 (54%) were returned. The response rate from the Dutch Shoulder and Elbow Society was 62% and from the Belgian Elbow and Shoulder Society 44%. One respondent was excluded from the analysis due to exceptional high numbers to several questions in which estimated numbers were asked. Due to the anonymity of the study, it could not be verified if these answers were realistic. Ninety-five percent of the responders works as a staff member and about half (52%) has more than ten years of experience in treating shoulder problems. More than half of the responders (60%) are currently working in a teaching hospital. The mean estimated number of patients treated with a frozen shoulder in one month was 11 (95% CI 10-13) per shoulder specialist.

## DIAGNOSIS AND EXAMINATION

Eighty-eight percent of the respondents agreed on the widely used definition for frozen shoulder coined by Zuckerman: *"Frozen shoulder is a condition characterized by functional restriction of both active and passive shoulder motion for which radiographs of the glenohumeral joint are essentially unremarkable except for the possible presence of osteopenia or calcific tendonitis".*[19]

There is large agreement among the surveyed orthopedic surgeons about the most severely restricted motion in patients with a frozen shoulder. External rotation was chosen by 80%, followed by internal rotation by 14%. The range of motion of the shoulder joint was recorded in clinical practice by estimation ('eyeballing') by 90% of the respondents, and only 6% used a goniometer with physical examination. A conventional X-ray of the shoulder was used by 90% to rule out other possible causes for shoulder pain and stiffness. Ultrasound examination of the shoulder was recommended in the

work up of shoulder pain and stiffness by 34% of the respondents. For MRI this was recommended by 2% only. Eighty-four percent of the responders considered it useful for clinical purposes to identify the stage of the condition.

## TREATMENT

Only 37% of the orthopedic surgeons indicated that there is a written protocol available in their clinical practice for the treatment of a frozen shoulder. However, three out of four (75%) considered that the management of a frozen shoulder could benefit from a nationwide written protocol.

Figure 1 shows which treatment modalities were considered appropriate for a typical primary frozen shoulder, specified to the different stages. The only obvious agreement between the respondents (>80%) was on advice and education, NSAID usage, and intra-articular corticosteroid injection in the first stage of the condition. Figure 2 shows a graph with the appropriateness of the many physiotherapy modalities for the different stages of frozen shoulder. Nearly all physiotherapy modalities were considered to be most appropriate in stage 3.



When referring patients with a frozen shoulder to a physiotherapist, 69% of the orthopedic surgeons indicate that they preferred a specialized shoulder therapist. Sixty-four percent assumed it is important to specify the stage of the condition when referring to a shoulder therapist. Only 19% declared that they do not specify any treatment modality, when referring.

Twenty four percent of the orthopedic surgeons do not use arthroscopic capsular release for frozen shoulders. For the 76% of the orthopedic surgeons that do perform arthroscopic capsular release, the median number of releases per year is 3 (range 1-50). Manipulation under anaesthesia is done by 43% of the orthopedic surgeons. For these surgeons the median number of manipulations per year is 5 (range 1-50).

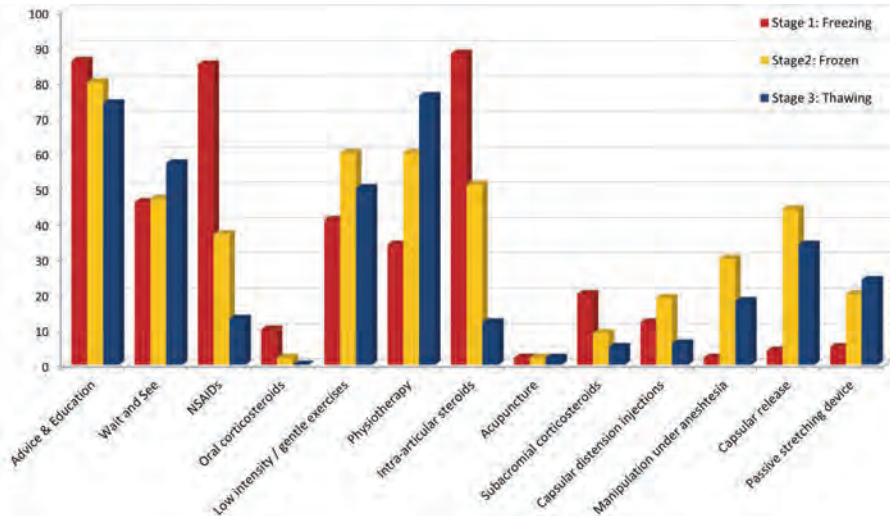


**Figure 1** Frequency histogram of treatment modalities considered appropriate in the different stages of a frozen shoulder. X-axis: Treatment modalities. Y-axis: percentage of respondents that considered the treatment modality appropriate

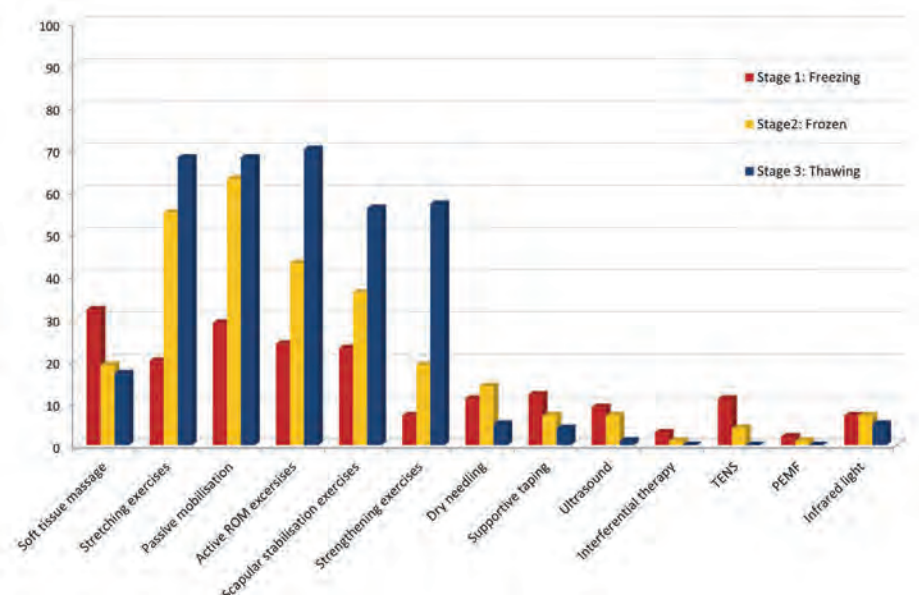


**Figure 2** Frequency histogram of physiotherapy modalities considered appropriate in the different stages of a frozen shoulder. X-axis: Treatment modalities. Y-axis: percentage of respondents that considered the treatment modality appropriate

(ROM = Range of Motion, TENS = Transcutaneous Electric Nerve Stimulation, PEMF = Pulsed ElectroMagnetic Field therapy)

## DISCUSSION

This online survey on the diagnosis and management of frozen shoulder was completed by a large number of experienced orthopedic surgeons from the Netherlands and Belgium, all of them with a special interest in the shoulder joint. Although a web-based survey provides limited evidence (level IV), it is a time-efficient method to collect information on a clinical topic and its current clinical practice. A response rate of 54 % was in line with other web-based surveys among orthopedic surgeons.[20,21] This response rate may yield a representative overview of the individual preferences and current clinical practice in the Netherlands and Belgium.

Eighty-eight percent agreed on the widely used definition by Zuckerman, which is comparable to the 82% agreement in the original article.[19] However, this broad definition is only descriptive for a frozen shoulder in general. We did not propose a new definition for the clinical diagnosis of frozen shoulder as strict cut-off values for the duration of the pain, or the amount of restriction, vary among the many reports. But in order to use future research for clinical purposes, it seems sensible to use narrower diagnostic criteria. By means of this, a specific study population is delimited and distinction is made with various other causes of shoulder pain.



Similar to what is known from previous studies, external rotation was considered to be the most severely restricted range of motion.[3] Although the use of a goniometer to measure the range of motion is encouraged in the literature, this survey illustrates that in clinical practice only a minority actually does use a goniometer.[22] For the diagnosis of a frozen shoulder, the true amount of restriction in degrees is probably not crucial to determine. However, 'eyeballing' might not be accurate enough to detect the differences in joint motion throughout the follow up.

In accordance with the current literature, the survey seems to confirm that NSAIDs and intra-articular corticosteroids are assumed important early on in the treatment.[23] The benefit of physiotherapy is assumed to be more important later on in the condition. Not one specific physiotherapy treatment is preferred by more than 35% of the orthopedic surgeons in stage one of a frozen shoulder. Stretching, passive mobilisation, and range of motion exercises are generally preferred by the majority of the orthopedic surgeons in stage three. There is no strong evidence to establish in which stage physiotherapy is most effective, although it is often recommended to respect the threshold of pain. Vigorous exercises or manipulations in the early painful stage might delay recovery.[24] This does match with recent guidelines of the American Physical Therapy Association.[25] In this article, the content and intensity of the physiotherapy program is guided by a stratification in tissue irritability level of the shoulder. The most ambiguity is observed in

stage two of the condition, where a lot of treatment modalities are preferred by about 50% of the respondents. This signifies disagreement among treating physicians, which is very likely caused by a lack of evidence that is also pointed out in recent reviews.[16,24,26] Another possible explanation is that the natural course of the condition (seemingly gradual improvement) can mimic a relative similar positive effect of various different treatment modalities.

According to the participating orthopedic surgeons, there is no role for passive physical treatment modalities including ultrasound treatment, interferential therapy, transcutaneous electrical nerve stimulation, pulsed electromagnetic field and infrared light, in the treatment of a frozen shoulder. In addition, the literature has shown a clear lack of efficacy of these treatment modalities.[16,17,27] This survey does have some limitations. In general, the wide variation in treatment preferences for a frozen shoulder are not surprising. This is presumably caused by a lack of high level evidence. However, the confirmation hereof in this survey points out the necessity for better evidence and more uniformity. In a number of questions, the preferred treatment modality was asked for the three different stages of a frozen shoulder. We did not clearly specify the different stages of a frozen shoulder as no precise definitions are available to date. Therefore, this was up to the interpretation of the participating orthopedic surgeon, similar to current practice. We do think that a written guideline should provide precise diagnostic criteria and that treatment recommendations must be specified for the different stages of a frozen shoulder.

No questions were asked whether orthopedic surgeons evaluated the effectiveness of their treatment. Recent guidelines that were developed in the Netherlands for other subjects (such as for subacromial pain), do provide recommendations for outcome measuring instruments (such as the Shoulder Pain and Disability Index, or the Dutch Oxford Shoulder Score). The Dutch Orthopedic Association also stimulates the use of patient reported outcome measures (PROMs). It could have been interesting to know whether orthopedic surgeons actually use these outcome measures, or which outcome instrument is considered to be the most valuable for the treatment of a frozen shoulder.

Another weakness of this study is that it evaluates which treatment modality is theoretically considered to be the most appropriate. But this does not necessarily correspond to clinical practice. In our opinion this specifically holds true for physiotherapy treatment, which is probably influenced by reimbursement modalities. In recent years, healthcare cuts have led to the fact that many patients are not reimbursed for physiotherapy treatment. This obviously leads to a lower compliance rate for this treatment modality.

The variation in clinical practice shown in the current survey could be an underestimation because of a pre-selection of orthopedic surgeons with interest in shoulder pathology. As in every survey, non-response bias can not be ruled out. Cold or cryotherapy was suggested by a few respondents who advised it to use for pain reduction in the freezing or frozen stage. This treatment modality was not included in the survey. It could have been interesting to know the individual decision rules for a more invasive intervention, being manipulation or arthroscopic release, because strict criteria are not available for these indications. However, this was not the focus of this survey.

## CONCLUSIONS

Frozen shoulder is an important cause for shoulder pain and stiffness. However, there seems to be no clear consensus on the diagnosis and treatment. This survey gives insight in the current preferences of Dutch and Belgian shoulder specialized orthopedic surgeons in the treatment of a frozen shoulder. There was a high degree of agreement on the proposed descriptive definition of the clinical entity of frozen shoulder. A wide variety of preferences for different treatment modalities was demonstrated in the different stages of frozen shoulder. This could be due to a lack of evidence or the relatively similar effectiveness of all the different treatment modalities available. Secondly, there is no written guideline for the frozen shoulder for orthopedic surgeons or physical therapists in the Netherlands and Belgium. Many surgeons reckon that the treatment of a frozen shoulder could benefit from such a written guideline. This guideline ideally consists of a classification system to guide treatment and should aim for more uniformity in treatment strategies for frozen shoulder in general. Also, it is clear that more research needs to be done on the effectiveness of the different treatment strategies for frozen shoulders to improve outcome.

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# CHAPTER FOUR

## Corticosteroid injection alone vs additional physiotherapy treatment in early stage frozen shoulders. D-FROST (Dutch Frozen Shoulder Trial) a randomized trial

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## ABSTRACT

**Background** Frozen shoulder is a common cause of shoulder pain and disability. Physiotherapy and corticosteroid injections are the most widely used treatment modalities in FS, in both primary and secondary healthcare settings. There is enough evidence to support a positive effect of intra-articular corticosteroid injections on shoulder pain and range of motion (ROM), at least at short term. However, the role of physiotherapy in the treatment of FS is more uncertain. Passive mobilisation and stretching at an early stage of the condition might even lead to worsening symptoms if done too aggressively. This study aims to investigate the additional value of physiotherapy after a corticosteroid injection in stage one or two idiopathic frozen shoulders.

**Methods** A two center, randomized controlled trial was done. Patients with a painful early stage idiopathic frozen shoulder were eligible for inclusion. After written consent, patients were randomly allocated into two groups. All patients received an ultrasound-guided intra-articular corticosteroid injection. One group underwent additional physiotherapy treatment (PT) and the other group did not (non-PT). The primary outcome measure was the Shoulder Pain and Disability Index (SPADI). Secondary outcomes were pain (numeric pain rating scale), range of motion (ROM), quality of life (RAND-36 score), and patient satisfaction. Follow-up was scheduled after 6, 12 and 26 weeks.

**Results** Twenty-one patients were included, 11 patients in the non-PT and 10 in the PT group, with a mean age of 52 years. Both treatment groups showed a significant improvement at 26 weeks. At 6 weeks follow-up, median SPADI score was significant decreased in the PT group (14 IQR: 6-38) *vs* the non-PT group (63 IQR: 45-76) ($P = 0.01$). Pain decreased significantly in both groups but no differences were observed between both treatment groups at any time point. Significant differences in all three ROM directions were observed after 6 weeks in favor of the PT group ($P \leq 0.02$ for all directions). A significantly greater improvement in abduction ($P = 0.03$) and external rotation ($P = 0.04$) was also present in favor of the PT group after 12 weeks. RAND-36 scores showed no significant differences in health-related quality of life at all follow-up moments. At 26 weeks, both groups did not differ significantly with respect to any of the outcome parameters. No complications were reported in both groups.

**Conclusions** Physiotherapy, guided by the level of tissue irritability, after an intra-articular corticosteroid injection improves ROM and functional limitations in early-stage frozen shoulders up to the first three months.

# BACKGROUND

Frozen shoulder (FS), a common cause of shoulder pain and disability, affects approximately 2% to 4% of the general population.[1–3] The peak incidence of FS is between the fifth and sixth decade of life, occurring slightly more frequently in women than in men. The pathophysiology of FS is poorly understood.[4] The generally accepted theory comprises an inflammatory cascade causing contracture of the anterosuperior capsule, the rotator interval and the coracohumeral ligaments of the shoulder joint. These events lead to the typical loss of the passive external rotation seen in FS.[2] Although there are histopathological similarities with Dupuytren's disease, FS follows a different natural course.[5] Historically, FS is considered to be self-limiting with three different stages; the freezing, frozen, and thawing stages.[6,7] However, clear distinction between separate stages is difficult without clear cut-off criteria, and a continuing spectrum is more appropriate. Functional recovery mainly takes place within one to three years.[8,9] However, the remaining pain and restriction in range of motion (ROM) of the shoulder joint can even persist long-term.[10–12]

There is no widely agreed consensus about the most optimal treatment regimen for FS. Systematic reviews point to a large gap in evidence for treatment strategies for FS.[13–15] Currently, there seems to be a trend towards more invasive treatments, like manipulation under anesthesia and particularly arthroscopic capsular release.[16] However, there is insufficient evidence to recommend these treatment modalities.[13] Less invasive treatment options are intra-articular corticosteroid injections and physiotherapy. These are the most widely used treatment modalities in FS in both primary and secondary healthcare settings.[2,17,18] Corticosteroid injections demonstrated a positive effect on shoulder pain and ROM, at least in the short-term.[19,20] However, the role of physiotherapy in the treatment of FS is more uncertain.[14,21,22] Passive mobilisation and stretching at an early stage of the condition might even lead to worsening symptoms if done too aggressively. Supervised neglect, consisting of supportive therapy and exercises within pain limits, has been advocated as an appropriate treatment for FS.[23] In a systematic review, Blanchard *et al* hypothesized a potential beneficial effect of combining corticosteroid injections with physiotherapy.[24] Conclusive evidence to support this is lacking, which warrants further trials. The objective of this randomized controlled trial was therefore to investigate the additional value of physiotherapy treatment (PT) after an intra-articular corticosteroid injection in the management of early-stage idiopathic FSs. It is hypothesized that, with respect to ROM and shoulder function, additional physiotherapy is superior to corticosteroid injection alone.

# METHODS

Approval for a prospective randomized clinical trial (D-FROST; Dutch frozen shoulder study) was obtained by the MC Slotervaart Hospital Medical Ethics Committee (NL47325.048.13). The trial was registered in the Dutch Trial Register (NTR4587). The study was undertaken in accordance with the declaration of Helsinki. Patients were recruited between February 2014 and December 2015 in two participating hospitals in Amsterdam. Patients were eligible for participation if they exhibited clinical signs of FS, including pain and stiffness of the involved shoulder without preliminary trauma persisting for more than three months. The required level of pain was a minimum score of six out of ten on a numeric pain scale. Restriction of the passive ROM of the shoulder joint of more than 30° in external rotation and a second direction (*i.e.*, abduction and/or forward flexion) when compared to the unaffected contralateral side was required for inclusion. Conventional radiographs of the shoulder joint and ultrasound studies were used to rule out osteoarthritis and rotator cuff ruptures. Exclusion criteria were: corticosteroid injection in the shoulder joint region in the previous 6 weeks, previous surgery to the shoulder, systemic inflammatory disease, neurological disorder with impairment of the upper limb, and the use of anti-coagulation therapy using a therapeutic dosage. These selection criteria are intended to select a clearly defined population of patients with early-stage (stage one or two) idiopathic FSs. Patients were informed both in word and with an information leaflet. Informed consent was obtained from all included patients.

## RANDOMIZATION AND INTERVENTIONS

Patients were randomly assigned into two groups. The intervention group undergoing a PT program (PT-group), or the control group without physiotherapy (non-PT). Patients were allocated to one of the study groups using an online website. Randomization was stratified by the participating hospital and performed in variable blocks using computer-generated randomization software. Participating orthopedic surgeons who assessed patient eligibility had no access to the randomization software, hereby securing allocation concealment. Within two weeks after inclusion, patients in both study groups received an ultrasound-guided glenohumeral joint injection of 1 mL kenacort 40 mg in 4 mL lidocaine 1%, administered by an experienced radiologist. Both groups were informed about the possible self-limiting nature of FS, and received counseling about optional analgesics like acetaminophen, nonsteroidal anti-inflammatory drugs or tramadol, if needed. The non-PT group did not receive PT. Advice was given to try to use the affected arm in daily life activities within their pain limits. Patients in the PT group were referred to a participating physiotherapy clinic. All participating physiotherapists treated the referred study patients according to a standardized protocol, twice a week with a maximum duration of three months. This physiotherapy protocol was composed after

a thorough literature review by the participating shoulder surgeons in accordance with two experienced shoulder-treating physiotherapists. The aim of the PT was to increase ROM of the shoulder, decrease pain, and restore the function of the shoulder for daily activities. Tissue irritability of the shoulder joint was taken into account to guide the intensity of the treatment.[25] Passive mobilization techniques were used, except for Maitland grade five mobilizations.[26] Attention was paid to scapulothoracic movement, with the purpose to improve the scapulohumeral kinematics. Also, active and auto-assisted stretching techniques were part of the physiotherapy program. If there was an increase in pain lasting for more than four hours after the PT session, the next session had to be less intense. Hot packs, icing, and massage techniques were allowed to reduce pain. Transcutaneous electrical nerve stimulation, pulsed electromagnetic field, infrared, dry needling and medical taping were not allowed due to the lack of evidence of these treatment modalities in the treatment of FS.[27]

## OUTCOME PARAMETERS AND FOLLOW-UP

The main outcome parameter of this study was the Shoulder Pain and Disability Index (SPADI) at the 26 weeks follow-up, consisting of 13 questions divided into two domains (pain and disability). Item responses were rated on a eleven-point scale (0-10) leading to a score between 0 (best) and 100 (worst).[28] The SPADI has been translated and validated in Dutch.[29,30] Pain on average last week, and pain at night were scored on a ten-point numeric pain-rating scale (NPRS). Health-related quality of life was assessed using the RAND-36.[31,32] Passive ROM was measured in the standing position with the use of a goniometer. External rotation was measured in the horizontal plane, with the elbow at the side. Abduction was measured in the frontal plane and anteflexion in the sagittal plane. Patient satisfaction about their change in pain and function was assessed on a five-point Likert scale (“worse’’, ‘‘unchanged’’, ‘‘unsatisfactory improved’’, ‘‘satisfactory improved’’ and ‘‘good to very good improved”).[33] Repeated corticosteroid injections were allowed after 6 weeks if the level of pain had not dropped by at least 50%. Follow-up was scheduled after 6, 12 and 26 weeks.

## STATISTICAL ANALYSIS

Statistical analysis was performed by use of the SPSS statistical package software (version 22.0; Armonk, NY: IBM Corp) according to the intention to treat principle. Statistical review was performed by a clinical epidemiologist. Due to the small sample sizes and skewed distributions, analyses were performed non-parametrically. Patient demographics and baseline characteristics were described and compared between groups according to their distributions. Continuous and ordinal data are presented as medians with interquartile ranges (IQR) and differences between the treatment groups were assessed by use of Mann Whitney *U* tests. Wilcoxon Signed Ranks tests were performed to assess changes

from baseline at 26 weeks. $\chi^2$ tests were performed in case of categorical variables. A *P*-value < 0.05 was considered statistically significant.

# RESULTS

## PATIENT POPULATION

A total of 21 patients were included, with 11 patients in the non-PT and ten in the PT group (Table 1). All patients had conventional radiographs of the shoulder without abnormalities. At baseline, external rotation was limited in both patient groups with a median external rotation measuring five degrees for all patients (IQR: 0-20). Median NPRS on average last week was eight (IQR: 7-8.5). In both groups, two patients were too disabled to work due to their FS symptoms. Two patients in both groups had received a previous corticosteroid injection more than three months prior to inclusion. After 26 weeks, ROM measurements were available for 81% of the patients. Questionnaires were completed by 15 out of 21 patients (71%). An intra-articular corticosteroid injection was repeated after 12 weeks in two patients in both groups. No complications or adverse events were reported in both groups.

**Table 1** Demographics and patient characteristics

| | **Total (%)** | **non-PT (%)** | **PT (%)** | **p-value** |
|---|---|---|---|---|
| No. of patients | 21 | 11 | 10 | |
| Age (yr) | 51.9 (SD 5.1) | 50.4 (SD 6.1) | 53.3 (SD 3.8) | 0.17 |
| Gender | | | | |
| male | 9 (43) | 4 (36) | 5 (50) | |
| female | 12 (57) | 7 (64) | 5 (50) | 0.67 |
| Stage of frozen shoulder | | | | |
| Freezing (stage I) | 8 (38) | 6 (55) | 2 (20) | |
| Frozen (stage II) | 13 (62) | 5 (45) | 8 (80) | 0.18 |
| Duration of symptoms prior to intervention | | | | |
| <6 mo | 13 (62) | 9 (82) | 4 (40) | |
| > 6 mo | 8 (38) | 2 (18) | 6 (60) | 0.08 |
| Previous injection around the shoulder | 11 (52) | 5 (45) | 6 (60) | 0.67 |
| Previous physiotherapy | 15 (71) | 7 (64) | 8 (80) | 0.64 |
| Disabled to work related to shoulder | 4 (19) | 2 (18) | 2 (20) | 1.00 |
| Diabetes Mellitus | 2 (10) | 2 (18) | 0 (0) | |

## CLINICAL AND FUNCTIONAL OUTCOME

The median total SPADI scores for all patients at baseline was 81 (IQR: 58-87), which confirmed the severe pain and disabilities of FS in the early stages. Both treatment groups showed a significant improvement at the primary endpoint of 26 weeks for SPADI scores (non-PT: $P = 0.05$, PT: $P = 0.03$). At the 6 weeks follow-up, median SPADI scores had decreased to 63 (IQR: 45-76) in the non-PT group and 14 (IQR: 6-38) in the PT group. This difference was significant ($P = 0.01$) and exceeded the minimal clinical important difference (range 8-13) of the SPADI,[34] but this difference had disappeared after 26 weeks ($P = 0.23$). At the final follow-up, median SPADI scores were 24 (IQR: 12-19) in the non-PT and ten (IQR: 2-28) in the PT group (Figure 1 and Table 2). Passive ROM increased significantly compared to baseline in both groups ($P < 0.03$ for all comparisons). Significant differences in all three ROM directions were observed after 6 weeks in favor of the PT group ($P \leq 0.02$ for all comparisons). At the final follow-up, all ROM measurements were still in favor of the PT group, but were not significant (Table 3).

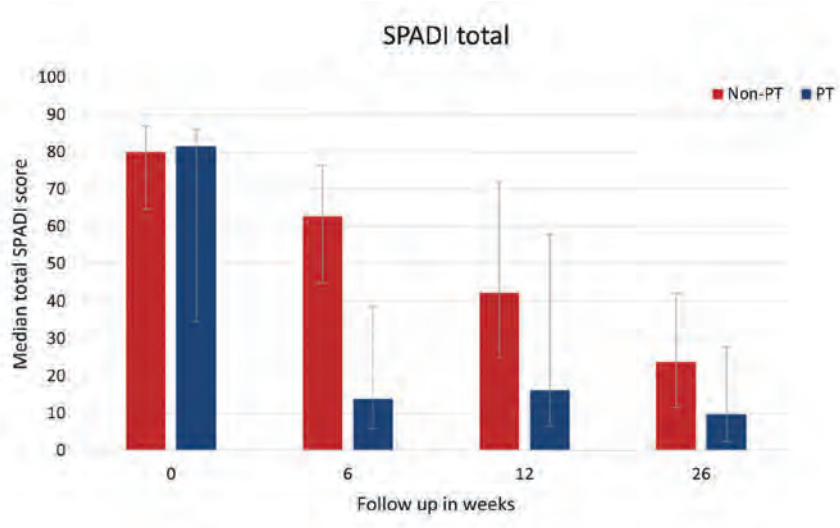


**Figure 1** Median total SPADI score compared between both groups (non-PT and PT). Error bars represent Inter quartile range (IQR)

**Table 2** SPADI scores for pain, disability and SPADI total scores (medians with interquartile range)

| | Non-PT (IQR) | PT (IQR) | p-value |
|---|---|---|---|
| **SPADI pain** | | | |
| Baseline | 82 (70-90) | 86 (46-92) | 0.68 |
| 6 weeks | 71 (24-79) | 18 (9-43) | 0.09 |
| 12 weeks | 48 (22-68) | 20 (9-57) | 0.17 |
| 26 weeks | 14 (8-30) | 13 (4-32) | 0.94 |
| **SPADI disability** | | | |
| Baseline | 81 (58-88) | 74 (28-84) | 0.42 |
| 6 weeks | 69 (47-76) | 11 (4-36) | 0.01 |
| 12 weeks | 38 (25-72) | 14 (5-58) | 0.15 |
| 26 weeks | 10 (9-50) | 8 (1-25) | 0.35 |
| **SPADI total** | | | |
| Baseline | 80 (65-87) | 82 (35-86) | 0.54 |
| 6 weeks | 63 (45-76) | 14 (6-38) | 0.01 |
| 12 weeks | 42 (25-72) | 16 (7-58) | 0.17 |
| 26 weeks | 14 (11-39) | 10 (2-28) | 0.44 |

**Table 3** Range of motion measurements (medians with interquartile range)

| | Non-PT (IQR) | PT (IQR) | p-value |
|---|---|---|---|
| **Abduction** | | | |
| Baseline | 50 (40-60) | 50 (41-102) | 0.39 |
| 6 weeks | 70 (43-90) | 100 (80-140) | 0.01 |
| 12 weeks | 80 (65-98) | 100 (90-165) | 0.03 |
| 26 weeks | 85 (80-149) | 130 (85-170) | 0.33 |
| **Anteflexion** | | | |
| Baseline | 70 (70-80) | 95 (48-120) | 0.25 |
| 6 weeks | 90 (75-111) | 140 (105-165) | 0.02 |
| 12 weeks | 90 (80-146) | 130 (115-155) | 0.06 |
| 26 weeks | 100 (90-160) | 155 (110-170) | 0.17 |
| **External rotation** | | | |
| Baseline | 0 (0-5) | 8 (0-24) | 0.14 |
| 6 weeks | 13 (5-26) | 40 (30-43) | 0.01 |
| 12 weeks | 18 (8-29) | 40 (25-65) | 0.04 |
| 26 weeks | 30 (13-44) | 50 (35-60) | 0.07 |

Both of the NPRS items "night pain" and "average pain last week" showed significant decreases at the 26 weeks follow-up for both groups ($P < 0.03$ for all comparisons). However, significant differences between both treatment groups were not observed at any time point, except for night pain at 6 weeks in favor of the PT group ($P = 0.02$, Table 4). The results of the RAND-36 showed no significant differences between both groups regarding health-related quality of life at all follow-up moments. A slightly higher satisfaction score was reported by the PT group compared to the non-PT group at the 6 weeks follow-up ($P = 0.02$). At all other follow-up moments, the degree of satisfaction was comparable between the two treatment groups (Table 4).

**Table 4** Pain scores (NPRS), RAND-36 physical component scale and mental component scale. Satisfaction scores (1 = worse, 2 = unchanged, 3 = unsatisfactory improved, 4 = satisfactory improved and 5 = good to very good improved). Median scores with interquartile range

| | Non-PT (IQR) | PT (IQR) | p-value |
|---|---|---|---|
| **NPRS average last week** | | | |
| Baseline | 8 (7-9) | 8 (5-8) | 0.37 |
| 6 weeks | 4 (2-8) | 2 (1-4) | 0.19 |
| 12 weeks | 4 (2-7) | 1 (0.5-5) | 0.17 |
| 26 weeks | 3 (1-4) | 2 (0-3) | 0.41 |
| **NPRS night** | | | |
| Baseline | 8 (8-9) | 9 (7-9) | 0.94 |
| 6 weeks | 4 (3-7) | 2 (0-3) | 0.02 |
| 12 weeks | 5 (2-7) | 1 (0-6) | 0.11 |
| 26 weeks | 2 (1-3) | 2 (0-3) | 0.48 |
| **RAND-36 PCS** | | | |
| Baseline | 33 (31-40) | 39 (34-46) | 0.11 |
| 6 weeks | 43 (35-46) | 47 (44-52) | 0.10 |
| 12 weeks | 45 (43-50) | 47 (43-55) | 0.63 |
| 26 weeks | 43 (35-56) | 40 (46-56) | 0.56 |
| **RAND-36 MCS** | | | |
| Baseline | 47 (36-54) | 44 (35-54) | 0.94 |
| 6 weeks | 49 (35-52) | 50 (42-56) | 0.33 |
| 12 weeks | 43 (29-51) | 52 (40-55) | 0.20 |
| 26 weeks | 52 (50-57) | 52 (35-57) | 0.56 |
| **Satisfaction** | | | |
| 6 weeks | 3 (2-3) | 4 (3-4) | 0.02 |
| 12 weeks | 2 (0-4) | 3 (2-4) | 0.22 |
| 26 weeks | 3 (3-4) | 3.5 (3-4) | 1.00 |

# DISCUSSION

The aim of this trial was to investigate whether physiotherapy is of additional value after an intra-articular corticosteroid injection into the shoulder joint in the treatment of patients with FS in stage one or two. At the final follow-up after 26 weeks, no clinical or functional differences were observed between both groups, with or without additional PT. However, total SPADI scores, ROM measurements and NPRS for pain at night were significantly superior in the physiotherapy group at 6 weeks. The most considerable differences between the groups were observed for the ROM, in favour of the PT group until 12 weeks of follow-up. This could imply that PT after an intra-articular corticosteroid injection is of additional clinical value in the treatment of FS. The result of physiotherapy is improved shoulder function, with less limitation in the rehabilitation process of patients with FS up to the first three months after a corticosteroid injection in the shoulder joint.

An initial good improvement is frequently reported in studies using corticosteroid injection for FS.[22,35] The beneficial value of additional physiotherapy was also reported by Carette *et al*.[21] In his clinical trial, corticosteroid injection followed by physiotherapy provided a faster recovery of shoulder function compared to injection alone, or placebo injection combined with physiotherapy. Ryans *et al* conducted a RCT comparing four treatment strategies for FS.[22] The authors concluded that corticosteroids were effective for pain relief and shoulder disability in the short-term, and physiotherapy was effective in restoring external rotation. In both studies, the differences were most distinct at the early follow-up and at 6 and 12 weeks, but not significant after more than three months. This is quite similar to our findings. A reason for this might be the self-limiting natural course of the disease. Nevertheless, the beneficial effect of physiotherapy in the short-term can be of clinically-relevant value in case the duration of both symptoms and disabilities is shortened with this strategy.

On the contrary, other studies do not support the use of physiotherapy in the treatment of FS.[23,24] In a systematic review, Blanchard *et al* found inferior results of PT compared to corticosteroid injection.[24] Some even consider physiotherapy to be inappropriate during early (painful) stage of FS.[2,36] A possible explanation for inferior results from physiotherapy in the treatment of FS is inadequacy to take in to account the tissue irritability level. Irritability is a term to reflect the tissue's ability to handle physical stress, presumably related to the extent of inflammatory activity. Tissue irritability can be categorized into three levels based on: patient reported pain, pain at end ROM, and the difference between active and passive ROM.[25] PT intensity can vary in the length of treatment, frequency of sessions, intensity of mobilization techniques, and types of exercises. Intensive physiotherapy at an early stage of FS without taking into account the tissue irritability level, can potentially worsen the symptoms of FS. For example, Diercks *et*

*al* reported a negative effect of PT, including passive stretching and manual mobilization, compared to supportive therapy within pain limits.[23] However, no corticosteroid injections were used in the trial of Diercks *et al*. Intra-articular corticosteroids have an anti-inflammatory effect, which is likely to attenuate tissue irritability.[37] We believe that in order to optimize treatment of early-stage FS, PT intensity should be guided by tissue irritability level. Moreover, PT is preferably started after an intra-articular corticosteroid injection.

In this prospective RCT, the study population was clearly defined according to strict criteria to include patients with idiopathic FS in stage one or two with symptoms lasting at least three months. The corticosteroid injections were administered under ultrasound guidance by experienced radiologists. Rehabilitation was performed according to a uniform physiotherapy protocol and carried out by specialized shoulder physiotherapists. The ROM measurements were assessed by the treating orthopedic surgeon. Although not blinded for the allocated intervention, these measurements were done consistently and by an experienced surgeon.

The major limitation of this study is the relatively small number of included patients. The results of this trial should therefore be interpreted with caution. A sample size of 41 subjects per group with a power of 90%, alpha 0.05 and a 10% drop-out rate was calculated at the beginning of the study. This was based on the primary outcome parameter SPADI, with a minimal clinically important difference of 13 and a standard deviation of 17. Unfortunately, it was impossible to include this number of patients within a reasonable period of time. This was attributable to two factors. Firstly, the costs for physiotherapy were supported by the Slotervaart Center of Orthopedic Research and Education, however this was only available for a limited number of patients. Three separate research grant applications for funding of the trial were declined. Secondly, there was an unexpected amount of unwillingness to participate among eligible patients. We tried to increase the number of inclusions by attracting attention for the trial in several ways. Printed posters were exposed in the waiting rooms of the orthopedic department, an article about the trial was published in the local hospital journal, and an information letter was sent to more than 200 general practitioners in the catchment area. However, even with these small numbers, a positive effect of physiotherapy was observed up to three months of follow-up. It is possible that more significant differences between both treatment groups would have been found with a larger number of included patients.

A control group without corticosteroid injection was not made available in the study design to monitor the true natural course of the condition. This was because of our assumption that this could raise more difficulties persuading patients to participate in

the trial. Study patient compliance to physiotherapy sessions was not recorded. However, a high compliance rate was expected, as the provided PT was free of charge. We are not aware of any patient cross-over, *i.e.*, starting physiotherapy on their own once assigned to the non-PT group. A possible explanation for inferior SPADI scores and ROM measurements at 6 weeks in the non-PT group could be the confounding role of diabetes in two patients in this group. A prolonged refractory course of FS can be expected with diabetes.[38,39] However, the results from additional analysis that excluded these two diabetic patients did not change the conclusions.

Nevertheless, it is important to note that there is no clear understanding of the exact mechanism responsible for the natural course of FS as well as its improvement over time for most patients. We do agree that an important aspect of treatment is expert advice and the education of patients, with attention paid to the patients' perspectives regarding their expectations and experiences with FS.

With the results of this trial and the current literature, we suggest to offer patients additional PT after an intra-articular corticosteroid injection in the treatment of early-stage FS. The SPADI scores, ROM and pain at night scores are significantly better in the PT group *vs* the non-PT group at 6 weeks. With time, the positive effect of PT had faded out. There were no significant differences between patients in both groups at the final follow-up at 26 weeks. Additional PT can improve shoulder function and shorten the duration of functional limitations during recovery for early-stage FS patients up to the first three months.

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# PART THREE

## THE ROLE OF MANIPULATION UNDER ANESTHESIA IN THE TREATMENT OF FROZEN SHOULDERS

# CHAPTER FIVE

## Arthroscopic capsular release and manipulation under anesthesia for frozen shoulders: A hot topic

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# ABSTRACT

**Background** A frozen shoulder is a common cause of shoulder pain and stiffness. The etiology and pathophysiology of frozen shoulders is not fully understood yet. Frozen shoulder is characterized by a decrease in intra-articular volume and capsular compliance. This can lead to significant limitations in daily life. The majority of the patients can be treated conservatively, with functional recovery to be expected in two to three years. However, if conservative treatment fails, manipulation under anesthesia and arthroscopic capsular release are the main two interventions that can be chosen. A literature overview regarding the pros and cons of both procedures is given.

**Management** Manipulation under anesthesia is a traditionally well-established technique but in recent years it seems that arthroscopic capsular release has gained popularity. Manipulation is a relative time efficient and technically low-demanding procedure in which the glenohumeral joint is forced into different directions under general anesthesia to release the capsular contracture, thereby increasing the range of motion. In arthroscopic capsular release the glenohumeral capsule can be released in a more controlled manner under direct vision. Both procedures do have their own specific risks, which can be serious, but complication rates are generally low.

**Conclusions** Both manipulation under anesthesia and arthroscopic capsular release can be considered appropriate treatment options for refractory frozen shoulders. With early postoperative physiotherapy, range of motion and function seems to improve fairly quick after both procedures. There are no prospective comparative trials available to display superiority of one procedure over the other. Furthermore, the optimal timing of both interventions still has to be determined.

# BACKGROUND

## EPIDEMIOLOGY

A frozen shoulder is a commonly encountered condition in the orthopedic surgeons' practice. Pain and restricted range of motion of the shoulder may lead to disability and a decrease in quality of life. In 1872 Duplay described a painful stiffening of the shoulder, which he named humero-scapular periarthritis.[1] Codman was the first to coin the term frozen shoulder in 1934, for a condition which was characterized by painful restriction of shoulder motion.[2] Neviaser suggested the term adhesive capsulitis after a cadaveric study and intra-operative findings of a thickened capsule, adherent to the humeral head.[3] Both terms, frozen shoulder and adhesive capsulitis, are now used interchangeable in the literature for the same condition.

Frozen shoulder affects approximately 2-4% of the general population.[4,5] The peak incidence is mainly between the age of 40 and 65 years, slightly more frequent in women than in men.[6] The most important associated systemic condition is diabetes mellitus, followed by thyroid disorders. The prevalence of frozen shoulder increases to 10-20% in diabetic patients. These patients seem to have a prolonged course of the disease, less response to conservative treatment and bilateral involvement is seen more frequently.[7,8]



The natural history of a frozen shoulder is described in a relative limited amount of studies. In the majority of patients, it seems to be a self-limited condition with functional recovery after 2-3 years.[9] However, some patients experience continued pain and limited range of motion. After recovery, recurrence of a frozen shoulder is extremely rare.[10]

## DIAGNOSIS

Although frozen shoulder is a well-known clinical entity, there are still many controversies existing about the definition, the different stages and certainly about the optimal treatment regimen. Zuckerman proposed this descriptive consensus definition, which was agreed by 82% of members of the American Shoulder and Elbow Surgeons: *A condition characterized by functional restriction of both active and passive shoulder motion for which radiographs of the glenohumeral joint are essentially unremarkable except for the presence of osteopenia or calcific tendinitis.*[11] Commonly clinical findings consist of: painful stiff shoulder for at least 4 week; severe shoulder pain that interferes with activities of daily living or work; night pain; painful restriction of both passive and active shoulder range of motion and normal radiographic appearance.[12,13] With physical examination, the selective loss of passive external rotation is typical.[14]

Frozen shoulder is usually categorized in primary (or idiopathic) and secondary frozen shoulder. In a primary (idiopathic) frozen shoulder, an underlying aetiology cannot be

found. In secondary frozen shoulder, local or intrinsic factors (such as proximal humeral fracture, rotator cuff disorders, biceps tendonitis), remote or extrinsic factors (e.g. ipsilateral breast surgery, cervical radiculopathy, cerebrovascular accident, postoperative immobilization) or systemic pathology (including diabetes mellitus, thyroid disorders, hypoadrenalism) may be related to the disease.[11,12]

In 1975 Reeves believed the condition to involve three separate stages. Stage one, the painful stage followed by stage two, the frozen stage in which pain persists and stiffness is aggravated. Stage three is named the thawing stage, where joint motion and pain gradually improve.[15] A wide variety in the duration of each stage is described, but most authors agree with spontaneous functional recovery after 2-3 years.[14,16]

Frozen shoulder is a clinical entity which can generally be diagnosed after a thorough history and physical examination. Plain radiographs are typical without abnormalities. Osteoarthritis of the glenohumeral joint can easily be ruled out. Calcifications in the rotator cuff is a common incidental finding. Ultrasonography is not required for the diagnosis but is appropriate to screen for rotator cuff or biceps tendon abnormalities when suspected. MRI arthrography can show thickening of the coracohumeral ligament and joint capsule in the rotator interval. Also, synovial thickening in the axillary pouch correlates with the stage of adhesive capsulitis.[17] However, MRI should not be routinely ordered in the evaluation of the frozen shoulder.

## PATHOPHYSIOLOGY

In a secondary frozen shoulder, a local or remote factor that leads to immobilisation of the limb or a systemic condition is an underlying cause to be held accountable for the development of a frozen shoulder. However, most cases of frozen shoulder are primary or idiopathic in which the pathophysiology is not yet fully understood. White et al suggest an increase in sedentary jobs with a low level of activity as a possible explanation for the increasing occurrence of a frozen shoulder.[18] A decrease in intra-articular volume and capsular compliance was already described in 1969.[19] An inflammatory contracture of the anterosuperior capsule, the glenohumeral ligaments and the coracohumeral ligament is demonstrated in cadaveric studies and MRI studies.[14,20] This corresponds with the characteristic clinical finding of loss of external rotation in adduction with physical examination. Significant synovial hypertrophy and neovascular proliferation, especially in the rotator interval is often observed during arthroscopy. A histologic study of Bunker et al demonstrates that the predominant cells involved are fibroblasts and myofibroblasts in the joint capsule that produce the extracellular matrix.[21] The produced type III collagen matrix is packed more densely, causing the shoulder capsule to contract. This excess of extracellular matrix is characteristic for fibroproliferative disorders. Other histologic changes consist of chronic inflammation and perivascular infiltration and fibrosis.[22] On a

cellular level, the extracellular matrix turnover (production, degradation and remodelling) is involved by matrix metalloproteinases (MMPs) and their inhibitors. An imbalance can lead to fibroproliferation, which is demonstrated in frozen shoulder patients.[23] The microscopic changes in the anterior capsule and the coracohumeral ligament are very similar to the changes seen in Dupuytrens' disease in the hand. Dupuytrens' disease is frequently observed in patients with a frozen shoulder.[21] Smith et al report an incidence of Dupuytrens' disease of 52% in a cohort of patients with a primary frozen shoulder.[24] Although frozen shoulder has a different natural history than Dupuytrens' disease (self-limiting versus progressive), a common biochemical pathway of both fibroproliferative disorders that leads to contracture is suggested.[24]

More recently, the role of inflammatory cytokines and growth factors in the pathogenesis of a frozen shoulder is investigated, because they regulate the growth and function of fibroblasts. The study of Lho et al confirmed the overexpression of inflammatory cytokines (such as interleukin 1-α, tumor necrosis factor- α and cyclooxygenase-2) in the joint capsule of patients with a frozen shoulder compared to a control group. Also, an overexpression of these inflammatory mediators was found in tissue samples of the subacromial bursa in frozen shoulder patients, possibly contributing to the cascade of inflammation eventually leading to fibrosis.[25]

A future better understanding of the pathophysiology of a frozen shoulder on a cellular level can possibly lead to targeted therapy with anti-inflammatory medication.[26]



## MANAGEMENT

There are many different strategies in the treatment of a frozen shoulder: including but not limited to supervised neglect[9], physiotherapy[27,28], corticosteroid infiltration[29,30], manipulation under anesthesia (MUA)[31], arthroscopic capsular release (ACR)[32], arthrographic capsular distension[33] and stretching devices.[34] The optimal treatment regimen has not yet been established. Systematic reviews point to a lack of good quality evidence to give evidence based supported recommendations.[35,36] Non-steroidal anti-inflammatory drugs, intra-articular corticosteroid injections and physiotherapy are among the most widely used treatment modalities in the treatment of a frozen shoulder, in both primary and secondary healthcare settings.[35,37] Because the natural history of a frozen shoulder develops in different stages, it is suggested that the timing of different treatment modalities might be important in this regard. However, there is only a limited amount of good quality studies that have investigated this matter. The positive effect of intra-articular corticosteroid injections appears to be most obvious at an early painful stage of the condition.[38,39] Shin et al found a similar positive effect of a subacromial corticosteroid

injection compared to an intra-articular injection.[40] The role of physiotherapy is still controversial.[41] Most authors are convinced that the physiotherapy protocol must be adjusted to the stage of the condition with a more important role for physiotherapy in later, less painful stages of the condition. Hanchard suggest different physiotherapy modalities for a pain-predominant or stiffness-predominant frozen shoulder.[42] Kelley et al distinguishes three levels of tissue irritability (high, moderate or low irritability) in frozen shoulder patients to adjust the physiotherapy protocol.[43] Furthermore, other than a primary (idiopathic) frozen shoulder, secondary frozen shoulders after trauma or surgery are often more resistant to conservative treatment.[44,45]

Taking above into account, conservative treatment seems to be sufficient for most cases, and almost full recovery takes place in two or three years.[14] Most authors state that failure of at least 6 to 12 months of appropriate non-operative treatment is an indication for more invasive interventions.[46] However, it is questioned if the course of the disease can be shortened when more invasive interventions are undertaken earlier on in the disease.[47] On the other hand, early surgical intervention for symptomatic frozen shoulder may lead to overtreatment in patients with a mild, self-limiting natural course. It might be interesting to know if it is possible to identify which patients will develop a prolonged course, thus could benefit from early invasive treatment. Prospective studies of non-operative treatment showed that approximately 10% of the patients with an idiopathic frozen shoulder develop a refractory frozen shoulder in which further intervention such as MUA or ACR should be considered.[6,9] MUA is a traditionally well-established technique. However, according to the number of publications on this subject in recent years, ACR is gaining more attention. Both procedures have their own specific advantages and disadvantages.

## MANIPULATION UNDER ANESTHESIA

The same Duplay who described painful stiffening of the shoulder as humero-scapular periarthritis in 1872 suggested MUA as an appropriate treatment for frozen shoulder.[1] Before the improvement in arthroscopic shoulder surgery, MUA was the standard treatment of a frozen shoulder if conservative treatment had failed.

Different techniques have been described, but a fixed order of manipulations is recommended. The use of a small lever arm and scapular stabilization is recommended to prevent fractures and brachial plexus traction injuries.[48] First the arm is brought in to full flexion, then cross body adduction followed by external rotation with the elbow adducted against the trunk. Then the arm is abducted and moved into internal and finally external rotation. A characteristic crepitus can be heard and felt by the surgeon as the contracted capsule is ruptured. The addition of an intra-articular injection with corticosteroids and local anesthetic agent is often used at the end of the procedure.

Consistently satisfactory results in both short- and long-term follow–up are reported with MUA. A significant improvement in range of motion and an overall satisfaction rate of 94% at short term is reported by Dodenhoff.[48] A major cause of satisfaction was to regain the ability to perform normal daily tasks within days of the manipulation. Long term results confirm that the results do not deteriorate after 15 years.[49] Equal range of motion to the contralateral shoulder and no pain was reported in 90% of the patients after 23 years of follow up in a small cohort.[50]

## ARTHROSCOPIC CAPSULAR RELEASE

ACR has gained popularity over the years.[51] The first ACR was described by Conti in 1979.[52] The exact procedure and the magnitude of the capsular release differs between various authors. Earlier techniques describe an anterior and inferior release.[46,53] More recent articles favour a complete circumferential (360 degrees) release.[32,54,55]

Both beach chair and the lateral decubitus position with the arm suspended in traction are possible to perform an ACR. However, in the beach chair position it is easier to assess the range of motion of the shoulder during surgery. A pressure pump system and a vasoconstrictive agent (e.g. adrenaline or epinephrine) in the irrigation solution are recommended to improve visibility. The capsular release is performed with a radiofrequency probe. The structures in the rotator interval and the anterior capsule must be released first. Ogilvie and Pearsall recommend to release the intra-articular portion of the subscapularis tendon, however, several studies show excellent results without sacrificing the subscapularis.[46,51,55,56] The superior capsule can be released parallel to the joint surface until the muscular fibres of the supraspinatus are visible. It is also possible to release the posterior inferior aspect of the capsule. However, the benefit of this posterior release could not be confirmed in a recent level 1 randomized controlled trial.[57] A gentle manipulation can be performed to assess the obtained range of motion. Some authors infiltrate the shoulder joint with corticosteroids at this point.[54] Good to excellent results with regard to function and pain at both short and long term after ACR are reported. A large prospective study of Smith et all reported good pain relief in 80% of the patients within six weeks.[55] Le Lievre demonstrated that the obtained improvements of pain and patient reported shoulder function maintained after a mean follow up of seven years. In addition, the shoulder range of motion was comparable with that of the contralateral shoulder at time of follow up.[54]

## POSTOPERATIVE TREATMENT AND PAIN MANAGEMENT

Similar rehabilitation protocols after MUA and ACR are described. An important aspect after both MUA and ACR is to start physiotherapy immediately, from day one after the surgical intervention. Postoperative pain management must be adequate to tolerate early physiotherapy treatment. This can be achieved in several ways. Pre-operative

regional interscalene block[53], a local intra-articular analgesic injection with or without corticosteroid, an indwelling pain pump in the subacromial space, oral analgesics and icepacks have all been described.[53] Immobilisation in a sling must be discouraged at all times to prevent the shoulder joint from getting stiff again.[54] With adequate pain management, both procedures are assumed to be very well tolerated with minimal postoperative pain.[48,51] Most authors agree on intensive supervised physiotherapy twice or three times a week, possibly supplemented by a home exercise program.[53,55]

## PROS AND CONS FOR MANIPULATION UNDER ANESTHESIA OR ARTHROSCOPIC CAPSULAR RELEASE

Comparable satisfactory results are reported by many authors for MUA as well as for ACR. To our knowledge there are no randomized controlled trials comparing manipulation with capsular release for frozen shoulder. A comparison between both procedures was attempted in a recent systematic review primarily based on level IV evidence. With caution, this study slightly favoured ACR over MUA in recalcitrant idiopathic or diabetic frozen shoulders.[12] The need for prospective higher level evidence is emphasized. The overall complication rate for both procedures is rather low with 0.5% complications reported. The advantages and risks of MUA and ACR are listed in Table 1.

One of the most important arguments used by opponents of MUA, is that it is a fairly uncontrollable procedure. You cannot see what is released, or torn within or around the shoulder joint. The potential risks of MUA are wide-ranging. Reported iatrogenic injuries are: proximal humerus or humeral shaft fractures[58], brachial plexus traction injury[59], glenohumeral ligament tears, rotator cuff tears, labral lesions, osteochondral fractures of the anterior glenoid rim.[60] Significant osteopenia can be considered as a relative contra indication to MUA. Although a lot of articles address the risk of a humeral fracture and the use of a short lever arm is emphasized, the complication itself is seldom reported.[58,61] Loew et al performed an arthroscopy directly after MUA in 30 persons to investigate the intra-articular damage. Hemarthrosis was found in all patients. The anterior capsule was ruptured in 22 out of 30 shoulders, mostly adjacent to and parallel to the labrum, where it is intended to tear. Unequivocal lesions were found in 12 out of 30 shoulders, this involved the anterior and superior labrum, partial tears of the subscapularis tendon, the supraspinatus tendon, the long head of the biceps and one small osteochondral fracture.[60] An evident advantage of MUA in comparison to ACR is that it is more time efficient and that it is associated with substantial lower costs.

Proponents of the ACR procedure believe that a complete release of the capsule can be achieved in a more controlled way. Associated intra-articular pathology can be identified and treated simultaneous. The risks are fairly low, with a documented complication rate of 0.5%.[12,45] However, serious complications as axillary nerve injury, chondrolysis and skin

burns due to heat generation or infection are documented.[3,45,62] Nowadays, temperature controlled diathermal probes are commercially available, possibly preventing overheating of the fluids in the joint during surgery. Different from MUA, ACR can be a more technical demanding procedure. Some authors even state that ACR should only be done when MUA has failed.[14]

Another option is to combine ACR with manipulation. The manipulation can be a gentle one only to release the capsule where it is difficult to reach or risky to release arthroscopically (for example in the area of the axillary nerve). Early significant improvement in shoulder range of motion with relief of pain and maintenance of these results at long term are reported.[41,54,55]

**Table 1** Advantages, disadvantages and risks of manipulation under anesthesia and arthroscopic capsular release in the treatment of frozen shoulders

| Procedure | Advantages | Disadvantages & risks |
|---|---|---|
| **MUA** | Time efficient | Uncontrolled (blind) iatrogenic lesions |
| | Cost efficient | fracture of humerus |
| | Technically low demanding | rotator cuff rupture |
| | | brachial plexus injury |
| | | labral lesions |
| | | (osteo)chondral fracture |
| **ACR** | Visually controlled capsular release | More expensive |
| | Identification and treatment of | Less time efficient |
| | associated intra-articular pathology | Technically demanding |
| | Prevention of excessive bleeding | Cartilage damage |
| | | Axillary nerve injury |
| | | Chondrolysis due to heat generation |
| | | Extravasation of fluid in surrounding tissues |
| | | Infection |

# DISCUSSION

A frozen shoulder is a common cause of shoulder pain and stiffness. The majority of the patients can be treated conservatively, with functional recovery to be expected after two to three years. However, if conservative treatment fails, manipulation under anesthesia and arthroscopic capsular release can both be considered as appropriate treatments. MUA is an easy, time- and cost-efficient technique, but is accompanied by the risk of iatrogenic damage. ACR seems to be a safer way to release the joint capsule. Associated intra-articular pathology can be identified and bleeding can be controlled. However, ACR is technically more demanding, and is also accompanied by the risk of damage to the cartilage or the axillary nerve. Both procedures are performed in large numbers and are considered safe and beneficial for the patient. Superiority of one technique over the other cannot be supported by randomized trials comparing both techniques. In addition, the optimal timing of any surgical intervention for frozen shoulder has to be determined yet. Therefore, the decision for either one procedure to treat a frozen shoulder is made by the orthopedic surgeon and the individual patient together.

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# CHAPTER SIX

## Manipulation under anesthesia for frozen shoulders; outdated technique or a well-established quick fix?

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# ABSTRACT

**Background** There is currently no consensus about the optimal treatment strategy for frozen shoulders if conservative treatment fails. With manipulation under anesthesia, the tight shoulder joint capsule is stretched and torn to improve range of motion. After the introduction of arthroscopy, manipulation can be considered controversial because it cannot be seen or felt what structures are torn with manipulation. The purpose of this systematic review was to evaluate whether manipulation under anesthesia is an effective and safe treatment option.

**Methods** A literature search was conducted in EMBASE, MEDLINE and The Cochrane Library databases in June 2016. Types of articles that were eligible for inclusion were: retrospective case series; cohort studies; or randomized controlled trials, reporting clinical results regarding pain and range of motion after manipulation under anesthesia. A minimum number of 15 patients with a follow up of six months and the publication date after 1985 was required for inclusion. Articles were excluded if manipulation was combined with another treatment procedure such as an arthroscopic capsular release or distension injections.

**Results** The search strategy resulted in 318 records of which 16 were eligible for inclusion. Pooled analysis showed a significant increase in shoulder joint ROM, improved Constant scores along with a significant reduction in VAS levels for pain after manipulation. Approximately 10% to 15% of patients are not satisfied with the results of manipulation. An overall complication rate of 0.4% was found and a re-intervention rate of 14%, although most of the included papers were not designed to monitor complications.

**Conclusions** This review shows that a considerable increase in ROM and Constant score, reduction in pain and around 85% of satisfaction are possible with manipulation under anesthesia. All but one study in this review lacked a control group without intervention. We recommend being careful when considering manipulation under anesthesia for frozen shoulders because the relative mild natural course of the disease in the majority of patients and potential serious complications. The following criteria are suggested to use before proceeding with manipulation under anesthesia: a patient unable to cope with a stiff and painful shoulder; clinical signs of a stage 2 frozen shoulder; lessening pain in relation to stage 1; external rotation < 50% compared to contralateral shoulder joint; a minimal duration of symptoms of three months; and failure to respond to an intra-articular corticosteroid infiltration.

## BACKGROUND

Frozen shoulder (FS), also known as adhesive capsulitis, is a common cause of a painful shoulder with restricted motion. It affects approximately 2% to 4% of the general population, mainly middle-aged persons, and occurs more frequently in women than men.[1,2] Loss of passive external rotation is the most characteristic finding at physical examination. The French physician S. Duplay first described the condition as 'peri-arthritis scapulo-humerale' in 1872.[3] Some 50 years later, Codman was the first to coin the term 'frozen shoulder' and formulated the Codman criteria for the diagnosis of FS (Table 1).[4] Codman already described FS as 'difficult to define, difficult to treat and difficult to explain'.[5] Nowadays, FS still is a condition with uncertainties about the aetiology, controversies about the optimal treatment strategy and the timing of intervention.

**Table 1** Codman's criteria for frozen shoulder

| **Symptoms** |
|---|
| Condition comes on slowly |
| Pain is felt near the insertion of deltoid |
| Inability to sleep on the affected side |
| Able to continue daily habits and routines |
| **Signs** |
| Painful restricted elevation |
| Painful restricted external rotation |
| Restriction of both the active and passive type |
| Atrophy of the spinate |
| Little local tenderness |
| **Investigations** |
| Normal results on radiography |

In 1945, Neviaser suggested the term adhesive capsulitis, because of his observation that the axillary fold became adherent to the humeral head. However, the existence of a true adhesion could not be confirmed in other studies.[6] Zuckerman et al formulated a descriptive consensus definition for FS: 'a condition characterized by functional restriction of both active and passive shoulder motion for which radiographs of the glenohumeral joint are essentially unremarkable'.[7] Based on the aetiology, FS can be classified into primary and secondary FS. In primary, or idiopathic, FS an underlying cause

cannot be identified. In secondary FS, intrinsic or extrinsic factors can be related to the aetiology of FS. A list of possible related conditions of secondary FS is shown in Table 2.

**Table 2** Related conditions associated with secondary frozen shoulder

| Condition | Example |
|---|---|
| Systemic conditions | Diabetes mellitus, hypothyroidism, hypo-adrenalism |
| Trauma | Proximal humeral fracture, clavicle fracture |
| Post-operative | Immobilization of the upper limb after rotator cuff surgery |
| Breast cancer treatment | Surgery or radiation therapy on the chest wall and axilla |
| Neurological conditions | Cervical radiculopathy, stroke |

The natural history of FS can be generally divided in three stages, as originally described by Reeves.[8] Stage 1 is called the freezing stage, with severe pain with every motion and increasing stiffness. At stage 2, or the frozen stage, there is established stiffness but with reduced pain levels, but specific pain at the end range of motion (ROM). In the third and final stage, the thawing stage, there is gradual recovery of shoulder joint motion with low levels of pain or no pain. The duration of different stages can vary and clear cut-off values for each stage have not been defined.

Although the underlying pathophysiology of a FS is not entirely understood, studies suggest a chronic inflammatory cascade leading preliminary to a contracture of the joint capsule. Similar to Dupuytren's disease, the cells that are mainly involved are fibroblasts and myofibroblasts. They produce densely packed collagen type III in the extracellular matrix of the articular capsule.[9] This leads to a decreased intra-articular volume, often < 5 mL instead of around 20 mL, and a reduced capsular compliance.[10,11] The identified affected anatomic structures in FS are the rotator interval, the superior and inferior glenohumeral ligaments, and also the coracohumeral ligament.[12,13] Apparently, reversibility of these pathological changes is likely, as natural history studies show that the majority of patients have a functional recovery within one to three years.[14,15] However, residual symptoms and restriction of shoulder joint motion in the long term are not uncommon.[16,17] Hand et al reported mild residual symptoms, measured as a reduced Oxford Shoulder Score (OSS), in 35% of patients after four years in a natural history study.[18] In addition, Griggs showed that ROM does not fully return to normal after conservative treatment, with ROM generally 10% to 15% less than the contralateral shoulder.[19] Although FS is considered to be a mild and self-limiting condition, patients experience pain and disabilities in daily activities, with a limited capacity to function at

work for an extensive period of time. The self-reported working ability of patients with a FS was 5 out of 10 in the study by Kivimäki.[20] Therefore, treatment of FS should be focused on limiting symptoms and shortening the duration of disabilities. A wide range of treatment modalities have been described, such as supervised neglect,[21] physiotherapy,[22] intra-articular corticosteroid injections,[23] capsular distension injections,[24] manipulation under anesthesia (MUA)[25] and arthroscopic capsular release (ACR).[26] Systematic reviews on treatment strategies for FS point to a lack of evidence; there is currently no consensus about the optimal treatment strategy.[27–29] Conservative treatment with (intra-articular) corticosteroid infiltrations with or without physiotherapy is sufficient to relieve symptoms for the majority of patients. However, conservative treatment can fail in several cases with prolonged symptoms. MUA is believed to be the most widely used non-conservative treatment option for these refractory cases. With MUA, the tight shoulder joint capsule is stretched and torn with manipulation. It is a time-efficient procedure and relatively easy to perform, resulting in rapid restoration of the ROM of the shoulder joint and reduces the symptoms of FS.[30] Opponents argue that it cannot be seen or felt what other structures than the joint capsule are damaged during manipulation. In addition, serious complications of MUA have been reported, such as a humeral shaft fracture, glenoid rim fracture, shoulder dislocation, brachial plexus traction injury or intra-articular damage to the cartilage or rotator cuff.[31–34] As a result, MUA can be considered a controversial procedure for FS, and orthopedic surgeons have a different threshold for MUA.[35] Moreover, the optimal indication for MUA and the right timing of MUA are unclear. To gain better insight in the role of MUA in the treatment of FS, this systematic review was undertaken. The results of MUA on pain levels and the ROM in patients with FS are pooled and summarized. Patient demographics, indications, technical varieties in the MUA procedure itself, the post-operative rehabilitation protocol and the complications of MUA are addressed in this review. Furthermore, the purpose of this systematic review was to evaluate whether MUA is an effective and safe treatment option.



# METHODS

## LITERATURE SEARCH

A literature search, assisted by a librarian, was conducted in EMBASE, MEDLINE and The Cochrane Library databases in June 2016. After removing duplicates, two reviewers (SP and TK) blindly screened the available titles and abstracts that were potentially relevant and these were retrieved as full-text documents for further analysis. Any disagreements about selection of certain titles were resolved through consultation with two senior authors (BT and LB). References from the selected full-text articles were also checked to retrieve additional relevant articles that were missed in the first phase of the original search strategy. The flow diagram in Figure 1 shows the processing of the search results.

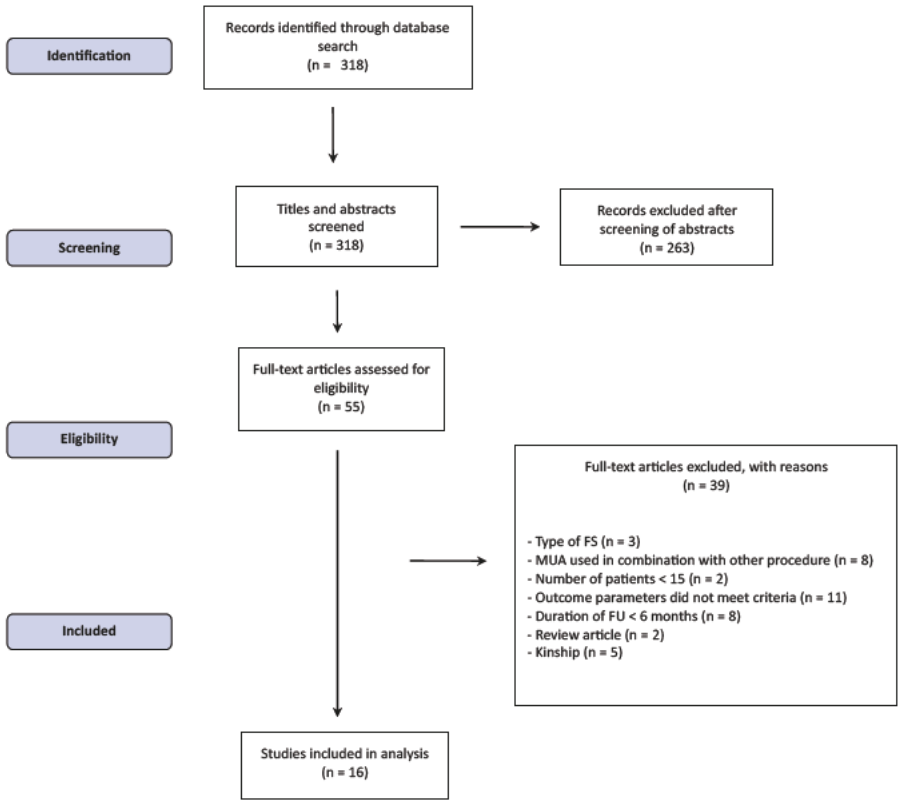


**Figure 1** Flow chart showing the results and evaluation process of the search, according to the PRISMA algorithm

## STUDY SELECTION

The main intention was to find all published articles describing the clinical results of MUA in patients with a primary, idiopathic FS. Articles that reported on the results of MUA in patients with diabetes mellitus were allowed for inclusion because this is a substantial and important subgroup of patients with a FS. Articles with > 25% post-traumatic or post-surgical FS were not included. Types of articles that were eligible for inclusion were: retrospective case series; cohort studies; or randomized controlled trials (RCT). Outcome parameters should at least include a pain score and ROM of the shoulder joint or a functional outcome score including pain and ROM. Articles should report a minimum follow-up of six months and the publication date not before the year 1985. MUA in combination with an injection of corticosteroids in the shoulder region was allowed for inclusion.

Articles were excluded if MUA was combined with another treatment procedure such as ACR or distension injections. Furthermore, articles were excluded if the number of treated patients was < 15, if no full text was available and if the language was other than English, Dutch or German. When more specific information than published was requested, the authors of the retrieved articles were contacted by email for any additional information. The retrieved studies were assessed again by three independent authors (SP, TK and BK) to ensure that they fulfilled the inclusion criteria.

## METHODOLOGICAL QUALITY ASSESSMENT

For assessment of the methodological quality of the selected studies, the MINORS (Methodological Index for Non-Randomized Studies) criteria were used.[36] MINORS is a validated instrument for either comparative and/or non-comparative studies. For non-randomized studies, it consists of eight methodological items comprising three answer options: 'not reported' (0 points); 'reported but inadequate' (1 point); and 'reported and adequate' (2 points). Four additional items are scored for comparative studies. The best score for methodological quality for non-randomized studies is 16 points and 24 points for comparative studies. All included studies were independently assessed by two reviewers (SP and TK). A third senior reviewer (IS) was consulted for a final assessment if needed.

## STATISTICAL ANALYSIS

Weighted mean differences (WMD) with 95% confidence intervals (CIs) of pre- and post-operative outcome measures (ROM, CMS and VAS) were calculated at three time intervals after MUA: short term (< six weeks); mid-term (seven weeks to six months); and long term (> 12 months). Calculation of the WMD was based on means, standard deviations (SD) and number of patients of each cohort. Study results were pooled by use of the random effects model. In cases when only ranges were reported, SDs were calculated using the method by Walter and Yao.[37] For studies reporting the 95% CIs, the SD was estimated according to Higgins et al.[38] Heterogeneity between the studies was assessed by use of both $\chi^2$ and the $I^2$ statistics. An $I^2$ value > 50% was considered substantial. Review Manager (Version 5.3, Cochrane Reviews, London, UK) was used to perform the meta-analysis.

# RESULTS

The search strategy resulted in 318 records eligible for inclusion. Of those, 263 studies were excluded after reviewing of the titles and abstract. Final full-text assessment of the 55 potentially relevant articles resulted in 16 eligible studies for this review. These consisted of three prospective randomized trials,[20,39,40] four comparative non-randomized trials[41–44] and nine non-comparative cohort studies.[25,30,45–51] The mean MINORS was 10.6 (7 to 13) for comparative studies and 8.3 (7 to 9) for non-comparative studies.

Some authors have published multiple studies concerning MUA. They were contacted by email to verify if different study populations were used in the studies. We included three studies by Vastamäki et al, after the first author ensured us that the findings of different study populations were reported. Othman et al published two articles[46,52] from the same cohort of patients. We therefore chose to include only his first publication.[46] We found two reports by Wang et al[44,53] with an overlapping study population. We chose to include only the most relevant article, with the results of MUA concerning patients with or without diabetes.[44] The articles by Jenkins[41] and Leonidou[54] report the results of the same cohort of patients. The article by Jenkins focused on the subgroup of diabetic patients with a FS and the article by Leonidou on patients with a secondary FS after breast cancer. The control group in both studies is of interest to us but is overlapping. There was no response to our enquiries and only the most relevant article by Jenkins was included.[41] The characteristics of the included studies are shown in Table 3.

## DEMOGRAPHICS

The final selection of included studies comprised a total of 858 FS patients that were treated with MUA. The mean age of the patients was 52 years. The mean time from onset of symptoms to the intervention was seven months, with a wide range from one month[46] to three years.[25]

The diagnosis of FS was made by different criteria in the included articles. Most authors described a loss in both active and passive ROM for which no other cause could be identified. Pain at the end ROM was noted as a requisite by some authors.[43,48] Various diagnostic criteria and cut-off values that were used are shown in Table 4.

Conventional radiographs were used to rule out other diagnoses including osteoarthritis by most authors.[25,30,39,40,46] Additional imaging with ultrasound or MRI was sparsely reported.[42,44,47]

**Table 3** Characteristics of studies included in this review

| Investigator | Year | Study design | Type of FS (as stated by authors) | Patients (n) | Age (mean, years) | Onset to MUA (months) | Diabetes | Cortico-steroids | Follow-up (mean, months) | MINOR score |
|---|---|---|---|---|---|---|---|---|---|---|
| Dodenhoff | 2000 | Prospective cohort | Primary, 'frozen' | 39 | 53 | 8 (3-15) | Excluded | Yes | 11 (6-18) | 8 |
| Farrel | 2005 | Retrospective cohort | Idiopathic | 19 | 50 | 11 (2-36) | n = 8 (not reported separately) | No | 180 (97-247.2) | 9 |
| Flannery | 2007 | Retrospective cohort | Idiopathic | 145 | 60 | 6.5 | Excluded | Yes | 62 (12-125) | 9 |
| Jacobs | 2009 | Prospective randomized trial | Primary, 'freezing' | 25 | 57 | 4.2 | Excluded | No | Mean not reported, goal 24 | 13 |
| Jenkins | 2012 | Retrospective case control | Primary and secondary | 214 | 51 | 6 | n = 39 | Yes | 43 (8-127) | 10 |
| Kivimäki | 2007 | Prospective randomized trial | Not clearly stated | 65 | 53 | 7.4 (3-22) | n = 9 (not reported separately) | No | Mean not reported, goal 12 | 13 |
| Meyer | 2015 | Prospective (non-randomized) comparative | Idiopathic, 'frozen' | 30 | 52 | 9.9 | Excluded | Yes, subacromial in 50% | Mean not reported, goal 12 | 12 |
| Othman | 2002 | Retrospective cohort | Not clearly stated, post-traumatic excluded | 74 | 53 | 7.2 (1-20) | n = 5 (not reported separately) | Yes | 33 | 7 |

**Table 3** (Continued) Characteristics of studies included in this review

| Investigator | Year | Study design | Type of FS (as stated by authors) | Patients (n) | Age (mean, years) | Onset to MUA (months) | Diabetes | Cortico-steroids | Follow-up (mean, months) | MINOR score |
|---|---|---|---|---|---|---|---|---|---|---|
| Pap | 1998 | Prospective cohort | Idiopathic | 39 | 50 | 7.3 (4-12) | Excluded | No | 40.8 (26.4-51.6) | 9 |
| Placzek | 1998 | Prospective cohort | Not clearly stated | 32 | 49 | 7.3 | n = 4 (not reported separately) | Yes, orally | 14.4 | 8 |
| Quraishi | 2007 | Prospective randomized trial | Primary, stage II | 16 | 55 | 8.8 (4-23) | n = 3 (re-intervention) | Yes | 2.6 | 11 |
| Sokk | 2012 | Prospective cohort | Idiopathic | 15 | 54 | 8.6 (3-12) | Not reported | Yes | Mean not reported, goal 6 | 9 |
| Vastamäki | 2012 | Retrospective cohort | Idiopathic 'spontaneous' | 22 | 53 | Not reported | n = 5 | No | 168 (24-288) | 8 |
| Vastamäki | 2013 | Retrospective cohort | Idiopathic 'spontaneous' | 16 | 49 | 7.6 (4-12) | n = 4 | No | 276 (228-360) | 7 |
| Vastamäki | 2015 | Retrospective cohort | Idiopathic 'spontaneous' | 65 | 54 | Not reported | n = 10 (not reported separately) | No | 72 | 9 |
| Wang | 2010 | Retrospective, non-randomized, comparative | Idiopathic | 42 | 56 | 7.4 (3-18) | n = 21 | Yes | 95 (18-189) | 7 |

## THE INDICATION FOR MANIPULATION UNDER ANESTHESIA

The indication for MUA varied between the different articles. A clear indication for manipulation in frozen shoulders could not be extracted from the available literature. Failure of conservative treatment was often not clearly defined. A minimal duration of symptoms was required by most authors. However, this varied highly, from one month,[46] two to four months,[44,45,47,48] until a minimum duration of six months.[42,43] Physiotherapy, analgesics and corticosteroid infiltrations (both subacromial and intra-articular) were the mainstay of the conservative treatment modalities before MUA.[40,44–46,49]

## THE INTERVENTION MANIPULATION UNDER ANESTHESIA

MUA was performed under short general anesthesia,[45] alone or with an additional brachial plexus block.[30,48] The sole use of regional brachial plexus anesthesia for MUA was not reported in the included studies, although this is also a possibility according to other authors.[55] The patient was positioned supine in most papers. The use of the lateral decubitus position was reported by Jacobs.[39] The pre-manipulation ROM of the shoulder joint can be measured at this stage. The scapula was stabilized by the supine position, by gripping the top of the shoulder,[41] with the help of an assistant[49] or by supporting the scapula against the thoracic cage manually.[20] The use of a short lever arm was indicated by most authors to prevent fractures. The described sequence of manipulation is varying, as well as the additional methods to reduce the risk of complications (Table 4). The sequence of manipulation can be repeated until the maximal ROM of the shoulder joint was obtained. A typical cracking sound, a definitive snap or characteristic feeling of tissue breakdown in the shoulder was frequently reported.[20,44,46] MUA was combined with an intra-articular corticosteroid injection in around half of the included studies.[30,40,41,44–46,49]



## PHYSIOTHERAPY AFTER MANIPULATION UNDER ANESTHESIA

The purpose of physiotherapy after MUA is to maintain the shoulder joint ROM that is achieved during the manipulation. Overall, physiotherapy was frequently commenced immediately after MUA and continued on a daily basis for a short period of around one week.[30,47–49] After the initial phase, the frequency and duration of physiotherapy sessions varied among the included studies or was left up to the individual therapist and patient.[44] Pool exercises, or one to three hydrotherapy sessions succeeded by 'land-based' physiotherapy, was reported in two articles.[41,50]] Home exercise programs are reported often, but only in a minority of studies without supervised physiotherapy sessions. Quraishi used a self-exercise program consisting of pendular exercises and wall climbing movements without further physiotherapy.[40] In the trial by Kivimaki et al, FS patients were instructed in two physiotherapy sessions and received written information for a home exercise program after MUA.[20]

**Table 4** Diagnostic criteria, minimal duration of symptoms prior to manipulation and imaging used in the diagnosis of frozen shoulder. The sequence of manipulation and the preventative measures as described in the included studies

| Investigator | Year | Diagnostic criteria | Minimal duration of symptoms (months) | Imaging | Sequence of manipulation | Additional preventative measures |
|---|---|---|---|---|---|---|
| Dodenhoff | 2000 | Lessening pain compared to stage I | n.a. | CR | ABD, EXT in ABD, EXT at side, ADD, INT | Scapular stabilization, short lever arm |
| Farrel | 2005 | Pain and limited active and passive ROM | n.a. | CR + MRI or arthrography | FLEX, EXT in ABD, ABD, INT, ADD | Gentle pressure on distal humerus |
| Flannery | 2007 | Codman's criteria | 3 | n.a. | FLEX, EXT, ADD, INT | Scapular stabilization, grip on inner aspect proximal humerus |
| Jacobs | 2009 | n.a. | n.a. | CR | ADD, FLEX, EXT, INT, ABD | Scapular stabilization, short lever arm |
| Jenkins | 2012 | n.a. | n.a. | n.a. | ABD, FLEX, EXT, ADD, INT | n.a. |
| Kivimäki | 2007 | Gradually increasing pain and stiffness, FLEX < 140, EXT < 30 | n.a. | n.a. | FLEX, ABD, INT in 90, EXT in 90 | Scapular stabilization |
| Meyer | 2015 | Codman's criteria, ABD < 90 | 6 | CR + MRI | ABD, EXT in ABD, EXT in ADD, INT | Scapular stabilization |
| Othman | 2002 | FLEX < 100, EXT < 50% compared to contralateral side | 1 | CR | Alternate FLEX, ABD, EXT | Scapular stabilization, grip high on the proximal humerus |
| Pap | 1998 | Lessening pain | 4 | CR + ultrasound | ABD, ADD, FLEX, EXT, INT | n.a. |

**Table 4** (Continued) Diagnostic criteria, minimal duration of symptoms prior to manipulation and imaging used in the diagnosis of frozen shoulder. The sequence of manipulation and the preventative measures as described in the included studies

| Investigator | Year | Diagnostic criteria | Minimal duration of symptoms (months) | Imaging | Sequence of manipulation | Additional preventative measures |
|---|---|---|---|---|---|---|
| Placzek | 1998 | Pain at end ROM, total ROM loss > 40% | 2 | n.a. | ABD and FLEX, INT and EXT | Translational gliding technique, scapular stabilization |
| Quraishi | 2007 | Global loss of active and passive ROM, EXT < 50% | n.a. | CR | n.a. | Short lever arm |
| Sokk | 2012 | ROM < 50% compared to contralateral side in 1 of 3 directions, inability to sleep on affected side | n.a. | CR | FLEX, EXT at side, EXT in 90, INT, ADD | Scapular stabilization, using thumb and opposing 2 fingers |
| Vastamaki | 2012 | FLEX < 135, ABD < 125, 'severe' restriction in EXT, pain at end ROM | 5 to 6 | CR | n.a. | n.a. |
| Vastamaki | 2013 | FLEX + ABD < 120, EXT + INT 'almost absent' | 6 | CR | Gradual alternate ABD, FLEX, EXT, INT | 'Care not to fracture the humerus' |
| Vastamaki | 2015 | FLEX < 120, ABD < 110, 'severe' restriction in EXT | n.a. | CR | Gradual alternate ABD, FLEX, EXT, INT | 'Care not to fracture the humerus' |
| Wang | 2010 | FLEX < 100, EXT < 50% compared to contralateral side | 1 | CR + ultrasound | FLEX, EXT at side, EXT in 90, INT, ADD | Scapular stabilization, force carefully applied with two thumbs |

(n.a., not available; CR, conventional radiograph; FLEX, flexion; ABD, abduction; EXT, external rotation; ADD, adduction; INT, internal rotation)

## RANGE OF MOTION

All authors report a significant increase in shoulder joint ROM after MUA in the short term and a retained effect in the long term was persistently present. Passive ROM was measured, except for the articles by Meyer and Sokk, wherein the active ROM was reported.[42,49] Mean pre-operative range of motion was 80 (SD 29) degrees of flexion, 66 (SD 25) degrees of abduction and 22 (SD 14) degrees of external rotation. The weighted mean increase in degrees of shoulder joint motion from baseline for flexion, abduction and external rotation after MUA is shown in Table 5. How shoulder joint ROM measurements were done was frequently not specified. For example, abduction measurements can be done in the true frontal (coronal) plane or in the scapular plane. Internal rotation measurement methods vary widely. A pooled analysis for internal rotation measurement values was not possible because of the heterogeneity of the data.

Vastamäki was the only author with higher abduction than flexion values of the shoulder joint after MUA in his group of patients. Since this is inconsistent with all other reports, this publication was left out of the analysis for ROM. Pap reported markedly lower values for abduction after MUA compared to the other articles.[47] It is unsure whether this difference can be clarified by an alternative measurement technique.

## PAIN AND FUNCTIONAL OUTCOME SCORES

Improvement in pain can be measured with several methods. The visual analogue scale (VAS) from zero (no pain) to ten (maximum pain) was used most frequently in the included articles. Alternatively, pain levels were measured as part of a functional outcome score. The mean VAS pre-manipulation was 6.9 (SD 1.4). A significant reduction in weighted mean pain scores after MUA was found in the short, middle and long term. The mean reduction in VAS for pain after MUA in FS patients was 3.5 points (SD 3.4) within six weeks, 4 points (SD 1.5) within six months and 5.1 points (SD 1.8) after > 12 months. (Table 6).

A variety of functional outcome scores were used: Constant score; OSS; Simple Shoulder Test; American Shoulder and Elbow Surgeons Score (ASES); and Shoulder disability questionnaire. The Constant score was by far the most common reported score. A pooled analysis was only possible for this score. The Constant score was developed in 1986 by Constant and Murley to asses pain, shoulder motion, strength and function.[56] Thirty-five points are reserved for patient-reported subjective assessment, 40 points for ROM measurement and 25 points for strength of the shoulder. The maximum Constant score is 100, with 75 for the adjusted constant score without strength measurement. The Constant scores must be compared with normative constant scores based on age and gender. In the age category of 50 to 59 years, the normative Constant score is 94 for men and 84 for women.[57] The pre-manipulation mean Constant score was 32.9 (SD

8.8). The weighted mean increase in Constant score and adjusted Constant score is shown in Table 6.

**Table 5** Results of the pooled analysis in shoulder joint range of motion (ROM), per follow-up period after manipulation. Results are shown as weighted mean differences (WMD) from baseline with 95% confidence intervals (CI) for flexion, abduction and external rotation. Study heterogeneity is shown as $I^2$

| | Baseline mean (SD) | WMD | 95% CI | p-value | $I^2$ value % |
|---|---|---|---|---|---|
| **Flexion** | 80.4 (29.4) | | | | |
| 1-6 weeks | | 55.2 | 32.7-78.0 | < 0.0001 | 98 |
| 6-12 weeks | | 45.0 | 34.3-55.7 | < 0.0001 | 53 |
| 3-6 months | | 66.4 | 45.3-87.6 | < 0.0001 | 92 |
| 6-12 months | | 69.4 | 37.8-101.1 | < 0.0001 | 96 |
| > 12 months | | 67.3 | 54.6-80.1 | < 0.0001 | 89 |
| **Abduction** | 65.8 (24.7) | | | | |
| 1-6 weeks | | 72.5 | 48.5-96.4 | < 0.0001 | 97 |
| 6-12 weeks | | 70.5 | 62.6-78.4 | < 0.0001 | 0 |
| 3-6 months | | 86.6 | 29.2-116.1 | < 0.0001 | 95 |
| 6-12 months | | 95.4 | 71.9-118.9 | < 0.0001 | 94 |
| > 12 months | | 91.8 | 84.3-99.3 | 0.03 | 62 |
| **External rotation** | 22.2 (14.2) | | | | |
| 1-6 weeks | | 30.5 | 17.4-43.6 | < 0.0001 | 96 |
| 6-12 weeks | | 21.2 | 9.2-33.2 | 0.008 | 79 |
| 3-6 months | | 29.4 | 12.0-46.7 | < 0.0001 | 93 |
| 6-12 months | | 44.8 | 38.9-50.6 | 0.23 | 32 |
| > 12 months | | 42.0 | 32.8-51.3 | < 0.0001 | 83 |

**Table 6** Results of the pooled analysis of pain (visual analogue scale (VAS)), Constant score (CMS) and adjusted Constant score, per follow-up period after manipulation. Reduction in pain and improvement in Constant score are shown as weighted mean difference (WMD) from baseline with 95% confidence intervals (CI). Study heterogeneity is shown as $I^2$

| | Baseline Mean (SD) | WMD | 95% CI | p-value | $I^2$ value % |
|---|---|---|---|---|---|
| **VAS** | 6.9 (1.4) | | | | |
| 1-6 weeks | | -3.5 | -7.0 - -0.1 | < 0.0001 | 99 |
| 6-12 weeks | | -2.0 | -3.6 - -0.4 | 0.02 | 82 |
| 3-6 months | | -4.0 | -5.5 - -2.4 | 0.03 | 78 |
| 6-12 months | | -5.1 | -5.2 - -5.0 | < 0.0001 | n.a. |
| > 12 months | | -5.1 | -6.9 - -3.3 | 0.002 | 93 |
| **CMS** | 32.9 (8.8) | | | | |
| 1-6 weeks | | 43.5 | 31.8-55.2 | 0.001 | 90 |
| 6 weeks to 6 months | | 41.8 | 22.6-61.1 | < 0.0001 | 96 |
| 6-12 months | | 52.1 | 33.0-71.3 | < 0.0001 | 97 |
| > 12 months | | 41.6 | 38.0-45.3 | n.a. | n.a. |
| **Adjusted CMS** | 24.8 (5.7) | | | | |
| 1-6 weeks | | 30.2 | 27.5-32.9 | < 0.0001 | n.a. |
| > 12 months | | 48.6 | 46.8-50.3 | 0.19 | 43 |

## SATISFACTION

Six articles report relevant information about patient satisfaction scores after MUA.[25,30,40,45,50,51] Short-term satisfaction is given solely by Dodenhoff et al, who report 41% of FS patients with a satisfactory result after six weeks and 87% after three months.[30] At six months, 81% of the patients are satisfied or very satisfied in the study of Quraishi.[40] In the long term (> 6 months), 94% of patients are satisfied with the result of MUA in the study of Dodenhoff.[30] Farrel et al described a mean 8/10 satisfaction level after an average of 15 years.[25] In the article by Flannery, 90% of patients were satisfied after a mean follow-up of 62 months.[45] Similar to these results, Vastamäki et al report 55% of patients as very satisfied and 30% as satisfied after an average follow-up of nine years.[43] Overall, a minority of approximately 10% to 15% of patients are dissatisfied with the result of MUA.

## DIABETES MELLITUS

A total of 108 patients with diabetes are present in nine out of the 16 included articles in this review. Diabetic patients were excluded in the remainder of the articles.[30,39,42,45,47]

Vastamäki et al report the same results after MUA in the long term in a small subgroup of patients with diabetes compared to non-diabetic patients.[43] Jenkins compared the results of MUA in a diabetic group to a non-diabetic group and found a similar improvement in ROM and OSS, but an increased need for a repeated MUA procedure in diabetics (IDDM 39%, NIDDM 31%) compared to 15% in non-diabetic controls.[41] Wang et al report the results of MUA in 21 diabetic shoulders compared to 42 non-diabetics.[44] They found no significant differences with regard to shoulder pain, ROM and adjusted Constant score. However, only Asian people with non-insulin dependent diabetics were included. Quraishi report on a failed MUA followed by a successful hydrodilation procedure in one out of the three included patients with diabetes.[40] Furthermore, in the remaining articles, small subgroups of patients with diabetes were included, but the authors did not report their results separately from the non-diabetic patients.[20,25,46,48] As few results were separately reported for diabetics, a pooled analysis of the results of MUA in diabetic patients compared to non-diabetics was not possible.

## COMPLICATIONS AND RE-INTERVENTIONS

A total of three known complications out of 696 patients were described in 11 studies reporting complications. This is an overall complication rate of MUA in FS patients of 0.4%. Six articles did not mention complications at all. The three reported complications were two inferior glenoid rim fractures and one anterior subluxation. In all cases, the authors stated that the clinical outcome was not affected.[46,50] In our opinion, this might be an underestimation of the actual complication rate; for example, if the study design was not intended for the registration of complications, such as retrospective case series.



Six of the included studies report on re-interventions. A total re-intervention rate of 14% (56 out of 389 patients) after MUA was calculated. Dodenhoff reported one patient who needed an arthroscopic decompression, due to impingement with the increased ROM after MUA.[30] Jenkins report a second MUA procedure rate of 15%, in 42 out of 274 patients.[41] However, 214 out of these 274 patients were primary FS and there are no specific data which patients underwent the second MUA. Because of this relative high percentage of non-idiopathic FS, this is potentially biasing the re-intervention rate of truly idiopathic FS.

One repeated MUA procedure was reported by Othman. This patient had an optimal Constant score two weeks after manipulation, but symptoms recurred wherefore repeated MUA was done after one year.[46] In the article by Pap et al, 4/39 patients (10%) underwent ACR after MUA had failed.[47] Quraishi report on one diabetic patient who had an unsatisfactory result after MUA, but did well after a hydrodilatation procedure.[40] Farrel reports on one patient with an excellent initial result of MUA, but needed surgery for a symptomatic rotator cuff tear three years later.[25]

# DISCUSSION

This review summarizes the results of MUA in the treatment of idiopathic and diabetes-related FS. A significant increase in shoulder joint ROM and improved Constant scores along with a significant reduction in VAS levels for pain was found after MUA in the short term (< six weeks). In the long term (> 12 months), even better shoulder joint ROM, Constant scores and lower VAS scores were reported after MUA in FS patients. Around 85% of patients were satisfied with the result of MUA. However, these result must be interpreted with caution, because only one out of the 16 studies in this review is a RCT with a control group without an intervention procedure.[20] With a favourable natural history in the long term in the majority of FS patients, a control group demonstrating the course of the natural history of FS is of utmost importance to recognize the true effect of the manipulation.

A FS can certainly lead to disability and absence from work for a prolonged period. It appears justifiable to investigate if MUA shortens the duration of symptoms and does influence the ability to return to work. This subject seems underexposed in the articles in this review, since only two articles provide information about working ability with contrasting findings. Kivimaki et al were unable to find a positive effect of MUA compared to home exercises on working ability.[20] Meyer et al report that 90% of their patients with an idiopathic FS were unable to work, but that 80% were able to return to work six months after MUA.[42] In 1988, Hill et al stated in a small retrospective study that 70% of FS patients were able to return to work after an average of 2.6 months after manipulation.[58]

## WHAT IS THE RIGHT INDICATION FOR MANIPULATION UNDER ANESTHESIA?

A clearly defined indication for MUA in FS patients cannot be extracted from this review or the available literature. In addition, there is no consensus on the criteria of failure of conservative treatment, as is demonstrated by the included literature. Orthopedic surgeons with a low threshold for manipulation of FS may risk over-treatment. On the other hand, a wait and see policy in these patients can presumably lead to an unnecessary prolonged duration of symptoms. Differences are shown in the minimal duration of symptoms before MUA is indicated, whether corticosteroid injections are used and regarding physiotherapy treatment before proceeding to MUA. The use of corticosteroid injections in the conservative treatment of FS is generally accepted in the painful inflammatory first stage of the FS condition. However, De Carli et al showed in a prospective RCT that the results of an intra-articular corticosteroid injection were similar to MUA in stage 2 FS.[59] Taking this into account, and after a thorough review of the literature, we suggest the following criteria in FS patients before proceeding to MUA: a patient unable to cope with a stiff and painful shoulder; clinical signs of a stage

2 idiopathic FS; lessening pain in relation to stage 1; external rotation < 50% compared to contralateral shoulder joint; a minimal duration of symptoms of three months; and failure to respond to an intra-articular corticosteroid infiltration.

## THE IMPORTANCE OF PHYSIOTHERAPY AFTER MANIPULATION UNDER ANESTHESIA

We found a large variety in physiotherapy protocols in FS. Intensive physiotherapy, commenced immediately after MUA and continued on a daily basis for a short period, was reported frequently.[30,47–49] On the other hand, non-supervised home exercise programs are also used.[20,40] It would be interesting to know whether the intensity of physiotherapy after MUA influences the results. However, a well-defined dichotomous distribution of studies with intensive physiotherapy *versus* a less demanding physiotherapy program or home exercises could not be made. In the study by Kivimaki et al, MUA followed by a home exercise program was not beneficial to a home exercise program alone. Intensive supervised physiotherapy was absent in this trial. The authors report initially successful manipulation, but with limited effect at longer follow-up, and recurrence of adhesions is hypothesized by the authors.[20] Although the data of this review are insufficient for a clear conclusion, immediate physiotherapy after MUA seems to be a generally accepted important factor for the result of MUA.

## COMPLICATIONS AND RE-INTERVENTIONS

An overall complication rate of 0.4% after MUA in FS patients was found. This is in accordance with the estimated complication rate of 0.5% reported by Grant et al.[60] However, this must be interpreted with caution because the majority of articles were not specifically designed to register complications. There are concerns for iatrogenic damage to the cartilage, labrum and rotator cuff during manipulation, which are shown by Loew et al with arthroscopy after manipulation.[31] Inferior clinical results because of such lesions were not reported in the included articles; however, this can also be due to the fact that these lesions were not identified and could have gone unnoticed. Serious complications, such as humeral shaft fracture[34] or brachial plexus traction injuries,[32] were not reported in the included papers. Concerns about the rotator cuff integrity after MUA are contradicted by Atoun et al.[61] In their study, the rotator cuff was evaluated with ultrasound before and after manipulation; all rotator cuffs remained undamaged after MUA. Similar to this, Sasanuma et al found no rotator cuff tears on MRI scans after manipulation.[62]

Re-intervention procedures were mainly repeated MUA, ACR or hydrodilatation. An overall re-intervention rate of 14% after MUA in FS patients was calculated. Similarly, 10% to 15% of patients were dissatisfied with the result of MUA. It cannot be made clear out of this review which patients are at risk for failure of MUA, but an increased risk of

failure to respond to MUA in diabetic patients is supported by the article by Jenkins.[41] These results are in accordance with the recently published findings of Woods et al, who report a repeated MUA procedure in 17.8% of a large consecutive series of patients. Even more, in patients with type 1 diabetes, an increased risk of 38% of requiring a second MUA procedure was found. Still, they found a good outcome and a low complication rate (0.2%) in this single surgeon consecutive series in patients treated with FS treated with MUA.[63]

The prevalence of FS in diabetic patients is as high as 10% to 20% and it is generally approved that the course of the disease can be prolonged and has a more refractory nature of the FS.[15,19,64] There are inconsistencies in the literature about the classification of FS in patients with diabetes mellitus. According to the definition of Zuckerman, diabetes mellitus is an underlying systemic condition and should be referred to as a secondary FS.[7] Other authors refer to diabetes mellitus as an associated condition in FS, but not causative related, and name it an idiopathic (spontaneous) FS in diabetics.[50]

## ALTERNATIVE INTERVENTIONS FOR MANIPULATION UNDER ANESTHESIA

One might consider whether MUA is the right procedure when conservative treatment of a FS fails. Other possible interventions are ACR and hydrodilatation, the latter also known as capsular distension injections. Systematic reviews were not able to demonstrate superiority of one of these treatment modalities.[27–29] Grant et al compared MUA with ACR and concluded no clear difference in ROM or patient-reported outcomes.[60] The available evidence was mainly level 4. MUA is relatively easy to perform and time efficient. ACR is visually controlled, but technically more demanding, less time-efficient and has its own specific risks (for example, chondrolysis due to thermal heat with coagulation, axillary nerve damage).[65] Furthermore, a combination of partial ACR followed by gentle manipulation of the shoulder joint seems to be a safe alternative. This potentially reduces the risks of MUA alone, because less force is needed for the manipulation. A clear indication for such a combined procedure is not evident, but is suggested for patients with diabetes.[64] Currently, a large RCT comparing conservative treatment, MUA and MUA combined with ACR is being undertaken in the UK (UK-FROST).[66]

Hydrodilatation is an alternative procedure for FS patients, which can be performed as an outpatient treatment. Quraishi compared hydrodilatation with MUA and found superior VAS, Constant scores and satisfaction in the hydrodilatation group. ROM was equal in both groups.[40] A Cochrane review on hydrodilatation in FS patients concluded that it provides short-term benefits in pain, ROM and function, but that it is uncertain whether hydrodilation is better than alternative interventions.[24]

## LIMITATIONS

The quality of a systematic review is determined by the level of evidence and methodological quality of the available articles. Only three prospective RCTs could be included in this review and the majority of articles were non-comparative studies. The mean MINORS score is 10.6 for the comparative studies and 8.3 for the non-comparative studies, which indicates relatively low methodological quality. Another important limitation is that not solely idiopathic FS were included. Also, the type of the FS and the corresponding stage was frequently not clearly described. It remains difficult to extract if all included patients truly had a FS and no other shoulder morbidity. A pre-operative golden standard diagnostic test is not available. More certainty about the correct diagnosis can be obtained with examination under anesthesia, the typical snapping or tearing sound during manipulation, or with evident synovitis in the rotator interval during arthroscopy. However, the rate in which the diagnosis was verified by these means is rarely reported. For example, Dodenhoff described that in only 27 of 39 shoulders was this typical tearing sound present during manipulation.[30]

## CONCLUSION

This review shows that considerable increase in ROM and Constant score, reduction in pain and around 85% of satisfaction are possible with manipulation under anesthesia for FS patients. A low overall complication rate of 0.4% was found and a re-intervention rate of 14%. However, all but one study lacked a control group without intervention. Based on this review, there is hardly any evidence in favour of or against MUA. We recommend being careful when considering MUA in FS because the relative mild natural course of the disease and potential serious complications. If considered appropriate, we suggest the following criteria before proceeding to MUA: a patient unable to cope with a stiff and painful shoulder; clinical signs of a stage 2 idiopathic FS; lessening pain in relation to stage 1; external rotation < 50% compared to contralateral shoulder joint; a minimal duration of symptoms of three months; and failure to respond to an intra-articular corticosteroid infiltration. Immediate physiotherapy after MUA is generally recommended to avoid a loss of ROM in the first weeks after MUA. However, to recognize the true effect of MUA on symptoms, RCTs with a control group should be undertaken on shoulder joint ROM and the ability to return to work.

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# CHAPTER SEVEN

## Manipulation under anesthesia for frozen shoulders: a retrospective cohort study

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# ABSTRACT

**Background** Manipulation under anesthesia is a well-established, but also a controversial intervention for frozen shoulders. A survey among shoulder specialists in Belgium and The Netherlands showed that manipulation was done most frequently at out institution. This retrospective cohort study critically evaluates patient reported results, satisfaction, and safety of manipulation under anesthesia in stage two frozen shoulders.

**Methods** Questionnaires were sent to 65 patients with stage 2 frozen shoulders, treated with manipulation under anesthesia between January 2012 and January 2014. Manipulation was performed after an interscalene plexus block, in the supine position with stabilization of the scapula. An intra-articular corticosteroid injection was administered after manipulation. Physiotherapy was initiated immediately the day after the intervention. Outcome parameters consisted of SPADI, OSS, EQ-5D, pain and satisfaction.

**Results** A response rate of 75% (n = 49) was obtained. Mean follow up was 21 months (range 11-36). The median SPADI score was 11.2 (IQR 0.8-25.2) and median OSS was 39.0 (IQR 30-43). Ninety percent of patients reported much or very much improvement with respect to the function of the shoulder for daily life activities. A satisfaction rate of 92% was reported. Only 72% of patients reported that they reached their pre-injury level of functioning. No complications were seen during manipulation nor reported by patients afterwards.

**Conclusions** Manipulation is a relatively easy intervention with a high satisfaction rate. We assume that manipulation could potentially shorten the duration of symptoms compared to conservative treatment. However, this needs to be confirmed in a randomized trial with a control group.

# BACKGROUND

Frozen shoulder (FS), also known as adhesive capsulitis, is a common cause of shoulder pain, and affects approximately 2-4% of the general population.[1] FS is historically classified in three different stages, freezing (one), frozen (two) and thawing (three).[2] An inflammatory cascade leads to fibrosis and thickening, resulting in contracture of the anterosuperior shoulder capsule and rotator interval, as well as the glenohumeral and coracohumeral ligaments. On clinical examination, there is a typical manifestation of restricted passive external rotation.[3,4] Although the etiology and pathophysiology of FS are not fully understood yet, it is known that this process is reversible and, left alone, will show functional recovery within one to three years in most patients.[2,5] Despite this, persistent symptoms or restrictions can occur.[6,7] Even if the natural course is mostly self-limiting, patients often experience a prolonged period with a considerable amount of pain and disability in daily life. This disorder has a peak incidence between the age of 40 and 65 and can occur in otherwise healthy people.[5,8] Therefore, these patients experience substantial limitations in their ability to work. Although some authors suggest that supervised neglect is the most appropriate regimen[9], we believe it is important to endeavor to improve mobility hereby limiting the duration and severity of symptoms. The optimal treatment regimen has not yet been determined, and systematic reviews point to a lack of good quality evidence.[10–12]

Although nowadays arthroscopic capsular release is probably gaining popularity, manipulation under anesthesia (MUA) is a traditionally well-established, straightforward treatment method in frozen shoulder. There are no good quality randomized controlled trials in favor of arthroscopic capsular release in comparison to MUA.[13] It is unclear at which stage of disease MUA is most beneficial. Consequently, a clear protocol for orthopedic surgeons in treatment of frozen shoulder is lacking. Dodenhof et al describe the capability of MUA to rapidly restore the range of motion and reduce symptoms within days after the procedure.[14] However, the role of MUA in the treatment of FS is controversial as it can potentially lead to serious complications such as humeral fracture, glenoid rim fracture, glenohumeral dislocation, brachial plexus traction injury or intra-articular damage to the cartilage or rotator cuff.[15–17] The true incidence rate of these complications is unknown, but estimated to be 0.5%.[13] These are possible reasons why orthopedic surgeons may have a cautious attitude concerning MUA. A recent survey among shoulder specialists in Belgium and The Netherlands showed that MUA was carried out most frequently at our hospital. We assume that MUA is well tolerated and can lead to satisfactory results with a quicker recovery of function and faster subsequent return to work, compared to a conservative approach. This retrospective study, will critically evaluate the patient reported results, satisfaction after MUA, and safety of the procedure.

# METHODS

Questionnaires were sent to all 65 patients who were treated by a single orthopedic surgeon with MUA between January 2012 and January 2014. The clinical diagnosis of a stage two FS was made on clinical merits by the treating orthopedic surgeon. Stage two is characterized by diminished pain compared to stage one, marked restriction of passive and active shoulder movements and significant pain mainly at the end range of motion. Conventional radiographs were used to rule out bony abnormalities. Diabetes, thyroid disorders and previous surgery to the shoulder for other reasons were not excluded. Some patients underwent conservative treatment before presenting in the Orthopedic Department. Conservative treatment options included a course of physiotherapy and an intra-articular corticosteroid injection.

The questionnaires included the following patient reported outcome measures; Shoulder Pain And Disability Index (SPADI), which consists of five domains of pain and 8 domains of shoulder disability scores on a zero to ten scale. This generates a score between 0 (best) and 100 (worst);[18] Oxford Shoulder Score (OSS), 12 questions related to pain and function of the arm in daily life. Items are responded on a zero to four point scale. This leads to an OSS score between 0 (worst) and 48 (best);[19] EQ-5D, a standardised health questionnaire addressing five domains (mobility, self-care, daily activities, pain/complaints and mood). In addition, patients report their health condition on a 0-100 VAS scale; The Numeric Pain Rating Scale (NPRS) at rest and during activity was reported.

We used two anchor questions regarding patients' pre and post treatment pain (anchor-Pain), and pre and post treatment level of daily functioning (anchor-ADL). This was reported on a seven-point scale. In addition, we asked if reached their pre-injury level of functioning and if patients would opt again for MUA as a treatment procedure in case of a contralateral frozen shoulder. Patients were also how likely it would be on a scale from zero to ten that they would recommend the procedure to others.

The actual procedure of MUA was performed by a single surgeon in a standardized, identical way in all cases. An interscalene plexus block was used in all cases. If necessary, short duration general anesthesia or sedation was used in a minority of patients when there was still pain or active muscle resistance, or at the request of the patient. The scapula is indirectly stabilized by the supine position. A short lever arm with the elbow flexed at 90 degrees, is used to prevent fractures and brachial plexus traction injuries. The glenohumeral joint is forced through a full range of motion in a strict pattern: anteflexion, abduction, external rotation in 90 degrees' abduction, internal rotation in 90 degrees' abduction, horizontal adduction with dorsal compression and external rotation in neutral. A recognizable tearing sound was always more or less present, which in our

experience confirms the diagnosis of frozen shoulder. The sequence was repeated until maximum range of motion was acquired. At the end of the procedure, an infiltration of kenacort 40mg (1ml) and chirocaine (4ml) was administered in the glenohumeral joint. Postoperative physiotherapy was started directly the same day to maintain the full range of motion that was obtained. Patients remained as hospital in-patients until the morning following their procedure. Intensive physiotherapy was advised, with an aim for a total treatment plan of 2 weeks (6 days a week), and was continued if deemed necessary by the treating physiotherapist.

## RESULTS

Of 65 patients, 49 people (75%) completed and returned the questionnaires. Table 1 shows the patient characteristics, associated comorbidity and pre-manipulation range of motion. No patients with mamma carcinoma, cerebral vascular accident with shoulder involvement or previous shoulder fractures were involved. Conventional X rays showed no abnormalities in 37 patients (75.5%), mild glenohumeral arthrosis defined as Kellgren Lawrence ≤ 1 in 7 patients (14.3%) and calcifications were seen in 5 patients (10,2%). There were seven patients (14.3%) with previous surgery to the affected shoulder for other reasons.

**Table 1** Patient characteristics at baseline

| | **n (%)** | **mean (SD)** |
|---|---|---|
| Total number of patients | 49 | |
| Age (yrs) | | 57.6 (6.9) |
| Time from onset to MUA (months) | | 8 (2-25) |
| Female | 30 (61.2%) | |
| Dominant side affected | 25 (51%) | |
| Smoking | 12 (24.5%) | |
| Thyroid disorder | 5 (10.2%) | |
| Diabetes | 5 (10.2%) | |
| Previous shoulder surgery | 7 (14.3%) | |
| Previous physiotherapy | 29 (59.2%) | |
| Previous injections | 30 (61.2%) | |
| Pre-MUA anteflexion | | 106° (13) |
| Pre-MUA abduction | | 105° (13) |
| Pre-MUA external rotation | | 24° (14) |

The mean time from onset of symptoms to MUA was 8 months (range 2-25). The mean follow up was 21 months (range 11-36). The median SPADI score at follow up was 11.2 (IQR 0.8-25.2) and the median OSS was 39.0 (IQR 30-43). The mean EQ-5D was 73.8 (SD 18.1). Median NPRS for pain at rest was 1 (IQR 1-2) and median NPRS during activity was also 1 (IQR 1-3). An overview of these results is presented in Table 2.

Forty-five patients (92%) reported to be satisfied or very satisfied with the treatment and stated that they would chose the same treatment again if they should suffer a frozen shoulder on the contralateral shoulder. Sixty-five percent reported a pre-injury level of functioning within three months after MUA, and 72% after six months. The maximum effect of MUA was reported within six weeks by 61% of the patients. Forty-one patients (83.7%) reported that the benefits following MUA were retained. The result of both anchor questions related to change in pain and change in daily functioning are shown in Figure 1. Eighty-four percent reported much or very much improvement with respect to the pain after the procedure and even 90% reported much or very much improvement with respect to the functioning in daily life.

No complications were seen during manipulation nor reported by the patients afterwards.

**Table 2** Overview of the patient reported results

| **Outcome Measure** | **mean (SD), median (IQR) or n (%)** |
|---|---|
| Follow up (months) | 21 (11-36) |
| NRS pain rest | 1 (1-2) |
| NRS pain activity | 1 (1-3) |
| SPADI | 11 (0.8-25.2) |
| OSS | 39 (30-43) |
| EQ-5D | 73.8 (18.1) |
| Recommendation | 9 (8-10) |
| Benefits MUA retained | 41 (83.7%) |

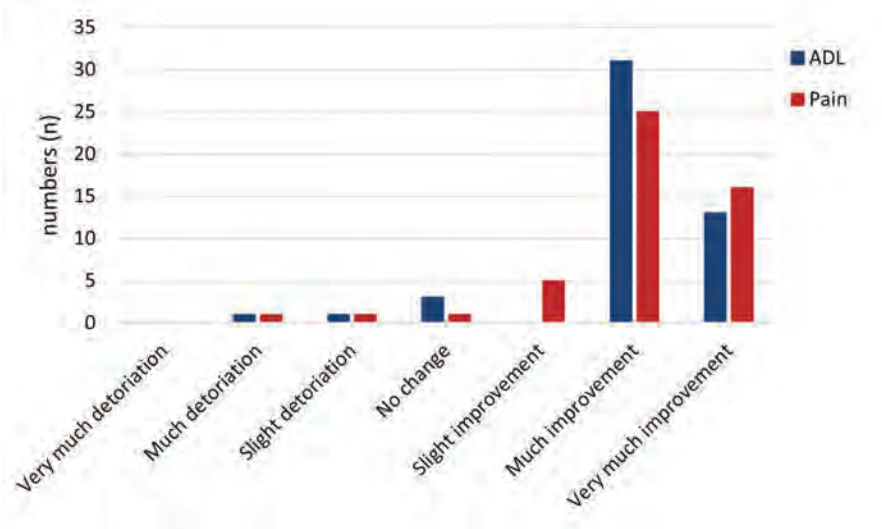


**Figure 1** Results of two anchor questions. Patients were asked to rate their change after manipulation regarding pain (pain) and function in daily life (ADL) on a seven point scale

## DISCUSSION

This retrospective cohort study tends to demonstrate that MUA followed by physiotherapy treatment is an effective treatment option for patients with a FS in stage two when conservative treatment fails. A high percentage of patients (92%) is satisfied with the procedure. Seventy-two percent of patients reported to reach their pre-injury level of functioning within six months. And the beneficial effect of MUA was retained in 84% (n=41) of patients at a mean follow up of 21 months.

Conservative treatment is widely used in the management of idiopathic frozen shoulders. Conservative treatment mainly consists of corticosteroid injections and, or physiotherapy therapy.[12] MUA is indicated when conservative treatment fails. However, it remains unclear when to decide that conservative treatment fails. Some authors doubt the fact if MUA influences the natural course of the disease at all. Kivimäki et al conducted a randomized trial in which MUA was compared to a home exercise program.[20] They were not able to demonstrate a beneficial effect of MUA. Unfortunately, 37% of patients were lost to follow up at final follow up. The physiotherapy intervention in their study was markedly different than in our cohort. We advocate intensive stretching and range of motion exercises supervised by a physiotherapist on a daily basis for the first two weeks to preserve the obtained range of motion. In the study of Kivimaki et al, patients were instructed in only two sessions to exercise by themselves.

Our results regarding satisfaction are in line with the results of Dodenhoff et al, a prospective cohort in which 94% of the patients were satisfied with the procedure after MUA.[14] We agree with Dodenhoff et al that this high satisfaction rate might be due to an early recovery of functional activities, within days of the procedure. We found good outcomes on the pain and disability scores SPADI and the OSS, but because of the retrospective nature of the study, we are not able to demonstrate this effect specifically at short term. However, the maximum effect of MUA in our study is reported within six weeks by 61% of patients. Although quite an amount of patients (39%) do not experience an immediate response to MUA.

The reports of Vastamäki and Farrel confirm our finding that the obtained results of MUA persists at long term.[21,22] Unfortunately, there is a small group of patients (four patients, 8%, in our study) without a positive response to MUA regarding pain and disability. It would be interesting to predict why these patients failed to respond to MUA. However, in the current literature we did not find any risk factors for failure of MUA.

We think that potentially decreasing the duration of pain and disability justifies MUA in patients with frozen shoulder when conservative treatment fails. The disorder is mainly considered self-limiting, so it could be suggested that use of MUA could lead to over-treatment. However, a high threshold for MUA, or late intervention, can lead to an unnecessarily long duration of complaints. Vastamäki et al describe an optimal timing between 6-9 months.[23] They retrospectively compared a group treated with MUA between 6 and 9 months, with grossly all the other time points (less than 6 months combined with more than 9 months). From our perspective, this is not convincing evidence to conclude that the optimal time point is between 6 and 9 months from onset of symptoms.

There were some limitations to the current study. The most important is that it lacks a control group to compare these results with the natural course of the disease. Therefore, it is not possible to conclude if the duration of symptoms is shortened by MUA. And more, due to the lack of a control group it is not possible to conclude that patients are better off treated with MUA than if they were left alone. Also, the potential magnitude of overtreatment cannot be estimated without a control group. The range of motion was only measured when there was an unexpected result. Patients with a good, to very good result, after MUA did not have their range of motion reported in the notes. This cohort does not consist of patients solely with primary idiopathic frozen shoulders. This variety of patients were chosen with the intention of analyzing the entire population who underwent MUA. We included patients with diabetes mellitus and patients with a previous surgical procedure to the affected shoulder. Both groups are too small for reasonable subgroup analysis. It is known that a frozen shoulder in patients with diabetes

tends to have a more severe and protracted course.[5,24] Non response bias is a possible confounder with a reasonable response rate of 75%.

In conclusion, MUA is a short and relatively easy procedure to perform. If duration of symptoms can be decreased, we hypothesize that it can be cost effective when the socio-economic issues are taken into account. In this retrospective cohort study, good results regarding pain and disability were obtained and patients reported a high satisfaction rate of 92%. However, only 72% of patients reached their pre-injury level of functioning. We acknowledge that a control group is essential to evaluate the influence of MUA on the natural course of the disease. A randomized controlled trial with MUA followed by physiotherapy compared to conservative treatment is currently under preparation in our Upper Limb Centre.

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# CHAPTER EIGHT

## Manipulation under anesthesia versus physiotherapy treatment in stage two of a frozen shoulder: a study protocol for a randomized controlled trial

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# ABSTRACT

**Background** There is no consensus about the optimal treatment strategy for frozen shoulders. Conservative treatment consisting of intra-articular corticosteroid infiltrations and physiotherapy are considered appropriate for most patients. However, with just a conservative strategy, patients may experience a prolonged rehabilitation period with a considerable amount of pain and disabilities in daily life. Also, at long term, a residual amount of pain and restriction of range of motion is frequently reported. Manipulation under anesthesia (MUA) is a short and relative simple procedure with the potential to rapidly reduce symptoms and restore range of motion. The objective of this trial is to evaluate the effectiveness of MUA followed by a physiotherapy program compared to a physiotherapy program alone, in the treatment of patients with a stage two frozen shoulder. We hypothesize that the course of the disease can be shortened with MUA with a quicker functional recovery.

**Methods** This is a prospective, single center, randomized controlled trial. Eligible patients will be allocated to either the MUA group or the physiotherapy alone (PT) group. In the MUA group manipulation will be performed under interscalene block, directly followed by an intensive physiotherapy treatment protocol, with the goal to maintain the obtained range of motion. Patients allocated to the PT group are given advice and education and receive a written protocol to hand out to their physical therapist based on the recent guideline of the Dutch Shoulder Network for the treatment of frozen shoulders. Descriptive statistics will be used to describe the sample size, patient demographics, presence of diabetes mellitus, range of motion, duration of symptoms till randomization and will be presented for each treatment group. The SPADI is used as primary functional outcome parameter. Secondary outcome parameters are; OSS, NPRS, EQ-5D 3-L, passive range of motion, WORQ-UP, duration of symptoms, usage of analgesics and adverse events. A sample size of 41 subjects in each group was calculated. Follow up is planned after 1,3 and 12 months. The length of physiotherapy treatment in both groups is variable, depending on individual progression. Differences between groups in outcome parameters will be analyzed using the linear mixed modelling and the restricted maximum likelihood ratio technique for estimating the model parameters.

**Conclusions** Successful completion of this trial will provide evidence on the best treatment strategy for patients with a stage two frozen shoulder with either MUA followed by physiotherapy or physiotherapy alone. The results of this study can lead to a better understanding for the role of MUA in the treatment of frozen shoulders.

## BACKGROUND

Frozen shoulder (FS) is a common cause of shoulder pain and disability. It affects approximately 2-4% of the general population, with a peak incidence between the fifth and sixth decade.[1] FS is slightly more frequent in women than in men, and the most important associated condition is diabetes.[2] The pathophysiology of idiopathic FS is still poorly understood.[3] Idiopathic FS is characterised by a spontaneous onset of pain and stiffness of the shoulder, especially a loss of external rotation, without a prior traumatic event.[4] FS is traditionally divided in three stages.[5] Stage one is called the "freezing stage" and is characterised by severe pain and increasing stiffness. Stage two is the "frozen stage" with established stiffness and reduced pain at rest, but still painful at the end of the range of motion. In the third stage, the "thawing stage", gradual improvement of motion occurs. Earlier studies considered it to be a self-limiting, reversible condition.[5,6] Conservative treatment, most frequently consisting of physiotherapy (PT) and corticosteroid infiltrations, is considered appropriate for the majority of patients.[4] However, with conservative treatment residual pain is reported in up to 50% of patients and measurable restriction of motion in up to 60%.[7,8] Functional limitations at long term occur in 6 - 16% of patients.[9,10] Also, natural history studies suggest an average duration of 30.1 months.[11] Patients experience a prolonged rehabilitation period with a considerable amount of pain and disability in daily life. Their functional limitations can lead to absenteeism at work.[12–14] There are several invasive treatment procedures possible, like manipulation under anaesthesia (MUA), arthroscopic capsular release and hydrodilatation. However, good quality comparative studies concerning these procedures are scarce. Systematic reviews point to a lack of evidence, with no consensus about superiority of one of these procedures.[11,15–17]



Traditionally, manipulation under anaesthesia (MUA) is a well-established treatment for FS if conservative treatment fails.[13,18,19] MUA is a short and relative simple procedure by which capsular adhesions are torn apart by manipulation, with the potential to rapidly restore the range of motion and reduce symptoms within days after the procedure.[20] However, the role of MUA in the treatment of FS is still controversial because it might lead to serious complications in rare cases such as a humeral fracture, glenohumeral dislocation, and brachial plexus traction injury.[21,22] Other potential complications are intra-articular damage to the cartilage, glenoid rim fractures, or rotator cuff tears.[23] On the other hand, rotator cuff integrity was maintained after MUA in the study of Atoun[24] and the reported complication rate in cohort studies and reviews of 0.5% is rather low.[16,20,25]

There is only one randomized controlled trial, in which MUA is compared to conservative treatment. Kivimäki et al conducted a randomized trial with 110 patients in which MUA in

combination with a home exercise program was compared to a home exercise program alone.[14] A small difference regarding mobility and pain in favour of the manipulation group was found, but was considered clinically unimportant. However, 34% of patients were lost to follow up after six months, and only 3 patients of the manipulation group were available for follow up at 12 months. Therefore, no firm conclusions can be drawn based on that study. Moreover, the rehabilitation after MUA was far different from the physiotherapy protocol in the current study. In the study of Kivimäki et al, physiotherapy advice was given in two sessions and written instructions for a home exercise program were provided. We suppose that an initial period of one to two weeks of intensive physiotherapy treatment after MUA is essential to prevent recurrence of restrictions. Therefore, we advocate a more aggressive rehabilitation with intensive stretching and range of motion exercises in the first weeks after MUA to preserve the obtained range of motion.

In the current situation in our hospital, a variability in the threshold to decide for MUA between the different individual orthopedic surgeons in the treatment of FS was noticed. This variability was also demonstrated in a survey among Dutch and Belgian orthopedic surgeons.[26] In addition, we found that MUA was carried out most frequently at our hospital. In anticipation of the current protocol for an RCT, we reviewed our own results after manipulation in a retrospective cohort study. In two years, 89 patients were treated by manipulation for a FS. Eighty-five percent of the patients were satisfied with the procedure with good results. No complications were noticed.[27]

The objective of this trial is to evaluate the effectiveness of MUA followed by a PT program compared to a PT program alone in the treatment of patients with a stage two FS. We hypothesize that the course of the disease can be shortened with MUA with a quicker functional recovery and gain in range of motion and a subsequent faster return to work compared to physiotherapy treatment.

## METHODS

### STUDY DESIGN

This trial is a prospective, single center, randomized controlled trial. The study is conducted the Amphia hospital Breda, one of the largest teaching hospitals in the Netherlands. Four shoulder specialists represent the Upper Limb Unit and will participate in the trial.

## RECRUITMENT AND CONSENT

All adult patients presenting to the outpatient with the clinical diagnosis of a FS in stage two will be invited to participate in the trial. A general history is acquired. The upper extremity is examined and range of motion is measured. Conventional radiographs (true anteroposterior in the scapular plane, internal rotation with 90 degrees of flexion in the elbow and the forearm in front of the abdomen, and in maximal external rotation) are made at baseline, to rule out other pathology such as osteoarthritis. The treating orthopedic surgeon or a member of the study staff will introduce and explain the trial to the patient and address any further questions. The patient will receive a written information leaflet together with an informed consent form. After ample time to consider participation in the trial, patients return to the outpatient clinic. After receiving verbal and written consent, eligible patients will be randomized. A secure web based randomization program (CASTOR, https://www.castoredc.com/) is used for block randomization with differing block sizes and with a randomization allocation ratio of 1. This randomization schedule is only accessible for the research coordinator. Applicants will be allocated to either the MUA group or the PT group. Only the research coordinator (who is not a treating physician) will be authorized to use the randomization software module in CASTOR to allocate patients to their intervention group, hereby ensuring concealed allocation. A participant flow diagram is shown in Figure 1. Blinding of patients is not possible. Range of motion measurements are done by a nurse practitioner, blinded for the intervention. Crossing over (from PT to MUA) is potentially possible because patients are allowed to quit participation in the trial as a personal choice. However, the results will be analyzed based on the initial treatment allocation using the intention to treat (ITT) analysis (see 'statistical analysis' section for more details).

If patients visit the outpatient clinic with a stage one FS, they are not (yet) eligible for inclusion in the study. A standardized treatment regimen will be followed, as is the current usual care. They are given advice and education about the condition, the prognosis and the possible treatment options are discussed. An informative brochure and referral to a physiotherapist with instructions is given. An intra-articulair corticosteroid infiltration is discussed and directly administered if desired. Information about the trial is provided. Evaluation takes place after three months at the outpatient clinic and eligibility for inclusion in the study will be reassessed.

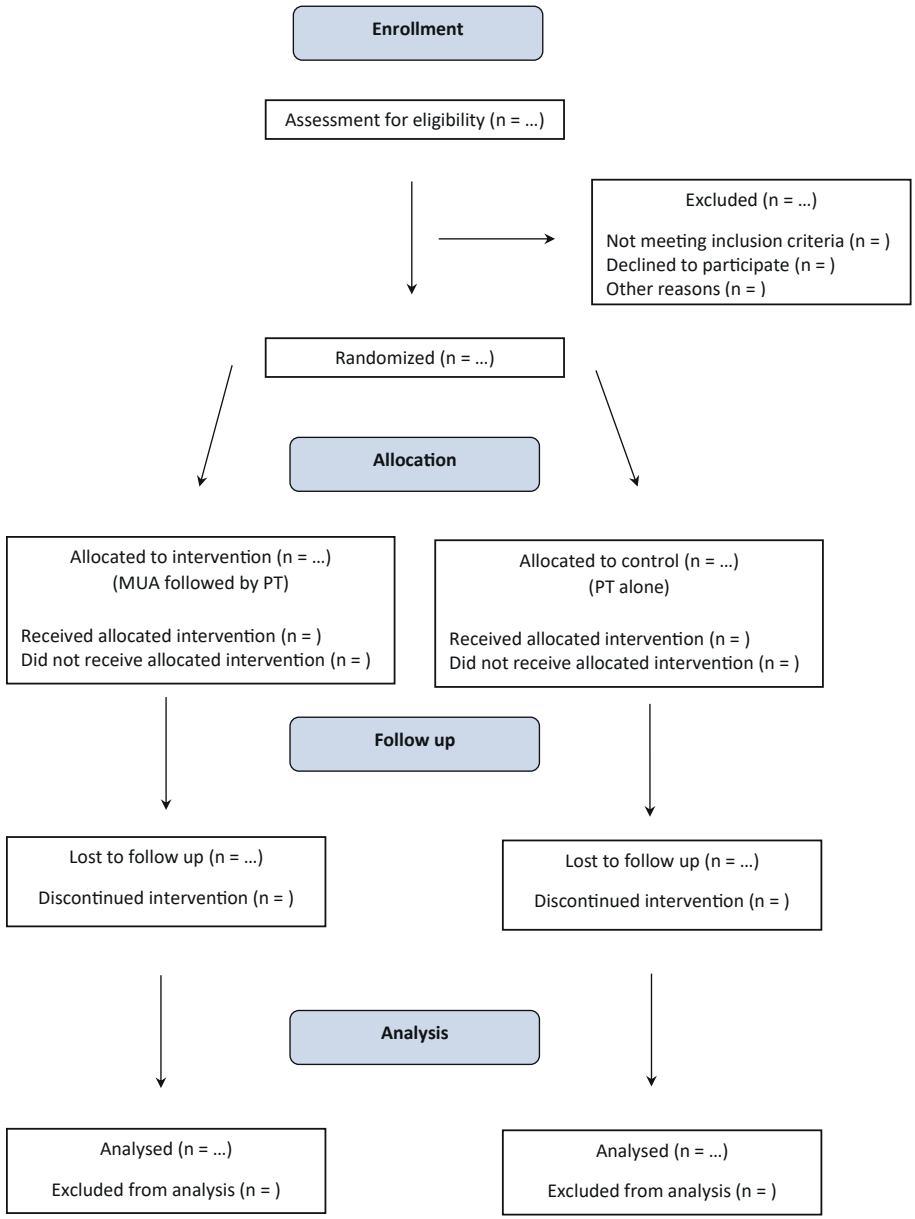


**Figure 1** Participant flow chart

## STUDY POPULATION

This study focusses on patients with a clinical diagnosis of a stage two FS. This is defined as symptoms of pain and stiffness, predominantly in one shoulder, persisting ≥ 3 months, without preliminary trauma which led to an anatomic abnormality. Characteristically, the pain is most severe at the end of the range of motion. Pain must be diminished compared to the maximum amount of pain in stage one of the condition.

In order to be eligible to participate in this trial, patients must meet all of the following criteria:

- Age > 18 years and ≤ 70 years
- Restriction of passive motion in the glenohumeral joint of ≥30° in external rotation and at least a second plane of movement with ≥30°restriction (compared to the contra-lateral side)
- Unsuccessful conservative therapy within the previous 3 months. This is considered as insufficient improvement after an intra-articular corticosteroid infiltration and physiotherapy treatment during at least six weeks.

Patients with diabetes are eligible for participation in this trial.

If any of the following criteria will apply, patients will be excluded from participation:
- Numeric Pain Rating Scale at rest ≥ 7
- Onset of symptoms ≥ 1 year ago
- Osteoarthritis of the glenohumeral joint, Kellgren-Lawrence osteoarthritis grading scale ≥ 2
- Previous surgery to the shoulder
- Systemic inflammatory joint disease
- Evidence of a complete rotator cuff tear on physical examination, ultrasound images or MRI
- Neurological disorders of the upper limb
- Therapeutic anticoagulation which can not be interrupted without bridging therapy
- Other known shoulder pathology such as infection or tumor
- Contra-indication to corticosteroid injection, allergy to contrast or local anaesthetic
- Inability to give informed consent and fill out questionnaires

## INTERVENTION

Patients assigned to the MUA group will be scheduled for the intervention within approximately 2-6 weeks (generally within 2 weeks). MUA is performed by one orthopedic surgeon (RB) at the recovery room under single shot interscalene brachial plexus block. The interscalene block is administered by the anesthesiologist using

ultrasound guidance. Levobupivacaine 0.375% is used, and a 'soak time' of approximately 45 minutes is pursued. If necessary or desired by the patient, general anesthesia can be added. The scapula is indirectly stabilized by the supine position, a short lever arm and 90 degrees of elbow flexion is used to prevent fractures and brachial plexus traction injuries. The glenohumeral joint is forced through a full range of motion in a strict pattern: anteflexion -> abduction, external rotation in 90 degrees' abduction-> internal rotation in 90 degrees' abduction -> horizontal adduction with dorsal compression and external rotation in neutral. A recognizable tearing sound is typically present when dealing with a FS. This sequence can be repeated until full range of motion is acquired. Postoperative physiotherapy is started directly on the same day (within four hours after MUA) to maintain the acquired full range of motion. People stay at the orthopedic ward for one night. The first week after MUA, patients have to visit a physiotherapist on a daily basis. The physiotherapy treatment is individualized in the need of the particular patient and its possibilities in ROM and dysfunction after a long period of stiffness. Therapy will exist of mobilizations in all end ranges known in arthrokinematics of the shoulder which are the same used by the orthopedic surgeon during MUA. Mobilizations are applied in (Maitland) grade 3, 4 or even 5 if necessary. This means that end feel is reached even if painful. The target is to reach the same end range as reached by the orthopedic surgeon after MUA, or the best possible after anesthetics are worked out. It is continuously tried to be within the pain area of NRS 0 to 5 or even up to NRS 7 for a short period of time, but only then when the pain vanishes within one or two hours after therapy. The goal is to give the maximum of stimulus which the patient can handle. Therefore, the frequency of therapy is high, but the period of inflammation after manipulation is respected. Patients are given a home exercise program to maintain ROM which they have to imbed in their daily activities. The exercises will mainly concern stretching in different angles with a total end range time of at least two minutes. After two weeks, if ROM is maintained, a general exercise program is applied to regain function of cuff and scapular muscles (using elastic exercise bands or halters) with the goal to return to normal shoulder girdle function.

Patients allocated to the PT group are given advice and education about the natural course of the disease. A corticosteroid injection in the glenohumeral joint of kenacort 40mg (1ml) and chirocaine (4ml) is given within the first three months of the condition, thus this will be done before inclusion in the study is possible. When the pain is not sufficiently diminished, this can be repeated. An advice for physiotherapy is given with a written protocol to hand out to their physical therapist based on the recent guideline of the Dutch Shoulder Network for the treatment of frozen shoulders (Figure 2). This guideline uses a categorization in "tissue reactivity" with parameters of pain and ROM that guides the treatment intensity and strategy (Figure 3).[28,29] A variety of treatments is used including, passive stretching, mobilization techniques, active scapulothoracic

exercises and cuff exercises. The Duration of physiotherapy treatment depends on the individual progression.

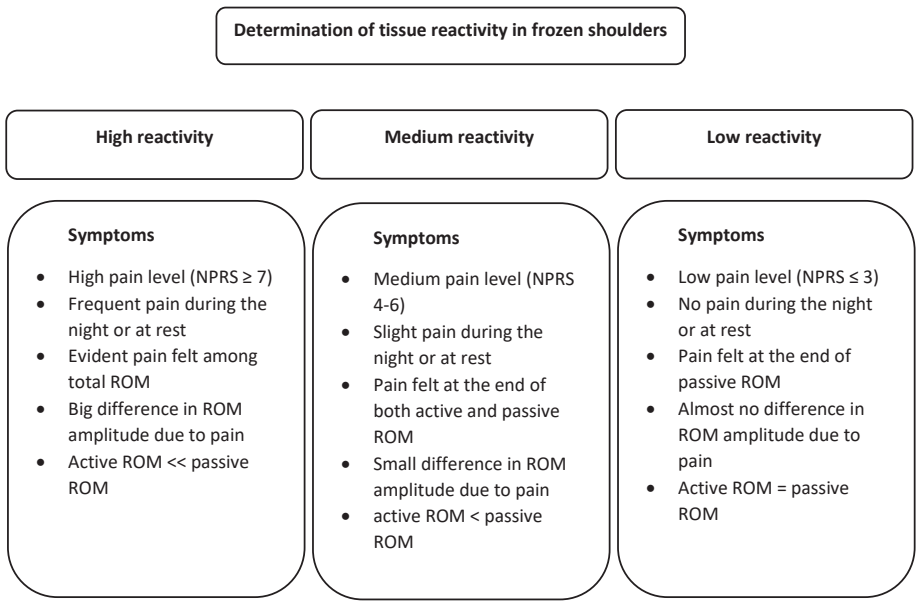


**Figure 2** Determination of tissue reactivity in Frozen Shoulders

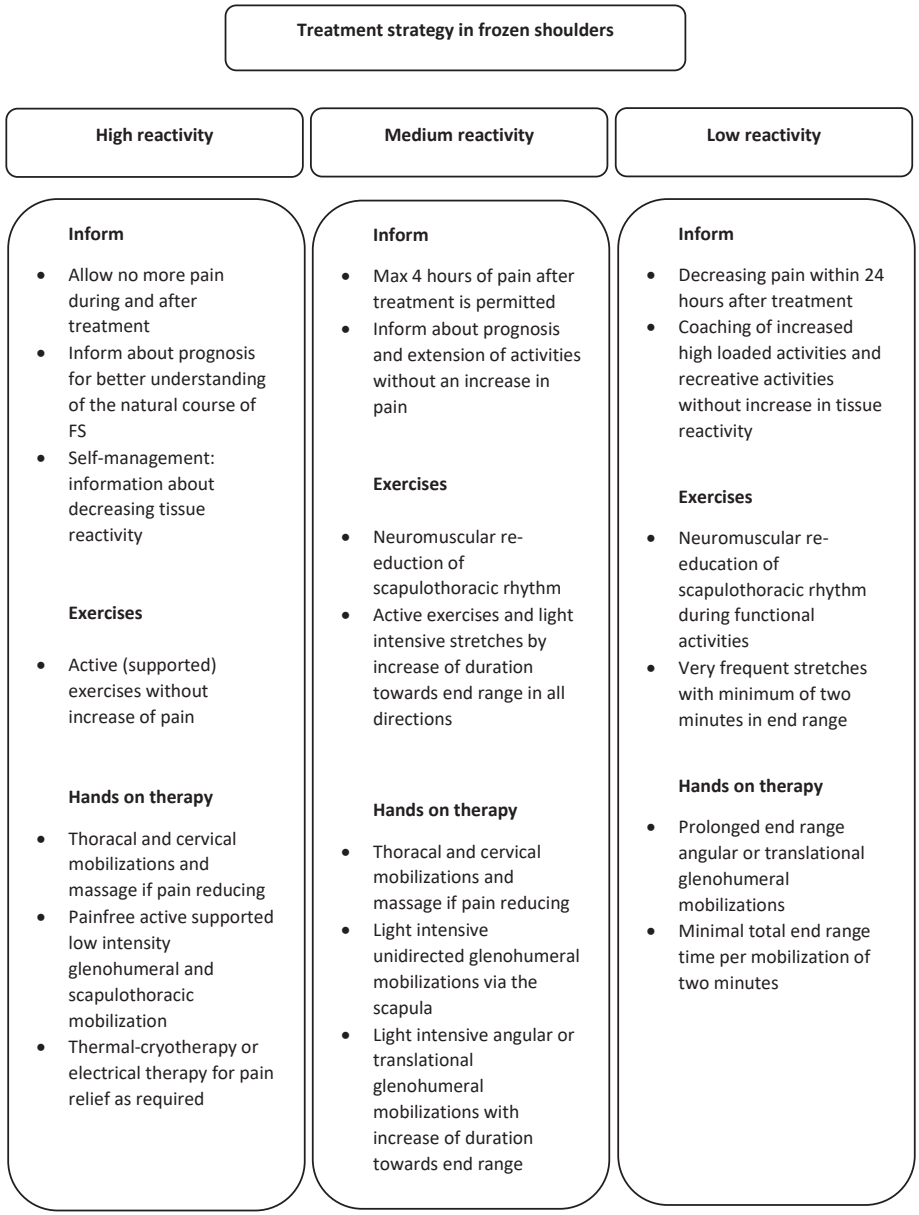


**Figure 3** Treatment strategy guideline based on tissue reactivity

## OUTCOME MEASURES

The primary objective of this study is to evaluate the difference in functional outcome after treatment of a FS with or without MUA, measured by the SPADI at one month compared to baseline. The SPADI is a self-reported questionnaire, with 13 questions responded on a ten-point scale divided in two domains: pain (5 items) and disability (8 items). A total SPADI score is calculated by summing up all 13 items and dividing by 130 (the maximum score) times 100. This leads to a score between 0 (best) and 100 (worst).[30] The SPADI has been translated and validated in Dutch.[31,32]

Secondary outcome measures consist of;

- Oxford Shoulder Score (OSS), which reflects both function and pain of the shoulder. The OSS is a patient reported questionnaire, which consist of 12 questions related to pain and function of the arm in daily life. Items are scored on a zero to four point scale. This leads to an OSS score between 0 (worst) and 48 (best).[33]
- Shoulder pain at rest, and during activity; Pain level will be determined using the Numeric Pain Rating Scale (NPRS). The NPRS is a validated eleven-point score to assess pain, which represents a valid measure of pain with a good construct validity. The NPRS ranges from zero to ten, in which zero expresses no pain and ten expresses the worst pain possible.
- Health related quality of life, determined using the three level EuroQol five-dimensional questionnaire (EQ-5D 3-L). The EQ-5D is a five question standardised questionnaire scoring on five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. It also includes a VAS self-rating health scale on which patients rate their health state (0 is worst imaginable health and 100 is best imaginable health)[34]
- Passive Range of Motion (ROM) is measured by a goniometer. Forward flexion and abduction in the standing position, external rotation measured with the arm held at the side and the elbow in 90° flexion. Internal rotation is estimated to which height the patient can reach on his back, appointed to the highest vertebral level of the wrist.
- The ability to work is evaluated by two questionnaires. The WORQ-UP is a patient reported questionnaire with 17 items of common physical tasks at work, scored on a five point scale.[35] Single item work ability Index is a single question whereby patients rate their ability to perform physical tasks at work on a ten point scale. Zero indicates no ability to perform work with any physical task at all. Ten indicates the best period in life to perform physical tasks at work.[36–38] Absenteeism at work is evaluated with a single question where patients register the amount of days absent at work past month due to complaints of the shoulder.
- Duration of symptoms is determined. Patients are asked to estimate the duration of symptoms in weeks from MUA or allocation to the PT group until almost full recovery.
- Two anchor questions will be asked regarding the change that is experienced since the start of treatment considering pain and daily functioning. This is reported on a seven-

point scale. These questions are based on an advice to use them from the division shoulder and elbow from the Dutch Orthopedic Society.
- Quantity of physiotherapy treatment sessions
- Usage of analgesics (acetaminophen, NSAID's or opioids)
- Number of repeated corticosteroid infiltrations
- Number of complications (infection, fracture, dislocation, neurovascular compromise, subsequent or intervention) will be registered and evaluated.

Passive range of motion is the only blinded outcome measure. All other outcomes are assessed unblinded or self reported.

## STUDY PROCEDURES

At one month, three months and one year, relevant outcome data are collected through clinical evaluation performed by the trained nurse practitioner, an orthopedic surgeon, or resident in orthopedic surgery. The range of motion is measured by a trained nurse practitioner who is blinded for the intervention. In the MUA group, the first follow up time is one month after the intervention. In the PT group, the first follow up time is one month after allocation. The schedule of enrolment, interventions, and assessments is shown in Table 1. The duration of the physiotherapy program in both groups is variable and depends on the individual result and desire of the patients. It is up to the patient to discuss this with their individual physiotherapist.

## SAMPLE SIZE CALCULATION

The SPADI is the primary outcome parameter. The sample size calculation is based on the ability to detect a difference between treatment groups of ≥13 points in the total SPADI scores. This is based on the study of Schmitt which describes a minimal clinical important difference (MCID) of 13.[39] The study of Carette shows a standard deviation of 17 on the SPADI.[40] Based on these parameters, we calculated a sample size of 41 subjects per group with a power of 90%, alpha 0.05 and a 10% drop out rate.

## STATISTICAL ANALYSIS

All data will be analyzed in an encoded fashion. We will use CASTOR (https://www.castoredc.com/), an online data-management program, designed for medical research purposes. The patient's demographic characteristics, EQ-5D score, range of motion at baseline, duration of symptoms before treatment starts and diabetes mellitus will be summarized and compared between groups. Also the distribution of all patients outcome variables will be summarized by treatment group and by time. The summaries will consist of the following descriptive statistics: number of patients involved, mean and standard deviation (or median and inter quartile range when appropriate) for continuous variables and relative frequencies (percentages) for categorical variables. We will report

the number of participants (denominator) included in each analysis and the intention to treat principle will be used with respect to group assignment. So, the final results of the patients will be analyzed in the group to which they were allocated at the start of the study."

**Table 1** Schedule of enrollment, intervention and assessments

| **Timepoint** | **-$t_1$** | **0** | **MUA** | **1 mo** | **3 mo** | **1 yr** |
|---|---|---|---|---|---|---|
| Eligibility screen | X | | | | | |
| Informed consent | X | | | | | |
| Allocation | | X | | | | |
| **Interventions** | | | | | | |
| MUA group | | | X | | | |
| PT group | | | | | | |
| Physiotherapy in MUA group | | | | | ? | |
| Physiotherapy in PT group | | | | | ? | |
| **Baseline parameters** | | | | | | |
| Handedness | | X | | | | |
| Profession | | X | | | | |
| Hours working per week | | X | | | | |
| Hobbies/sports | | X | | | | |
| Duration of symptoms | | X | | X | X | X |
| Health insurance covering physiotherapy | | X | | | | |
| **Outcome parameters** | | | | | | |
| SPADI | | X | | X | X | X |
| OSS | | X | | X | X | X |
| NPRS | | X | | X | X | X |
| EQ-5D | | X | | X | X | X |
| WORQ-UP | | X | | X | X | X |
| Single item work ability index | | X | | X | X | X |
| Absenteeism at work | | X | | X | X | X |
| Anchor question pain | | | | X | X | X |
| Anchor question function | | | | X | X | X |
| Amount of physio sessions | | X | | X | X | X |
| Analgesics usage | | X | | X | X | X |
| # corticosteroid injections | | X | | X | X | X |
| **Complications** | | | | X | X | X |

The SPADI-measurements will be analyzed using linear mixed modelling. The restricted maximum likelihood technique will be used for estimating the model parameters. The independent variables are time (3 levels: 1, 3 and 12 months) and treatment (2 levels), as well as their interaction. The following baseline covariates will also enter the model: SPADI at baseline, diabetes and duration of symptoms before intervention.

Primary efficacy measure is the treatment effect (MUA vs. PT) on total SPADI score after 1 month. This effect is estimated as contrast on the coefficients of the linear mixed model including the treatment-by-time interaction as mentioned above. Missing values in patients with incomplete observations will be appropriately dealt with by using the restricted maximum likelihood technique. Secondary efficacy measures are the treatment effects after 3 and 12 months and an average treatment effect over time obtained by deleting the treatment-by-time interaction. In addition, this interaction will be tested as part of the secondary efficacy analysis. Other secondary continuous outcome variables, such as OSS, NPRS, EQ-5D, WORQ-UP and ROM, will be analyzed similarly to SPADI, with the baseline measurement of the outcome variable at hand as covariate. When appropriate, the outcome variable will be transformed so as to obtain normally distributed residuals. Complications are counted by type and in total and will be analyzed using Poisson regression analysis with a correction for overdispersion when appropriate. Treatment effects on complication rates will be expressed as MUA to PT rate ratios. Safety will be assessed by identifying and summarising adverse events collected throughout the study. All estimated treatment effects will be accompanied by 95 % confidence intervals and p-values. Analysis will be performed by use of SPSS statistical package (IBM, version 18.0; SPSS, Chicago, Illinois)

## ETHICAL CONSIDERATIONS

There is insufficient evidence in the current literature for either one of the treatment allocations in this study. Both treatment strategies (MUA and PT) are regularly applied for a stage two FS in our hospital for many years. The intervention MUA will be performed by one orthopedic surgeon (RB) who has an extensive experience with this procedure. The treatment protocol of both treatment groups are kept close to the current routine care for patients with a similar condition not enrolled in the study. Patients will be exposed to radiation from conventional radiographs before inclusion of the study. This is part of routine clinical care and represents no increased risk. Patients may experience the questionnaires as inconvenient, but we consider this a minor inconvenience as they will take approximately 10 minutes to complete. The motivation for the study is a potential benefit to all patients with a stage two FS, as we increase our knowledge on optimal treatment strategy for this condition.

### MONITORING AND QUALITY ASSURANCE

The study was registered by the CCMO (National Central Committee of human bound research) under the number NL.56143.101.16 and registered in the Dutch Trial Register under the number NTR6182. The study protocol has been approved by the medical ethical committee TWOR (toetsingscommissie wetenschappelijk onderzoek rotterdam e.o.) Maasstad hospital Rotterdam and local feasibility was tested by the AMOA (adviescommissie mensgebonden onderzoek amphia) committee of the Amphia hospital Breda. Independent trial oversight was not deemed necessary by the medical ethical committee, because both treatments are already used for a long period in our hospital. For this reason, the patients are not expected to be at risk by participating in the current study.

All informed consent forms will be filed in a locked cabinet in the research office. Results of physical examination and questionnaires will be collected digitally and stored on a password-protected, secured server to which only study staff will have access.

All investigators will be responsible for reporting adverse events to the coordinating investigator. The coordinating investigator will report any adverse events to the ethical committee in accordance with the ethical committee adverse event reporting procedures. The coordinating investigator and the principal investigator are responsible for adherence to all ethical committee rules and guidelines and for the accuracy and completeness of all forms, entries and informed consent.

## DISCUSSION



There is no consensus in the literature which patients with a FS will benefit most from MUA.[11,15,17] MUA is considered as an option when conservative treatment fails. However, the optimal timing of MUA is unknown.[12,41] Furthermore, timing between the onset of symptoms and MUA can be a crucial parameter when the effectiveness of MUA is evaluated. In a condition that is mainly self-limiting, shortening of the duration of symptoms is probably more interesting than the end result at long term. Theoretically, the biggest advantage of manipulation is obtained when manipulation is done early. It could be suggested that early manipulation could lead to over-treatment in patients with a mild and natural course of the disease. Even more, early manipulation in stage one (the painful inflammatory stage) is sometimes considered to be counterproductive and can lead to recurrence of symptoms.[12] On the other hand, a high threshold for MUA, or late intervention, can lead to an unnecessarily long duration of complaints. In a retrospective study, Vastamäki et al considered between 6 and 9 months after the onset of symptoms as the most optimal period for manipulation.[12] However, only a general comparison

between group A (between 6 and 9 months) and group B (the others, including before six months and after 9 months) was presented. In our opinion, this is not convincing evidence to draw firm conclusions about the optimal timing. Although clear cut-off values between different stages of a FS are lacking, we decided to define in- and exclusion criteria as described above to select patients with a FS in stage two. The exclusion criteria NRS ≥ 7 is debatable because the lack of cut-off values in the literature. We added the important parameter that pain must be diminished compared to the maximum pain in stage one. Hereby, we try to prevent over treatment and recurrence after too early manipulation. Furthermore, with this study protocol, unnecessarily long duration of symptoms are potentially avoided. With the results of this study, we aim to increase our knowledge about the efficacy of MUA compared to physiotherapy treatment. We aim to solve a part of the uncertainty of the indication of MUA, and the safety of MUA is critically assessed.

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# PART FOUR

## DISCUSSION AND SUMMARY


LONDON 1738
LONDON 1738
LONDON 1753
MUSÆUM KIRCHERIANUM BONANNI
JOHNSTON ON GOVERNMENT
BACONI OPUS MAJUS
KIRCHERI OEDIPUS ÆGYPTIACUS
I
ROMÆ 1652
KIRCHERI OEDIPUS ÆGYPTIACUS
II
KIRCHERI OEDIPUS ÆGYPTIACUS
III
IV.

# CHAPTER NINE

## General discussion & Future perspectives

# GENERAL DISCUSSION & FUTURE PERSPECTIVES

This thesis is divided in three parts. A general introduction and the pathophysiology are discussed in **Part I**. Conservative management of FS with corticosteroid injections and physiotherapy is the focus of **Part II** and the role of manipulation under anesthesia (MUA) in the treatment of FS is outlined in **Part III.** In this chapter, the main findings of this thesis will be discussed and critically evaluated in relation to relevant literature. Implications for clinical practice and recommendations for future research are given.

## PART I INTRODUCTION AND PATHOPHYSIOLOGY

A frozen shoulder is a peculiar musculoskeletal condition. Codman described frozen shoulders back in 1934 as "*difficult to define, difficult to treat and difficult to explain*". There certainly is a lot more knowledge about frozen shoulders nowadays, although we have not solved the complete puzzle yet. A frozen shoulder is a special condition because it differs a lot from most other 'classical' musculoskeletal pathology. It is not like an acute injury with mechanical breakdown of anatomical structures that can be repaired. It is not a degenerative condition, and it is certainly not an overuse injury or repetitive strain injury. If anything, it can even be a shoulder specific expression of an over-active immune system related to metabolic dysfunction. That is complex and intriguing pathology for orthopedic surgeons. "*The more you learn, the more you realize how little you know".*

A frozen shoulder is characterized by pain and stiffness caused by a thickened, contracted, non-compliant capsule of the glenohumeral joint, resulting in marked disabilities in daily life. There is no consensus on a uniform definition of a FS, and studies use different cut off values for ROM for the diagnosis of a FS. The natural history of frozen shoulders is usually divided in three stages; freezing, frozen and thawing.[1] The length of these stages varies between patients, with spontaneous resolution of symptoms for the majority of patients within one to three years.[2,3] This is a rather long period with pain and disability, and we now know that residual symptoms, although usually mild to moderate, are common in up to 25-50% of patients.[4–6] And more, a small percentage of patients, probably around 5-10%, end up with an orthopedic intervention because spontaneous recovery does not take place at all.[7,8] This variable natural course makes it quite difficult to counsel patients about their expected natural course. It seems logical to assume that this variable natural course of FS is related to the pathophysiology of FS.

A thorough review of the pathophysiology of FS is set out in **Chapter 2.** There are several clues in the literature to assume that the process starts anteriorly in the joint, with involvement of the rotator interval and the CHL, before the entire joint is involved. That fits with the most characteristic finding of loss of passive external rotation. MRI scans of FS show contrast enhancement in the rotator interval, and around the CHL.[9] Corticosteroid injections were found to be effective when administered around the CHL,[10] neo-vascularization appears to be localized in the rotator interval,[11] FDG uptake was predominantly anteriorly in PET-CT scans of FS,[12] and upregulation of genes involved in the pathophysiology were found mainly in the rotator interval.[13]

The end result of the cascade resulting in tissue fibrosis is well described, namely a high number of fibroblast and differentiated myofibroblasts, within an extracellular matrix of abundant, densely packed and disorganized type III collagen.[14,15] Fibroblasts have a central role in ECM production and degradation, but this turnover is knocked out of balance in FS.[16] The homeostasis of ECM is regulated by fibroblasts which have mechanosensitive characteristics and is influenced by mechanical stress. Fibroblast can also act like sentinel cells involved in immune responses, and thereby modulate the recruitment of immune cells and regulate their behavior.[17,18] The process of tissue fibrosis is preceded by an inflammatory response with enhanced expression of pro-inflammatory cytokines, and a cell infiltrate with mast cells, macrophages, B and T cells.[19,20] The pathologic activation of fibroblasts and their differentiation into myofibroblasts is stimulated by cytokines of which TGF-β has an important role.

Our immune system certainly has a role in the early stage of the pathophysiology. Alarmins, or Damage Associated Molecule Pattern (DAMP) molecules, such as HMGB1, are the early activators of our immune system and are found to be elevated in capsular biopsies of FS.[21] Many different cytokines, growth factors, immune cells and markers of inflammation have all been shown to be related to frozen shoulders which points out the complexity of the pathophysiology. It's not just one pathway, but a multitude of factors are involved. It is still unknown what triggers the whole cascade. Microtrauma and oxidative stress with the formation of Reactive Oxygen Species are suggested as triggers,[22,23] but evidence to support this is limited. Diabetes Mellitus, thyroid disorders and cardiovascular disorders are identified as important risk factors for the development of FS.[24,25] The incidence of FS in diabetes is with 10-30% strikingly high.[26] The common link in these conditions predisposing for FS is suggested to be a chronic state of low-grade inflammation.[27] The same markers of chronic inflammation (ICAM-1) in cardiovascular disease are also shown to be elevated in joint capsule of FS patients.[28] Perhaps the variability between patients in the natural course of FS could be explained by a different inflammatory response of our immune system. To put it differently, metabolic dysfunction with chronic low-grade inflammation might lower the threshold for the

trigger of the pathophysiologic cascade in FS and may exaggerate the pathways leading to tissue fibrosis. We do not have solid prognostic markers for the natural course of FS, but immune composition in biopsies, markers of chronic inflammation in serum (ICAM-1), or biomarkers of persistent pathological fibroblast activation (CD 248, podoplanin) in synovial fluid might be relevant.[17,29]

Reasoning even further on what is known about the pathophysiologic process, it seems likely that preventative lifestyle strategies to reduce the risk of diabetes and cardiovascular disorders will also reduce the incidence and burden of FS. Frozen shoulders could even be an example why it is our task as orthopedic surgeons to emphasize healthy lifestyle strategies. However, there are certainly patients who appear to be healthy, active and slim without any comorbidities like diabetes or thyroid disorders, but still suffer from a FS. These patients might have a genetic predisposition to FS. Studies investigating the rates of frozen shoulder among relatives, showed that 20-30% of patients with a FS have a first degree relative with a past history of FS.[30,31] Although this can be caused by a shared environmental exposure, the existence of a genetic predisposition is suggested in a systematic review on this topic.[32]

Besides metabolic risk factors as DM and thyroid disorders, psychological factors and certain personality traits have been linked to the pathophysiology of FS already long ago, although a causal relation between has never been demonstrated.[33] Depression and anxiety have been shown to increase levels of certain inflammatory cytokines, which might predispose to the development of FS.[34] And indeed, symptoms of depression and anxiety are very common in FS patients, and these symptoms are highly correlated to worse pain scores and worse quality of life scores.[35] The pain at night and the associated sleep disturbance that is typical for FS might be an important cause of symptoms of depression and anxiety. Therefore, we should think about offering patients psychosocial support in the management of FS.[36]

All the literature that we have on the pathophysiology, does not explain the reversibility of stiffness in FS. Joint contractures are common in for example elbows and knees as well. But these contractures are usually more permanent in contrast to the reversibility of the stiffness that occurs most commonly in FS. The process of tissue fibrosis seems to be quite similar, but apparently, remodelling of the ECM in the capsular tissue does take place in shoulders. Apoptosis of myofibroblast is probably what occurs as this is how they normally disappear from granulation tissue after wound healing.[37] But is the capsuloligamentous tissue in shoulders different to that of other joints? As mentioned before, fibroblasts are the central cells responsible for the synthesis and remodelling of ECM. And it also known that fibroblast are versatile cells able to specialise and differentiate differently according to the tissue or anatomic region wherein they are situated.[18] Could it be that fibroblasts

in shoulders react in some way differently compared to their equals in elbows or knees? Shoulders are unique, for the wide range of motion that the joint allows and how stability of the joint is achieved. Elbows, hips, ankles and knees to a lesser degree have a whole lot more static stability compared to shoulders, because of the osteoarticular morphology. The stability of shoulders relies much more on dynamic stability from the balancing forces of the rotator cuff and capsuloligamentous complex. Perhaps this is related to the pathophysiology of FS. Could this explain why it's harder for fibroblasts in shoulders to maintain the right balance between too loose or too tight?

Advanced medical therapies to interrupt with the involved signalling pathways is still in its infancy. Lee et al suggested HMGB1 as a therapeutic target, but to what extend this is a realistic and safe option in the near future is unclear.[38] Interruption of the TGF-β signalling pathway in rats showed promising results.[39] Perhaps the intra-articular infiltration of a TGF-β inhibitor could be an option to intervene early on in FS. Calcitonin treatment might be an alternative treatment agent, especially in in FS associated with thyroid disorders.[40,41]

## CLINICAL IMPLICATIONS

- *FS starts anteriorly in the joint, and involves the rotator interval and CHL, which explains the characteristic finding of loss of passive external rotation*
- *A chronic state of low grade inflammation as in metabolic dysfunction in diabetes or thyroid disorders, predisposes to the development in FS*
- *Symptoms of depression and anxiety are very common in FS patients, and have a negative impact on the experience of pain, and quality of life. This might be related to sleep disturbance. Psychosocial support should be considered in the treatment strategy of FS patients.*
- *Based on the pathophysiology of frozen shoulders, it is hypothesized that preventative lifestyle strategies that reduce the risk of diabetes and cardiovascular disorders will also reduce the burden of FS*
- *Future research should focus on prognostic factors predicting the natural course of FS. This will aid clinical decision making in the treatment of FS. Serum markers of chronic inflammation, immune composition in biopsies or biomarkers of fibroblast activation in synovial fluid are potential prognostic factors*

- *Future research should focus on more advance medical therapies to interrupt the involved inflammatory signalling pathways. Glenohumeral injections with TGF-β inhibitors to interrupt the TGF-β pathway might be a promising option*

- *Future research should focus on the reversibility of the process, because there is a lack in our understanding why stiffness in FS is generally reversible compared to other joint contractures*

# PART II
# CORTICOSTEROID INJECTIONS AND PHYSIOTHERAPY

The majority of patients with a frozen will be encouraged to persist with conservative treatment strategies for a substantial period of time in order to await spontaneous recovery. Conservative treatment of FS consists mainly of corticosteroid injections and physiotherapy. In the survey presented in **Chapter 3** it was shown that only 37% of the shoulder specialist have a written protocol available in their hospital. A wide variety of preferred conservative treatment modalities was shown, with the highest disagreement in stage two. Fifty percent of the surgeons recommended intra-articular steroids and just over 50% recommended physiotherapy in stage 2. This signifies the disagreement among the shoulder specialists, probably caused by a lack of strong evidence in favour or against physiotherapy.[42] But it also indicates that uniformity in the treatment of frozen shoulders is still far away.

Conservative treatment often starts with a corticosteroid injection. There is robust evidence that intra-articular corticosteroid injections are effective, even when compared to sham injections, mainly in the reduction of pain and to a lesser extend in improving range of motion, at least at short term (up to three months).[43–45] Corticosteroids have a general suppressive effect on the inflammatory response and it has been shown that capsular biopsies of FS patients treated with corticosteroids have less myofibroblasts compared to patients without corticosteroids.[37] Since the inflammatory response precedes the fibrotic cascade, corticosteroids have their greatest potential early on in the condition. Ahn et al showed better clinical outcomes when the duration of symptoms prior to the injections was short, although the authors do not provide cut off values for 'early' injections.[46] Based on the knowledge of the pathophysiology and the relevant available evidence, it is suggested that intra-articular corticosteroids should be given within three months from the onset of symptoms. Studies on the optimal dosage of corticosteroid injections have shown that 10mg triamcinolone acetonide (kenacort) was

inferior to 40mg.[47] But no differences in outcome were found in a small randomized trial comparing 20mg triamcinolone acetonide with 40mg, indicating the preferred use of the 20mg dosage.[48]

Furthermore, it can be questioned whether glenohumeral injections should be administered image guided or 'blind'. A 'blind' technique is reasonable since it is quicker with less costs compared to ultrasound guided injections. Patel et al showed a significantly higher accuracy for ultrasound guided intra-articular injections compared to a freehand or landmark based technique, 92.5% vs 72.5% respectively in cadaveric specimens.[49] In frozen shoulders, when the capsule is thickened and contracted it seems plausible that it is even more difficult to localize a needle tip freehand in the glenohumeral joint. Indeed, a slightly faster reduction in pain, and better improvement of range of motion with ultrasound guided intra-articular injections compared to a 'blind' injection technique was shown in a small RCT by Lee et al in 2009.[50] On the contrary, two other randomized trials did not find any difference in outcome between subacromial or intra-articular injections, implying less importance of an accurate injection technique.[51,52] A recent meta-analysis comparing subacromial injections with intra-articular injections showed a similar outcome concerning range of motion, but an improved outcome for pain relief in the intra-articular group.[53] However, the weighted mean difference in VAS for pain that was found in this meta-analysis does not reach minimal clinical important difference.[54] A subsequent RCT compared ultrasound guided injections directed into the subacromial bursa, intra-articular directed from posterior versus rotator interval injections around the coracohumeral ligament. This interesting study showed superior outcomes of pain, range of motion and function for the rotator interval injections.[10] This fits with what is suggested about the pathophysiologic process, that it starts anteriorly, at the rotator interval. Although firm conclusions can not be drawn, it is believed that intra-articular corticosteroid injections should be given early on, within three months from onset of symptoms. The technique of the injection, 'blind' versus ultrasound guided can be left up to the surgeons preference based on his or her experience. The rotator interval injections seems promising, but needs confirmation in complementary studies.

Physiotherapy has a somewhat controversial role in the treatment of FS. This was also highlighted in the survey in chapter 3. Reviews point to a lack of high grade evidence to support physiotherapy alone for the treatment of FS.[22,42,55] Physiotherapy is a tailored treatment of a combination of several different modalities like stretching exercises, mobilizations, massage, application of heat or ice but also patient education and supportive care. Standardization of such a complex intervention in clinical trials is problematic. FS patients regularly report worsening symptoms after attempted physiotherapy treatment. This is especially true for the initial stage of FS. Physiotherapists can and should not be criticized for this, because the diagnosis is often not clear yet at

the onset of the condition. And more, the increase in pain might represent the worsening natural history of the condition in the first stage. Another reason for controversy about physiotherapy in the treatment of FS (at least in the Netherlands) was the publication of Diercks et al in 2004.[56] A cohort of patients was treated with supervised neglect, and compared to a successive cohort treated with intensive physical rehabilitation. Functional outcome was superior in the supervised neglect group. However, supervised neglect actually was more than just neglect, because supportive therapy was given and exercises within pain limits were recommended. In the physical therapy group, intensive passive stretching and manual mobilizations were used, beyond the pain threshold. This illustrates a worse outcome when tissue irritability is ignored. This can be explained with knowledge of the pathophysiologic process because fibroblasts are mechanosensitive and their differentiation into myofibroblasts is stimulated by mechanical stress.[57] The concept of tissue irritability is pointed out in the clinical practice guideline of the American Physical Therapy Association[58] and also highlighted in the guideline for physiotherapists from SchouderNetwerk Nederland.[59] Tissue irritability changes from high irritability in the freezing stage to low irritability in the thawing stage. Stretching exercises and gentle glenohumeral mobilization techniques may be used, but it is emphasized that the intensity should match the level of tissue irritability. This implies careful evaluation of the level of pain directly after a physiotherapy session.

It is sometimes questioned whether there is any need in FS for physiotherapy with range of motion exercises at all. Lubis et all showed that in a randomized trial that stretching up to a tolerable level of pain resulted in better Constant scores compared to supervised neglect with just painless pendulum exercises.[16] The authors concluded, based on serum measurements of MMP and TIMP that a certain degree of stretching is a prerequisite for adequate remodelling of the ECM. The effectiveness of additional physiotherapy after an intra-articular corticosteroid injection was investigated in a randomized trial presented in **Chapter 4**.[60] A beneficial effect of the combination of an intra-articular corticosteroid injection with physiotherapy was hypothesized. It was suggested that the corticosteroid injection might attenuate tissue irritability hereby making physiotherapy more tolerable. The main limitation of this study is the small number of included patients, so it does not have enough power. Indeed, range of motion was restored to a higher degree in the physiotherapy group up to three months. No differences between both groups were found at 26 weeks. Two other randomized trials on intra-articular corticosteroid injections in combination with physiotherapy found superior results for corticosteroid injections in combination with physiotherapy compared to corticosteroid injections alone or physiotherapy in combination with placebo injections. Similar to our study, this applied mainly for the range of motion and up to the first three months.[61,62] So yes, physiotherapy preceded by an intra-articular corticosteroid injection does result in a faster recovery of range of motion, but this effect diminishes after three months. An

alternative to a supervised physiotherapy program is a home exercise program and it can even be questioned if formal physiotherapy has any additional value over a home exercise program. It has been shown that satisfactory results can be accomplished with a home exercise program.[63–65] However, Russel et al did find superior results of formal physiotherapy over a home exercise program. Interestingly, there were even better results if the physiotherapy sessions were done by multiple patients together in an exercise class.[66] Opposite to this is a randomized trial of a home exercise program versus formal physiotherapy after hydrodilatation for FS, without significant differences between both groups. [63] To conclude, physiotherapy guided by tissue irritability should be offered to frozen shoulder patient, preceded by an intra-articular corticosteroid injection. At least a home exercises program with gentle stretching exercises within pain limits should be provided if it is chosen not to opt for formal supervised physiotherapy. Besides this, it is postulated that supportive care including patient education with attention for the patients expectations, mobilization of the cervical and thoracic spine, but also facilitation of aerobic endurance training and relaxation techniques, are important parts of physiotherapy that should not be underestimated.[59,67]

## CLINICAL IMPLICATIONS

- *Conservative treatment with an intra-articular corticosteroid injection (20mg or 40mg kenacort) and physiotherapy guided by tissue irritability is sufficient for the majority of FS patients. Non-surgical treatment should be the initial treatment of choice*

- *Intra-articular corticosteroids are most effective early on in the condition because they can counteract the inflammatory response, but corticosteroids can not undo the capsular fibrosis which has already been formed*

- *The central role of the fibroblast with its mechanosensitive characteristics and mechanical stress as a stimulus for differentiation into myofibroblasts, explains why over-aggressive stretching exercises or mobilization techniques can have an adverse effect in FS*

- *The combination of an early (within three months) intra-articular corticosteroid injection, which can attenuate tissue irritability, followed by physiotherapy restores range of motion more quickly compared to corticosteroid injections alone*

- *Future research should clarify the role of a home based exercise program compared with formal physiotherapy*

# PART III
# THE ROLE OF MANIPULATION IN THE TREATMENT OF FROZEN SHOULDERS

## WHAT IS THE RIGHT INDICATION FOR MUA?

Natural history studies and cohort studies on conservative treatment point out that around 90% of patients can be treated successfully without a surgical intervention.[5,7,68] This can be interpreted that only a small subset of patients with a prolonged and refractory course of their FS may need an orthopedic intervention. Solid prognostic factors are lacking, but we do know that a worse natural course can be expected in diabetics and patients with prolonged symptoms and severe restriction of range of motion on presentation.[69] It would be very interesting, and clinically relevant, to investigate if this subset of patients can be identified early on in the condition. As outlined in chapter 2, immune composition in biopsies, markers of chronic inflammation in serum, or biomarkers of persistent pathological fibroblast activation in synovial fluid might be relevant. But up to now, the treatment strategy is to start with conservative treatment in every case of a FS, until a point is reached where it is decided that 'conservative management has failed'. It must be realised that the indication for a surgical intervention for FS is controversial and varies between countries, regions, hospitals and individual shoulder specialists. The imprecise description 'failure of conservative treatment' is indicated as a plausible reason for a surgical intervention in a lot articles. In **chapter 6** it was tried to give a more specific description of the indication for MUA with the following criteria: a patient unable to cope with the pain and stiffness; clinical signs of a FS in stage 2 with external rotation being less than 50% compared to the contralateral shoulder; lessening pain in relation to stage 1; failure to respond to an intra-articular injection; a minimal duration of symptoms of three months. The latter criteria regarding timing of an intervention, chosen at a minimum of three months is highly debatable. A duration of symptoms of at least three months was about the average of the included studies in our review. The shorter this interval from onset of symptoms to intervention is taken, the bigger the effect on shortening the duration of symptoms, at least theoretically. However, if a short interval until intervention is chosen, this will most likely lead to a considerable amount of needless surgical procedures, given the natural course of a FS with spontaneous resolution of symptoms in the majority of patients. And more, some authors state that if MUA is done too early, still in the inflammatory stage of the condition, that this could lead to recurrence of stiffness.[70] Pap et al report superior results of MUA after an average duration of symptoms of 8.4 months compared to 5.4 months.[71] This is in line with the publication on timing of MUA of Vastamaki et al, wherein they report the best results of MUA within 6-9 months after onset of symptoms.[70] In contrast to these studies, no correlation between duration of symptoms and Oxford Shoulder Score after MUA was found in a retrospective series by Thomas.[72] This was a

single surgeon retrospective review including patients with anteflexion up to 170 degrees and external rotation up to 70 degrees. Taking the above into account, we suggest to use a duration of symptoms of at least six months, with failure to respond to adequate conservative management including an intra-articular corticosteroid injection and physiotherapy, as a criterium prior to proceed with MUA.

## MANIPULATION UNDER ANESTHESIA VERSUS ARTHROSCOPIC CAPSULAR RELEASE

If conservative treatment is not sufficient, MUA was traditionally a well-established treatment option for refractory FS, but arthroscopic capsular release (ACR) has gained popularity in the last two decades with the rise of arthroscopic surgery. It was also shown in our survey in chapter 3 that more surgeons use ACR compared to MUA in their practice.[73] Unfortunately, we did not ask individual surgeons to explain their preference or if they had any criteria to differentiate for the use of MUA versus ACR. **Chapter 5** outlines the pros and cons of both procedures. With ACR the capsular release can be visualized, and the procedure is more controlled compared to MUA. Although it can be challenging to perform an capsular release in a tight contracted shoulder without damaging the articular chondral surface, it is often considered as a safer option compared to MUA. Until recently, there were no randomized trials comparing the outcomes of MUA with ACR, and reviews did not show superiority of one of these procedures over the other.[74] If the outcomes are comparable, main advantages of MUA are that it is more time and cost efficient compared to ACR. However, MUA has potential serious complications such as; shoulder dislocation, humeral shaft fracture, rotator cuff rupture, osteochondral lesions and even plexus brachialis injury. Although these complications are rare, reported in case reports, this is most likely an important reason why shoulder specialist nowadays prefer ACR over MUA. This is very understandable, since *primum non nocere* is our most important principle in medicine. A relative contra-indication for MUA is significant osteopenia.[15] A short lever arm (grip high on the humerus) with the scapula stabilized, and flexion/abduction preceding rotations should be used to avoid complications. The overall complication rate of MUA in our systematic review in chapter 6 was 0.4%. This is in line with estimated complication rate of 0.5% in the article of Grant et al.[74] However, this can be an underestimation, since most articles were not specifically designed to register complications. We did not find serious complications of MUA in our own retrospective cohort (**chapter 7**) or in the randomized trial (**chapter 8**) which is still in progress. 'Hidden lesions' revealed by arthroscopy after MUA were shown to be present in 12 out of 30 patients in the article of Loew et al.[75] The identified lesions were superior labrum antero-posterior (SLAP) lesions, partial subscapularis tears, anterior labral detachments and tears of the middle glenohumeral ligament. Indeed, only the glenohumeral capsular ligamentous complex is intended to be ruptured with MUA. But the clinical relevance of the associated 'hidden lesion' can be questioned. In other words, it is unknown whether

these 'hidden lesions' are associated with an inferior clinical outcome after MUA. The middle glenohumeral ligament should be divided with ACR, so this lesion after MUA should not be seen as associated pathology. SLAP lesions are common degenerative findings, even in over 50% in a middle aged population with asymptomatic shoulders.[76] The intra-articular part of the subscapularis tendon is intentionally divided with ACR by some authors without inducing instability or loss of internal rotation.[77–80] Rotator cuff tears, were not found to be present in two studies, one with ultrasound the other with MRI evaluation before and after MUA.[81,82] Furthermore, as with all surgical procedures, experience is likely an important factor influencing the complication rate of MUA. It is up to the individual surgeon to decide how much force can be used to manipulate the shoulder. And to develop a feeling when to stop instead of pushing through. There is however, no research data on surgical experience and safety of MUA.

Another question is whether MUA should be used specifically in diabetic patients with a FS. There is limited data available to answer this question. Our own retrospective cohort study in chapter 7 had five patients with diabetes. There is a potential pathophysiologic explanation why FS in diabetics is more difficult to treat (chapter 2) compared to non-diabetics. Hyperglycaemia results in crosslinks between collagen fibers and the formation Advanced Glycation End products (AGEs) with pro-fibrotic effects.[83,84] Already back in 1995 Ogilvie et al compared ACR with MUA in a subgroup of patients with diabetes in a cohort study.[78] Interestingly, less improvement of range of motion was found in diabetics after MUA, but similar outcomes were found regarding pain and function. Although the evidence is weak, the authors stated in their conclusion that they prefer ACR over MUA in diabetics. Wang et al and Vastamaki et al reported similar results of MUA in diabetic and non-diabetic patients.[68,85] However, Wang et al included only Asian people with non-insulin dependent diabetes, and Vastamaki et al included only 5 patients with diabetes in a cohort of 20 patients. The strategy of Massoud et al was to start with a gentle manipulation, and to proceed with an additional arthroscopic release if the manipulation appeared to be insufficient. Patients with insulin dependent diabetes required an arthroscopic release more often compared to non-insuline dependent diabetes.[86] Furthermore, in the publications of Jenkins and Woods, 30 - 39% of patients with type 1 diabetes needed a repeated MUA because of an insufficient result or recurrence of stiffness, compared to 15% in non-diabetics.[87,88] So, although clear evidence that ACR has superior results over MUA in diabetes is lacking, until evidence proves otherwise, it is suggested to be particularly cautious with MUA in diabetics.

## HOW EFFECTIVE IS MANIPULATION UNDER ANESTHESIA?

A systematic review to evaluate the results regarding pain and range of motion with MUA is given in **Chapter 6**. A pooled analysis of the range of motion measurements showed an increase in passive anteflexion of 55 degrees after MUA within six weeks. Abduction

increased with 72 degrees and external rotation with 30 degrees in the first six weeks after MUA. The effect was retained and improved a little further in the first year after MUA. VAS scores for pain decreased with 3.5 points in at six weeks, and 5 points at one year. The Constant Murley score improved with 43 point at six weeks and 52 points at one year. In **chapter 7,** the results of a retrospective cohort of FS patients treated with MUA followed by physiotherapy are shown. With the use of an interscalene plexus block, MUA was generally well tolerated without the need for sedation. Ninety percent of patients reported much or very much improvement with respect to function of the shoulder for daily life activities. And a satisfaction rate of 92% was reported. So yes, satisfactory results can be obtained with MUA. But satisfactory results are also reported for the majority of patients with conservative treatment. A key question is whether MUA shortens the duration of symptoms compared to conservative management. Even if the outcome between MUA and conservative treatment is similar at long term, it can be a valuable intervention if duration of symptoms is shortened and if the ability to work is recovered faster after MUA. There is one randomized trial comparing MUA with a home exercise program.[89] The authors of this trial concluded that MUA does not add any additional value over an instructed home exercise program. Range of motion was slightly better in the MUA group, with significant better values for anteflexion at three months. Pain was also slightly better in the MUA group at all timepoints, but the difference was not considered clinically relevant. It should be noted that in this study, MUA was not followed by intensive physiotherapy which might potentially worsen the results of MUA. Furthermore, a very high dropout rate was found, especially in the MUA group with 55 patients at the start and only 3 patients who showed up at one year. Surprisingly, in the control group, 42 out of 55 patients did fulfil their one year follow up appointment. Contrary to the authors conclusion, this could suggest a clinical difference between both groups. Insufficient evidence and a clinical relevant question whether MUA shortens the duration of symptoms, was the reason to initiate a randomized controlled trial of conservative treatment (physiotherapy, PT-group) versus manipulation (MUA-group) of which the study protocol is outlined in **chapter 8**. Inclusion of patients has been completed in October 2020. Some preliminary results can be presented but should be interpreted with caution. The study is designed to include 82 patients. For the preliminary results, follow up is available for 53 patients at three months and for 28 patients at one year. The differences that were found between both groups are most pronounced at three months. At 12 months, results seem to be quite similar in both groups. Range of motion measurements are significantly better in the MUA-group compared to the PT-group at one and three months. There is a trend, but no significant difference, towards favourable results in the MUA-group at three months regarding pain (NPRS), function (SPADI) and quality of life (EQ-5D). At forehand, we considered the ability to work as an important outcome parameter, because this could potentially point out a clinically relevant additional value if MUA does shorten the duration of symptoms. Work ability is

being monitored with the single item work ability index and the WORQ-UP questionnaire. Improvement of work ability over time was seen in both groups. Although slightly better work ability scores were found for the MUA-group at three months, no significant difference was found between both groups. For all outcome parameters, the results of MUA were at least similar, at short term often slightly better, and certainly not worse compared to conservative treatment. It is well possible, that with higher numbers in both groups some of the differences that were found will reach statistical significance. However, a firm conclusions that MUA does shorten the duration of symptoms compared to a physiotherapy program can not be drawn from these preliminary results.

A large multicenter randomized trial from the UK has just been published recently (October 2020).[90] In the UK-FROST trial, primary FS patients were recruited from 35 hospital sites and randomly allocated to MUA (n = 201), ACR (n = 203) and early structured physiotherapy including a corticosteroid injection (n = 93). Based on the primary endpoint (Oxford Shoulder Score at 12 months), none of the three interventions was clinically superior. OSS scores at 12 months were 40.3 for ACR, 38.3 for MUA and 37.2 for physiotherapy. Although patients in the ACR group had statistically significant higher OSS scores compared to MUA and physiotherapy, the authors concluded that the magnitude of difference was unlikely to be clinically important. ACR carried higher risks with more adverse events in the ACR group (4%) versus the MUA group (1%). Based on a health economic analysis, MUA was considered to be the most cost-effective intervention. Although this is a large randomized trial with overlap of our trial in progress as presented in chapter 8, it does not make our trial redundant. We chose the primary outcome parameter (SPADI) to be at one month instead of at 12 months. Many frozen shoulder studies show that the longer the follow up, the closer the results of different treatments will be. We will present range of motion measurements which are not performed in the UK-FROST trial. The UK-FROST had 90 surgeons to perform on average 4 interventions. In our trial, MUA is done solely by one experienced surgeon. The ability to work, an important outcome parameter in our trial, is not analyzed in the UK-FROST study.

To conclude, the majority of FS patients can be treated conservatively with a corticosteroid injection and physiotherapy. But this may not be sufficient for every patient. At this point, I think it's reasonable to state that MUA still has it's place in the treatment of frozen shoulders, since it's proven to be cost efficient with a predictable outcome. ACR seems to have similar or slightly better outcomes, but comes at the expense of higher costs. The decision whether to proceed with an intervention is a shared decision making process, taking the preferences of the patient into account together with the experience of the surgeon.

## CLINICAL IMPLICATIONS

- *Around 10% of patients with a frozen shoulder will have a prolonged, refractory course of a FS*

- *Every FS patient should receive an intra-articular corticosteroid injection prior to proceeding with a more invasive intervention as manipulation under anesthesia or arthroscopic capsular release*

- *There is no evidence that arthroscopic capsular release is superior to manipulation under anesthesia*

- *We suggest to use the following criteria before proceeding with MUA*

    - *a patient unable to cope with the pain and stiffness of a FS*
    - *clinical signs of a FS in stage 2 with external rotation being less than 50% compared to the contralateral shoulder*
    - *decrease of pain in relation to stage 1, and pain mainly at the end range of motion*
    - *failure to respond to an intra-articular injection*
    - *a minimal duration of six months of conservative treatment including an intra-articular corticosteroid injection and physiotherapy*

- *When performing MUA, a short lever arm (grip high on the humerus) with stabilization of the scapula should be used to prevent complications*

- *MUA should be avoided in patients with severe osteopenia*

- *One should be cautious to use MUA in diabetics with a FS. The recurrence rate is high, and it might be safer to opt for arthroscopic capsular release in this population*

- *Associated lesions are common with MUA, although it can be questioned whether these 'hidden lesions' are clinically relevant*

- *Frequent sessions of physiotherapy should be initiated immediately after MUA to prevent recurrent stiffness*

- *Early improvement in of range of motion, pain and function can be achieved with MUA within six weeks to three months*

## CONCLUSIONS AND FUTURE REMARKS

Is supervised neglect the best we can do for patients with a frozen shoulder? I do hope that after reading this thesis, this can be interpreted as a rhetorical question. First of all, we should educate patients about their condition. We should acknowledge that they suffer from a very painful condition, which can lead to sleep disturbance, symptoms of depression and anxiety. We should support them how to cope with the pain and disabilities. Preventative lifestyle strategies to reduce the risk of diabetes and cardiovascular disorders should be encouraged, as this will most likely also reduce the burden of FS.

An intra-articular corticosteroid injection should be given as early as possible, preferably within three months from onset of symptoms. Coaching from a shoulder physiotherapist, with exercises guided by tissue irritability, is appropriate treatment and should be offered after the administration of a corticosteroid injection. The option to proceed with a more invasive intervention as ACR or MUA should be offered and discussed. This is always a shared decision process between a patient and surgeon. MUA is well tolerated with an interscalene block and is a well established procedure with a potential for quick recovery of symptoms. It is suggested to use a minimal duration of six months as a threshold before an intervention is indicated. This should limit needless surgical procedures but also avoid unnecessary long duration of symptoms.

Future research in this field should be done with a control group to compare the intervention with the natural history of FS. This is of paramount importance to determine the added value of an intervention to the natural history of FS. Studies should be aimed at shortening the duration of symptoms, and the ability to work, instead of the end result at long term. It is suggested that future research should focus on prognostic factors, such as serum markers of chronic inflammation, immune composition in biopsies or biomarkers of fibroblast activation in synovial fluid. This will help us to predict the individual natural course of FS and to counsel patients better. This will aid clinical decision making, and to customize the treatment of FS. Future research should also focus on more advanced medical interventions to intervene in the inflammation-fibrosis cascade to interrupt the development of a FS early on. Intra-articular infiltration of a TGF-β inhibitor could perhaps be a promising suggestion.[91]

### PRACTICE CHANGING ADVICES

- *Symptoms of depression and anxiety are very common in FS patients, and have a negative impact on the experience of pain, and quality of life. This is likely related to sleep disturbance in FS. Psychosocial support should be considered in the treatment strategy of FS patients*

- *Based on the pathophysiology of frozen shoulders, it is hypothesized that preventative lifestyle strategies that reduce the risk of diabetes and cardiovascular disorders will probably also reduce the burden of FS*

- *Intra-articular corticosteroids (20mg or 40mg triamcinolone acetonide) should be given early, within three months from onset of symptoms, because they can counteract the inflammatory cascade and decrease the differentiation of fibroblasts into myofibroblasts, but can not undo the capsular fibrosis which has already been formed*

- *Non-surgical treatment should be the initial treatment of choice for FS. This should consist of the combination of an early intra-articular corticosteroid injection, followed by physiotherapy guided by tissue irritability, including gentle stretching and home exercises within pain limits*

- *Every FS patient should receive an intra-articular corticosteroid injection prior to proceeding with a more invasive intervention as manipulation under anesthesia or arthroscopic capsular release*

- *We suggest to use the following criteria before proceeding with MUA*

    - a patient unable to cope with the pain and stiffness of a FS
    - clinical signs of a FS in stage 2 with external rotation being less than 50% compared to the contralateral shoulder
    - decrease of pain in relation to stage 1, and pain mainly at the end range of motion
    - failure to respond to an intra-articular injection
    - a minimal duration of six months of conservative treatment including an intra-articular corticosteroid injection and physiotherapy

- *Early improvement in of range of motion, pain and function can be achieved with MUA within six weeks to three months*

- *To answer the question whether or not MUA truly does shorten the duration of symptoms compared to conservative treatment, the results of our randomized trial should be awaited*

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POINT
GERMANY

# CHAPTER TEN

## Summary (English and Dutch)

# PART I
# INTRODUCTION AND PATHOPHYSIOLOGY

## CHAPTER 1: INTRODUCTION AND AIM OF THIS THESIS

Frozen shoulder (FS) is a common cause of shoulder pain and restricted range of motion, with an estimated prevalence of 2-4% in the general population. It affects mainly middle aged people in their fifth or sixth decade of life, occurring slightly more frequent in women than in men. FS is typically a clinical diagnosis, made on the basis of history and physical examination. Loss of passive external rotation is the most characteristic finding at physical examination. A decrease of 30 degrees in two planes of motion or 50% loss of external rotation compared the contralateral side is often used for the diagnosis. Idiopathic FS is most common, when no underlying cause can be identified. In secondary frozen shoulders, there is a known condition correlated to stiffness, such as immobilization after sustaining a fracture or surgery to the shoulder, or radiation to the chest wall in breast cancer. Diabetes mellitus is the most important systemic metabolic condition predisposing for the development of FS. The life time risk to develop a FS is 10-30% for patients with diabetes and FS tends to be prolonged in patients with diabetes.

The natural history of FS is divided in three stages. Stage 1 is called the freezing stage with severe pain, and increasing stiffness. In stage 2, the frozen stage, pain is typically present at the end range of motion. Restriction of range of motion is evident with a firm endpoint on passive examination. Stage 3 is the thawing stage, which is characterized by gradual recovery of range of motion and decreasing pain. The length of each stage varies from patient to patient. FS is often considered a self-limiting condition, with spontaneous resolution of symptoms within one to three years. However, residual symptoms, although usually mild to moderate, do occur in up to 25-50% of patients.

The majority of FS patients, estimated around 90%, can be treated conservatively with intra-articular corticosteroid injections and physiotherapy. If conservative treatment is not sufficient there are mainly three possible interventions. Arthrographic distension injections, manipulation under anesthesia (MUA) and arthroscopic capsular release (ACR). The pathophysiology of FS is discussed in Part I of this thesis. Optimizing conservative treatment with corticosteroid injections and physiotherapy is discussed in Part II. The focus of part III of this thesis is on the role of MUA in the treatment of FS.

## CHAPTER 2: THE PUZZLING PATHOPHYSIOLOGY OF FROZEN SHOULDERS – A SCOPING REVIEW

The restriction in passive range of motion in FS is caused by a thickened contracted glenohumeral capsule. There are several clues to assume that the process of a FS starts anteriorly in the joint, at the rotator interval. Neo-vascularization appears to

be localized in the rotator interval, FDG uptake was predominantly anteriorly in of FS, and upregulation of genes involved in the pathophysiology were found mainly in the rotator interval. The coracohumeral ligament is involved, which spans the rotator interval from the dorsolateral base of the coracoid and inserts on to the upper border of the subscapularis and the leading edge of the supraspinatus. Histologic biopsies of capsular tissue show a high number of fibroblast, differentiated into myofibroblasts, within an extracellular matrix densely packed and disorganized type III collagen. The process of tissue fibrosis is preceded by an inflammatory response with elevated levels of alarmins, the early activators of our immune system, and enhanced expression of pro-inflammatory cytokines. Fibroblasts become activated and differentiation into myofibroblasts occurs under influence of mechanical stress and TGF-β. This leads to an imbalance in the turnover of extracellular matrix with deposition of abundant type III collagen.

There is an increasing amount of evidence to support a chronic state of low-grade inflammation as an important predisposing factor for the development of FS. Inflammatory lipoproteins such as LDL and non-HDL, known risk factors for atherosclerosis, have also been identified as independent risk factors for FS. ICAM-1, a well-established marker of chronic inflammation related to vascular endothelial cell activation in cardiovascular disease, has been shown to be elevated in the joint capsule and synovial fluid of FS patients. Diabetes, the most important risk factor for the development of FS, is also associated with a chronic state of low-grade inflammation. Hyperglycaemia results in the formation of AGEs, which have pro-fibrotic effects and are responsible for pathological collagen crosslinking between collagen proteins making the tissue even more stiff.

There are still gaps in our knowledge about the understanding of FS. The overall duration of symptoms is highly variable between patients, but up to now prognostic factors for the variable natural course of the condition are lacking. And more, we do not understand yet how the process of tissue fibrosis is reversed over time in the majority of FS patients, and how it is different from more permanent joint contractures as in elbows or knees.

# PART II
# CORTICOSTEROID INJECTIONS AND PHYSIOTHERAPY

## CHAPTER 3: HOW TO TREAT A FROZEN SHOULDER? A SURVEY AMONG SHOULDER SPECIALISTS IN THE NETHERLANDS AND BELGIUM

Dutch and Belgian orthopedic surgeons with a special interest in shoulder pathology were asked for their preferred treatment strategy in FS. One hundred out of 186 shoulder specialist completed our questionnaire. A wide variety of treatment strategies in the different stages of a frozen shoulder was reported. In stage 1, over 80% of respondents advocate for; advice and education, NSAIDs and intra-articular corticosteroids. There is marked disagreement about the recommended treatment modalities of a FS in stage 2. Fifty percent of the surgeons recommend intra-articular steroids and just over 50% recommend physiotherapy in stage 2. Less than half (43%) of all surgeons used MUA, and 76% used ACR as an intervention for FS in their practice. The yearly numbers for both interventions per surgeon are low. The results of this survey indicate that there is no more than fair agreement for the treatment of FS among shoulder surgeons.

## CHAPTER 4: CORTICOSTEROID INJECTION ALONE VS ADDITIONAL PHYSIOTHERAPY TREATMENT IN EARLY STAGE FROZEN SHOULDERS. D-FROST (DUTCH FROZEN SHOULDER TRIAL) - A RANDOMIZED CONTROLLED TRIAL

Intra-articular corticosteroid injections and physiotherapy are among the most widely used treatment modalities in FS in both primary and secondary healthcare settings. The role of physiotherapy in the treatment of FS is somewhat controversial. In this trial, patients with a painful (VAS ≥ 6) early stage idiopathic frozen shoulder were randomly allocated into two groups. Both groups received an ultrasound-guided intra-articular corticosteroid injection. One group underwent additional physiotherapy treatment (PT) and the other group did not (non-PT). Tissue irritability was taken into account to guide the intensity of physiotherapy. If there was an increase in pain lasting for more than four hours after the physiotherapy session, the next session had to be less intense.

Both groups improved significantly over time regarding pain, range of motion and function. SPADI scores were superior in the PT group at six weeks. Range of motion was significantly improved in the PT group compared to the non-PT group at six and 12 weeks. No significant differences were found between both groups at final follow-up (26 weeks). The main limitation of this study is the relatively small number of included patients that does not meet the calculated sample size. The results of this study are therefore interpreted with caution. We concluded that additional physiotherapy after

an intra-articular corticosteroid injection appears to improve shoulder function and shortens the duration of functional limitations during recovery for early-stage FS patients up to the first three months.

# PART III
# THE ROLE OF MANIPULATION IN THE TREATMENT OF FROZEN SHOULDER

## CHAPTER 5: ARTHROSCOPIC CAPSULAR RELEASE AND MANIPULATION UNDER ANESTHESIA FOR FROZEN SHOULDERS - A HOT TOPIC

MUA and ACR are the two most common interventions for FS if conservative treatment fails. In this chapter, we provide a literature overview regarding the pros and cons of both procedures. With MUA the glenohumeral joint is forced into different directions under anesthesia to tear the contracted glenohumeral capsule. In ACR the release can be visualized arthroscopically and is considered to be more controlled. MUA is relatively easy to perform, more time efficient and most likely also more cost-efficient. Although rare, serious complications of MUA such as humeral shaft fractures and brachial plexus traction injuries have been reported. Other associated lesions have been found with arthroscopy after MUA such as; labral lesions, partial subscapularis tears and osteochondral fractures of the anterior glenoid rim. The clinical consequences of these lesions however, is unknown. ACR is technically more demanding, with the risk of damaging the cartilage, chondrolysis due to heat generation or injury the axillary nerve with the inferior release.

With early postoperative physiotherapy, range of motion and function seems to improve fairly quick after both procedures. Both manipulation under anesthesia and arthroscopic capsular release can be considered appropriate treatment options for frozen shoulders. Good results are also reported with a combination of both procedures, a safe but incomplete capsular release followed by gentle manipulation. We concluded that high quality evidence comparing both techniques is lacking, and superiority of one technique over the other has not been demonstrated.



## CHAPTER 6: MANIPULATION UNDER ANESTHESIA FOR FROZEN SHOULDERS; OUTDATED TECHNIQUE OR WELL-ESTABLISHED QUICK FIX?

We conducted a systematic review to evaluate whether MUA is an effective and safe intervention for frozen shoulders. Sixteen studies were found eligible for inclusion in this review, reporting the results of MUA in 858 patients. A clearly defined indication for manipulation in frozen shoulders could not be extracted from the included studies.

The required minimal duration of symptoms prior to proceeding with MUA varied from one to six months. Scapular stabilization and grip high on the proximal humerus (a short lever arm) were frequently cited measures to avoid complications. A pooled analysis showed an increase of 55 (95% CI 33-78) degrees anteflexion 72 (95% CI 49-96) degrees of abduction and 30 (95% CI 17-44) degrees of external rotation after MUA within six weeks. The effect was retained and improved a little further in the first year after MUA. VAS scores for pain decreased with a weighted mean difference of 3.5 points in at six weeks, and 5 points at one year. The Constant score improved with 43 (95% CI 32-55) points at six weeks and 52 (95% CI 33-71) points at one year. Around 85% of patients were satisfied with the result of MUA. An overall complication rate of 0.4% and a re-intervention rate of 14% was found. Serious complications such as humeral shaft fracture of brachial plexus injury were not reported in the included studies.

Based on this systematic review, we concluded that a considerable increase in ROM and function, a reduction in pain and around 85% of satisfaction are possible with MUA. However, all but one study in this review lacked a control group without intervention. We recommend being careful when considering manipulation under anesthesia for frozen shoulders because the relative mild natural course of the disease in the majority of patients and potential complications. To what extend MUA truly shortens the duration of symptoms of a FS could not be concluded based on the current evidence.

## CHAPTER 7: MANIPULATION UNDER ANESTHESIA FOR FROZEN SHOULDERS: A RETROSPECTIVE COHORT STUDY

The results of FS patients treated with MUA over a two year time frame were collected. Patients with diabetes and secondary frozen shoulders were also included. MUA was performed by an experienced orthopedic surgeon after an interscalene plexus block and the addition of short duration general anesthesia if deemed necessary or requested by the patient. A short lever arm, scapular stabilization and flexion of the elbow was used to prevent fractures and brachial plexus injuries. Immediate postoperative physiotherapy was started and continued intensively for a minimum of two weeks after MUA.

Forty nine out of 65 patients completed and returned the questionnaires after a mean follow up of 21 months. The mean time from onset of symptoms to MUA was 8 months (range 2-25). Ninety percent of patients reported much or very much improvement with respect to function of the shoulder for daily life activities. The median SPADI score at final follow up was 11.2 (IQR 0.8-25.2, with 0 as the best possible score and 100 as the worst score). The median OSS was 39.0 (IQR 30-43, with 48 as the best possible score and 0 is the worst score). Pain scores at rest and during activity were low. A satisfaction rate of 92% was reported. However, only 72% of patients reported that they reached their prior level of functioning. And more, the beneficial effect of MUA was not retained

in 16% of patients. No complications were seen during manipulation nor reported by patients afterwards. The results of MUA in this study are favorable, but a randomized trial is required to determine the additional value of MUA over conservative treatment. The protocol for this trial is described in the next chapter.

## CHAPTER 8: MANIPULATION UNDER ANESTHESIA VERSUS CONSERVATIVE TREATMENT IN STAGE TWO OF A FROZEN SHOULDER - A STUDY PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL

This study is initiated to evaluate whether MUA shortens the duration of symptoms compared to conservative treatment. This is a prospective, single center, randomized controlled trial, and the inclusion of patients has been completed. The first patient was included in 2017 and the results of this study are expected at the end of 2021. Patients with a clinical diagnosis of a stage two FS are allocated to either MUA followed by physiotherapy (MUA group) or to physiotherapy alone (PT group). Patients are eligible for inclusion if symptoms persist for at least three months and if improvement is insufficient after an intra-articular corticosteroid infiltration and physiotherapy treatment.

Physiotherapy in the MUA group is started directly on the same day as the intervention and is continued intensively in the first weeks after MUA. In the PT group, physiotherapy is based on the recent guideline of the Dutch Shoulder Network for the treatment of frozen shoulders. This guideline uses tissue reactivity to guide treatment intensity.

The primary outcome measure is the SPADI. Secondary outcome parameters are range of motion, pain (NPRS), functional score (OSS), quality of life (EQ-5D) and the ability to work (WORQ-UP and single item work ability index. The ability to work is of special interest to us. This is a relevant outcome, not only for the individual patient but also from a socioeconomic perspective.



The aim of this study is to increase our knowledge about the efficacy of MUA compared to conservative treatment including physiotherapy. We aim to give answer to the question whether MUA does indeed shorten the duration of symptoms. The safety of MUA is monitored in this study. The results of this study will improve the shared decision making process whether MUA is the right treatment strategy for individual FS patients.

# DEEL I
# INTRODUCTIE EN PATHOFYSIOLOGIE

## HOOFDSTUK 1: ALGEMENE INTRODUCTIE

Een frozen shoulder (FS) is een veel voorkomende oorzaak van pijn en bewegingsbeperking van de schouder. De prevalentie in de algemene bevolking is 2-4%, met name bij mensen van middelbare leeftijd en iets vaker bij vrouwen dan bij mannen. FS is typisch een diagnose die gesteld kan worden op basis van anamnese en lichamelijk onderzoek. Beperkte passieve exorotatie is de meest kenmerkende bevinding bij het lichamelijk onderzoek. Voor de diagnose wordt vaak een verlies van 30 graden in twee bewegingsrichtingen, of een verlies in exorotatie van 50% ten opzichte van contralateraal gehanteerd. De meest voorkomende vorm is een idiopathische FS, als er geen onderliggende oorzaak kan worden aangetoond. Van een secundaire FS is sprake als er wel een oorzaak van de stijfheid bekend is, zoals immobilisatie na een fractuur of een operatie, of bijvoorbeeld na bestraling van de oksel en borstwand bij borstkankerpatiënten. Een frozen shoulder komt veel frequenter voor bij patiënten met diabetes mellitus dan in de algehele bevolking. Voor diabetici is het risico om een FS te krijgen 10-30%. Bij diabetici is een FS vaak ernstiger en het beloop langduriger.

Het natuurlijk beloop van een FS wordt meestal ingedeeld in 3 fases. Fase 1 is de ‘freezing stage’ met veel pijn, en toename van stijfheid. In fase 2, de ‘frozen stage’, is er pijn aan het eind van de range of motion en is er een duidelijk eindpunt bij passief bewegingsonderzoek. Fase 3 is de ‘thawing stage’ waarin de beweging geleidelijk weer toeneemt en de pijn vermindert. De duur van de verschillende fases varieert per patiënt. FS wordt vaak een reversibele aandoening genoemd, die vanzelf over gaat bij het grootste deel van de patiënten in één tot drie jaar. Het is echter bekend dat restklachten na een FS, ook al zijn deze meestal mild, frequent voorkomen bij 25-50% van de patiënten.

De meerderheid van de patiënten met een FS, ongeveer 90%, kan conservatief worden behandeld met intra-articulaire corticosteroïd injecties en fysiotherapie. Als niet-operatieve behandeling onvoldoende helpt, zijn er grofweg drie opties: distensie injecties (hydrodilatatie), manipulatie onder anesthesie, en arthroscopische capsulaire release.

De pathofysiologie van FS komt in deel I aan de orde. Deel II gaat over het optimaliseren van conservatieve therapie met corticosteroïd injecties en fysiotherapie. De rol van manipulatie in de behandeling van FS komt aan de orde in deel III van dit proefschrift.

## HOOFDSTUK 2: DE PATHOFYSIOLOGIE VAN FROZEN SHOULDERS – EEN LITERATUURSTUDIE

De bewegingsbeperking die gepaard gaat met een FS wordt veroorzaakt door een verdikt en samengetrokken kapsel van het glenohumeraal gewricht. Er zijn verschillende aanwijzingen dat het ziekteproces start aan de voorzijde van de schouder, in het rotatoren interval. Nieuwvorming van bloedvaten is zichtbaar in het rotatoren interval, FDG opname op FDG-PET/CT scans is voornamelijk voor in de schouder zichtbaar en een verhoogde expressie van genen gerelateerd aan de pathofysiologie van een FS werd in het rotatoren interval gevonden. Het coracohumerale ligament is betrokken in het pathofysiologische proces. Dit ligament is aan de extra-articulaire zijde over het rotatoren interval gespannen. Histologische biopten van gewrichtskapsel in FS tonen fibroplasie en gedifferentieerde myofibroblasten in een extracellulaire matrix met overschot aan niet-georganiseerd collageen type III. Het proces van fibrose wordt vooraf gegaan door een verhoogde inflammatoire respons. Dit begint met een toegenomen hoeveelheid 'Alarmins', en verhoogde levels van pro-inflammatoire cytokines. Fibroblasten worden geactiveerd en differentiëren in myofibroblasten onder invloed van TGF-β en mechanische stress. Het gevolg is een verstoorde balans in de opbouw en afbraak van de extracellulaire matrix. Er wordt een overschot aan collageen type III geproduceerd wat het kapsel zo stijf maakt.

Er komt steeds meer bewijs beschikbaar dat een systemische chronische staat van laaggradige inflammatie een belangrijke risicofactor is voor het ontwikkelen van een FS. Inflammatoire lipoproteïnes zoals LDL en non-HDL zijn risicofactoren voor atherosclerose, maar zijn ook aangetoond als onafhankelijke risicofactoren voor FS. ICAM-1 is een bekende marker voor chronische inflammatie gerelateerd aan endotheliale activatie in cardiovasculaire aandoeningen. Maar ook in het kapsel en synoviaal vocht in FS is ICAM-1 aantoonbaar verhoogd. Diabetes mellitus is één van de belangrijkste risicofactoren voor de ontwikkeling van een FS, en gaat ook gepaard met chronische inflammatie. Hyperglycemie leidt tot de vorming van Advance Glycation End products (AGEs), welke een profibrotisch effect hebben. AGEs zijn ook verantwoordelijk voor vorming van crosslinks (covalente verbindingen) tussen collageen vezels waardoor het kapsel nog stijver wordt.

Er zijn nog steeds belangrijke hiaten in onze kennis over de pathofysiologie van FS. Het natuurlijk beloop is zeer variabel tussen patiënten. Er zijn nog geen biomarkers waarmee het natuurlijk beloop kan worden voorspeld. Ook begrijpen we nog niet goed waarom de capsulaire fibrose in FS veelal spontaan verbetert terwijl in andere gewrichten zoals ellebogen en knieën de stijfheid meer permanent is.

# DEEL II
# CORTICOSTEROÏDEN EN FYSIOTHERAPIE

## HOOFDSTUK 3: HOE WORDT EEN FROZEN SHOULDER BEHANDELD? EEN ENQUÊTE ONDER SCHOUDERSPECIALISTEN UIT NEDERLAND EN BELGIË

Met een online vragenlijst hebben wij 186 schouderspecialisten gevraagd naar hun voorkeuren in de behandeling van FS. Van 100 schouderspecialisten hebben wij de antwoorden verwerkt in dit hoofdstuk. Er werd een breed scala aan mogelijke behandelstrategieën voor een FS genoemd. In fase 1 pleitte 80% van de schouderspecialisten voor: uitleg en advies, NSAID's en intra-articulaire corticosteroïd injecties. Er was geen overeenstemming over het te voeren beleid in fase 2 van een FS. De helft van de geënquêteerde orthopeden pleitte vóór een intra-articulaire injectie en iets meer dan de helft geeft het advies voor fysiotherapie. Manipulatie onder anesthesie wordt door 43% van de orthopeden gebruikt en 76% gebruikt een arthroscopische capsulaire release als behandeling in zijn of haar praktijk. Voor beide interventies zijn de aantallen per jaar laag. Deze studie laat zien dat er weinig overeenstemming is onder schouderspecialisten wat de optimale behandelstrategie is van een FS.

## HOOFDSTUK 4: DE TOEGEVOEGDE WAARDE VAN FYSIOTHERAPIE NÁ EEN CORTICOSTEROÏD INJECTIE IN DE VROEGE FASE VAN FROZEN SHOULDERS. DUTCH FROZEN SHOULDER TRIAL (D-FROST) – EEN GERANDOMISEERDE STUDIE

Intra-articulaire corticosteroïd injecties en fysiotherapie zijn de twee meest gebruikte niet-operatieve behandelingen in FS in zowel de eerste- als de tweedelijns zorg. Er wordt wel eens getwijfeld aan de rol van fysiotherapie in de behandeling van FS. In deze studie werden patiënten met een pijnlijke FS (VAS ≥ 6 ) gerandomiseerd in twee groepen. In beide groepen kregen patiënten een echogeleide intra-articulaire corticosteroïd injectie. In één groep kregen patiënten aanvullend fysiotherapie (FT) en in de andere groep werd geen fysiotherapie gegeven (non-FT). Om de intensiteit van de fysiotherapeutische behandeling te bepalen werd rekening gehouden met de reactiviteit van het weefsel. Als er na de behandeling een toename van pijn was gedurende 4 uur of langer, diende de volgende sessie minder intensief te zijn.

Beide groepen verbeterden significant ten aanzien van pijn, bewegingsuitslagen, en functie. SPADI-scores (Shoulder Pain and Disability Index), de primaire uitkomstmaat, waren beter in de FT groep na zes weken. Bewegingsuitslagen waren significant beter in de FT groep ten opzichte van de controle groep na zes en 12 weken. Wij vonden geen significante verschillen tussen beide groepen na een half jaar. De belangrijkste beperking van deze studie is dat het beoogde aantal inclusies niet is gehaald en de

studie dus onvoldoende power heeft. Wij hebben hiermee rekening gehouden met de interpretatie van de resultaten en de formulering van de conclusie. Uit onze studie blijkt dat er een toegevoegde waarde is van fysiotherapie in de eerste drie maanden na een intra-articulaire corticosteroïd injectie in de behandeling van FS. Het lijkt erop dat met fysiotherapie de bewegingsbeperking sneller verbetert en hiermee de duur van functionele beperkingen kan worden verkort.

# DEEL III
# DE ROL VAN MANIPULATIE ONDER ANESTHESIE IN DE BEHANDELING VAN FROZEN SHOULDER

## HOOFDSTUK 5: ARTHROSCOPISCHE CAPSULAIRE RELEASE EN MANIPULATIE ONDER ANESTHESIE VOOR FROZEN SHOULDERS – A HOT TOPIC

Manipulatie onder anesthesie (MUA) en arthroscopische capsulaire release (ACR) zijn de twee meest voorkomende interventies als de niet-operatieve behandeling van FS onvoldoende blijkt te zijn. Dit hoofdstuk geeft een overzicht op basis van de beschikbare literatuur met de voor- en nadelen van beide procedures. Met MUA wordt het stijve, verdikte glenohumerale kapsel gescheurd door het schoudergewricht in de verschillende bewegingsrichtingen te forceren. Met ACR kan het verdikte gewrichtskapsel onder arthroscopisch zicht worden doorgenomen, wat over het algemeen wordt gezien als een meer gecontroleerde techniek. MUA is technisch relatief eenvoudig, is tijds-efficiënt en waarschijnlijk ook kosten-efficiënt. Er zijn echter wel ernstige complicaties beschreven van MUA, zoals fracturen van de proximale humerus en tractieletsels van de plexus brachialis. Deze ernstige complicaties komen erg weinig voor. Arthroscopie na MUA heeft ook andere letsels laten zien zoals het gedeeltelijk scheuren van de m. subscapularis, labrum letsels, en osteochondrale fracturen van de voorrand van het glenoid. Wat de klinische consequenties zijn van deze letsels is echter onduidelijk. ACR is technisch een lastigere procedure met het risico op kraakbeenschade, chondrolyse, en letsel van de nervus axillaris bij het doornemen van het inferieure kapsel.

Met vroege postoperatieve fysiotherapie kunnen de functie en de bewegingsuitslagen snel verbeteren na beide procedures. Beide interventies kunnen als geschikte behandelmethode worden gezien in de behandeling van FS. Goede resultaten worden ook beschreven met een combinatie van beide interventies, zoals een veilige maar incomplete arthroscopische release, gevolgd door een behoedzame manipulatie waar minder kracht voor nodig is. Studies met een sterk wetenschappelijke methode waarin

beide technieken met elkaar worden vergeleken zijn er niet, en vooralsnog is niet aangetoond dat de ene interventie beter is dan de ander.

## HOOFDSTUK 6: MANIPULATIE ONDER ANESTHESIE IN DE BEHANDELING VAN FROZEN SHOULDERS, EEN VEROUDERDE TECHNIEK OF EEN 'QUICK FIX' DIE ZIJN SPOREN HEEFT VERDIEND?

Het doel van deze systematische review is om de effectiviteit en de veiligheid van MUA te evalueren. Zestien studies werden geïncludeerd, met in totaal de resultaten van MUA in 858 patiënten. Van een eenduidige indicatie voor MUA was geen sprake en sommige artikelen stelden alleen 'het falen van niet-operatieve behandeling' als indicatie voor MUA. De minimale duur van klachten voorafgaand aan MUA varieerde van één tot zes maanden. Stabilisatie van de scapula en houvast hoog op de humerus (een korte hefboom) zijn frequent beschreven maatregelen om complicaties te voorkomen. Een analyse van de samengevoegde resultaten laat een toename zien van 55 graden anteflexie, 72 graden abductie, en 30 graden exorotatie binnen zes weken na MUA. Dit effect verbeterde nog iets gedurende het eerste jaar. De VAS-score voor pijn verbeterde met een gewogen gemiddelde van 3.5 punten in zes weken en 5 punten na 1 jaar. De Constant score verbeterde met 43 punten in zes weken en 52 punten na 1 jaar. Ongeveer 85% van de patiënten rapporteerde tevreden te zijn met het resultaat van MUA. Daarnaast vonden we een complicatie-risico van 0.4%, en een re-interventie risico van 14%. Ernstige complicaties zoals een humerus fractuur of plexus brachialis letsel werden in de geïncludeerde studies niet beschreven. Concluderend kan worden gesteld dat MUA leidt tot een aanzienlijke verbetering van de bewegingsbeperking en pijn, en een tevreden resultaat in ongeveer 85% van de patiënten. Echter, op één studie na ontbreekt bij alle studies een controle groep zónder interventie. Wij adviseren dan ook om voorzichtig te zijn met de indicatiestelling voor MUA gezien de potentiële complicaties en het relatief milde natuurlijk beloop van een FS in de meerderheid van de patiënten. Of MUA daadwerkelijk de duur van de klachten van een FS verkort, kan op basis van deze literatuurstudie niet worden geconcludeerd.

## HOOFDSTUK 7: MANIPULATIE ONDER ANESTHESIE VOOR FROZEN SHOULDERS – EEN RETROSPECTIEVE COHORT STUDIE

Dit hoofdstuk beschrijft de resultaten van MUA in patiënten met een FS gedurende een periode van twee jaar. Patiënten met diabetes en een secundaire FS werden in dit cohort ook meegenomen in de evaluatie. Manipulatie werd uitgevoerd door een ervaren orthopedisch chirurg, onder locoregionale anesthesie (plexusblokkade) eventueel aangevuld met kortdurende sedatie indien dit noodzakelijk werd geacht of de patiënt dit verzocht. De arm werd hoog op de bovenarm vastgepakt (korte hefboom), de scapula gestabiliseerd en de elleboog gebogen om fracturen en plexusletsel te

voorkomen. Fysiotherapie werd direct op de dag van de procedure opgestart en intensief gecontinueerd gedurende minimaal twee weken.

Van de 65 patiënten hebben er 49 de vragenlijsten compleet ingevuld na een gemiddelde follow up van 21 maanden. De tijd tussen het begin van de klachten tot aan MUA was 8 maanden (range 2-25). Negentig procent van de patiënten verklaarde veel danwel heel veel verbetering te hebben gemerkt met betrekking tot de functie van de schouder in het dagelijks leven. De gemiddelde SPADI score voor pijn en functie was 11.2 (IQR 0.8-25.2 met 0 als beste en 100 als slechts mogelijke score) en de gemiddelde OSS score 39 (IQR 30-43 met 48 als beste en 0 als slechts mogelijke score). Pijnscores in rust en tijdens activiteit waren laag. In 92% van de gevallen rapporteerden patiënten tevreden te zijn met het behaalde resultaat van MUA. Maar, slechts 72% van de patiënten gaf aan hetzelfde niveau qua schouderfunctie te halen in vergelijking met de schouderfunctie voorafgaand aan de FS. In 16% van de patiënten was het behaalde resultaat niet blijvend, en werd een terugval gerapporteerd na aanvankelijke verbetering. Er werden géén complicaties gezien tijdens MUA en bij navraag werden ook door de patiënten geen complicaties beschreven. De resultaten van MUA in deze studie zijn positief, maar zullen moeten worden afgezet tegen een controlegroep om daadwerkelijk de effectiviteit van MUA te kunnen beoordelen.

## HOOFDSTUK 8: MANIPULATIE ONDER ANESTHESIE VERGELEKEN MET CONSERVATIEVE BEHANDELING IN FASE II FROZEN SHOULDERS – EEN PROTOCOL VOOR EEN GERANDOMISEERDE STUDIE

Om de effectiviteit van MUA te kunnen vergelijken met de conservatieve (niet-operatieve) behandeling van FS, hebben we een gerandomiseerde studie opgezet. In de studie proberen wij antwoord te geven op de vraag of MUA de duur van de klachten van een FS kan verkorten. Het betreft een prospectief gerandomiseerde studie. De studie is gestart in 2017 en de resultaten worden verwacht aan het eind van 2021. Patiënten met een klinische diagnose van een FS in fase II worden gerandomiseerd voor MUA gevolgd door fysiotherapie (MUA groep) of voor alleen fysiotherapie (FT groep). Patiënten komen in aanmerking voor inclusie als er ten minste drie maanden klachten zijn, en er onvoldoende vooruitgang is na een intra-articulaire corticosteroïd injectie en fysiotherapie. In de interventie groep wordt MUA direct gevolgd door fysiotherapie. In de controle groep krijgen patiënten fysiotherapie volgens de recente richtlijn voor de behandeling van FS van SchouderNetwerk Nederland. In deze richtlijn wordt geadviseerd de intensiteit van fysiotherapie aan te passen op de reactiviteit van het weefsel.

De primaire uitkomstmaat is de SPADI. Secundaire uitkomstmaten zijn beweeglijkheid van de schouder, pijn (NPRS), functionele scores (OSS), kwaliteit van leven (EQ-5D) en

het vermogen om te werken (WORQ-UP score en work ability index). Het vermogen om te werken vinden wij een zeer relevante uitkomstmaat, niet alleen voor de individuele patiënt, maar ook vanuit een breder sociaal-economisch perspectief.

Het doel van de studie is om de effectiviteit van MUA te vergelijken met een niet-operatieve behandeling waarvan fysiotherapie deel uit maakt. Ook willen wij onderzoeken of MUA daadwerkelijk leidt tot een verkorting van de duur van de symptomen van een FS. Met de resultaten van deze studie kunnen patiënten beter worden voorgelicht over de effectiviteit van MUA ten opzichte van fysiotherapie. De gezamenlijke besluitvorming of MUA een juiste behandelstrategie is voor de individuele FS patiënt zal hierdoor verbeteren.

# APPENDICES

PhD portfolio - List of publications

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Dankwoord

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Curriculum Vitae

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# PhD PORTFOLIO – LIST OF PUBLICATIONS

**Name PhD student**: Timotheüs Kraal
**PhD period**: 2014-2021
**PhD supervisor**: prof dr. D. Eygendaal
**PhD co-supervisors:** dr. B. The, prof. dr. M.P.J. van den Bekerom

| **1. PhD training** | **Year** |
|---|---|
| **General courses** | |
| Advanced statistics SPSS | 2014 |
| Good clinical practice | 2018 |
| **Shoulder courses** | |
| Shoulder arthroplasty course – Gent | 2014 |
| Dissection course upper extremity – York | 2014 |
| NVA shoulder arthroscopy - Utrecht | 2015 |
| Arthrex shoulder arthroscopy course - München | 2016 |
| Wetlab around the shoulder – Rotterdam | 2016 |
| Shoulder arthroplasty course – Utrecht | 2016 |
| State of the art shoulder arthroplasty – Maastricht | 2017 |
| ESSKA 360° around shoulder instability | 2017 |
| Proximal humerus fractures – Rotterdam | 2018 |
| Arthroplasty & Arthroscopy of the shoulder – Utrecht | 2018 |
| Arthrex sports med fellow course - Naples | 2019 |
| Arthrex shoulder arthroplasty course – Naples | 2019 |
| Proximal humerus fractures – Nijmegen | 2019 |
| State of the art shoulder arthroplasty - Maastricht | 2019 |
| NVA advanced shoulder course - Rotterdam | 2019 |
| **Fellowships** | |
| NVA travelling fellowship – Germany | 2017 |
| Fellowship Reconstructive Arthroscopy – UBC, Vancouver | 2019 |
| Fellow Shoulder – Spaarne Gasthuis Hoofddorp | 2020 |
| **Presentations** | |
| NOV vergadering: | |
| - Ankle arthroplasty in rheumatoid arthritis, 10-23 years follow up | 2013 |
| - How to treat a frozen shoulder, a survey among specialists Traumaplatform challenges in Trauma - Leeuwarden | 2014 |
| - Experiences from a foreign fellowship Traumadagen – Amsterdam | 2019 |
| - Olecranon osteotomy for distal humeral fractures, no way | 2019 |
| Amphia FORCE symposium – Breda | |
| - Frozen Shoulders – Manipulation under Anesthesia vs Physiotherapy | 2020 |
| **Poster presentation** | |
| 18th EFORT Congress – Vienna | 2017 |
| D-FROST: Dutch FROzen Shoulder Trial. Additional physiotherapy after a corticosteroid infiltration in the treatment of frozen shoulders | |

| **2. Publications** | **Year** |
|---|---|
| **Book chapter**<br>Book title: 360° around shoulder instability<br>Chapter: Basic science on shoulder instability<br>Authors: T. Kraal, W.D. Regan, C.J.A. van Bergen | 2020 |

**Journal articles**

**For this thesis**

**Kraal T**, Beimers L. Arthroscopic capsular release and manipulation under anaesthesia for frozen shoulders: A hot topic. ***World J Meta-Analysis***. 2015;3(2):82.

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# Appendix

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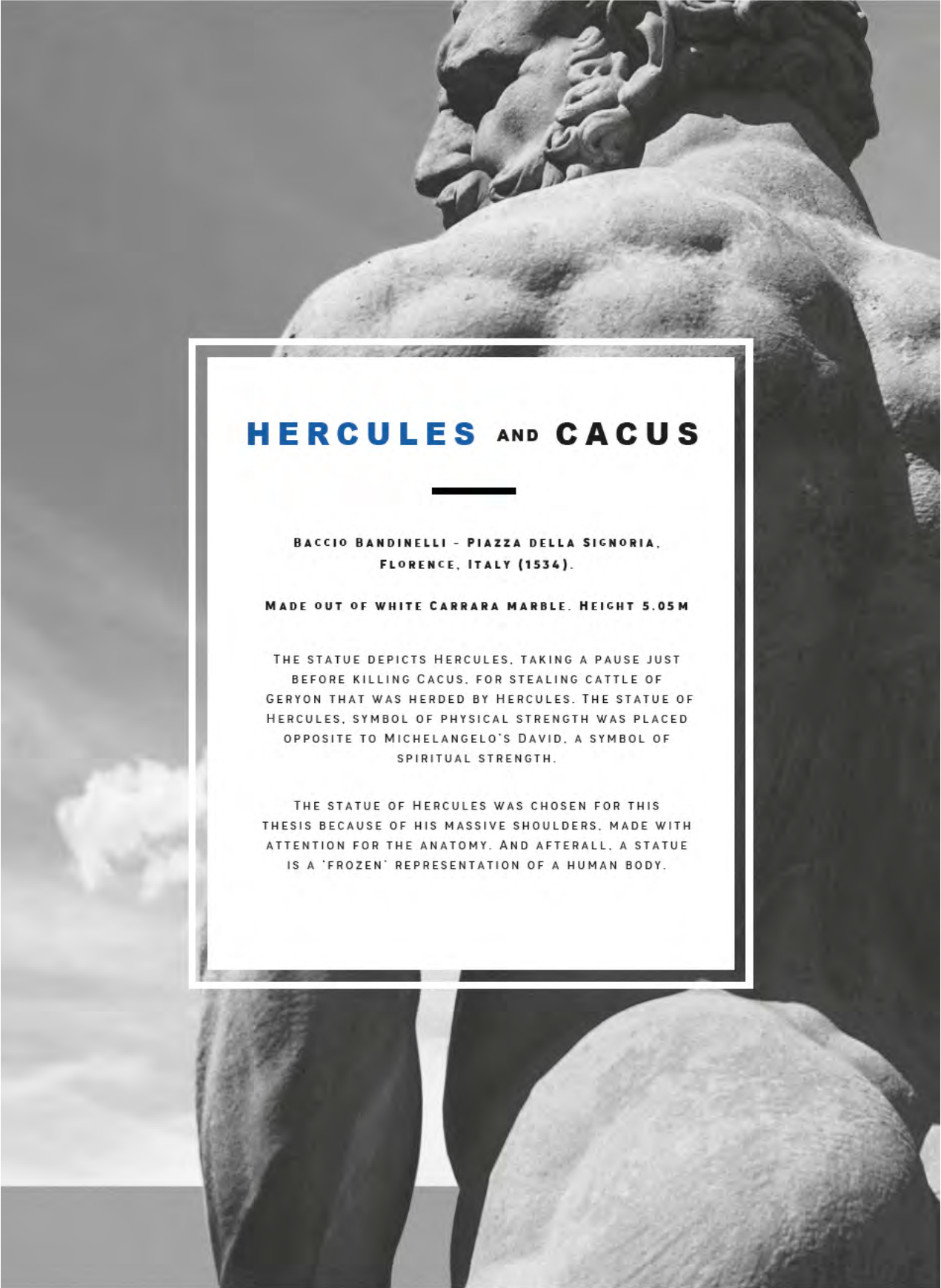
# Curriculum Vitae

Timotheüs (Tim) Kraal was born in Venhuizen on March 20, 1985. He graduated from high school (VWO, Martinus College, Grootebroek) in 2003. He decided to pursue the profession of orthopedic surgery after some injuries due to his career in gymnastics. His enthusiasm for the anatomy and understanding of our musculoskeletal system started here. He studied Medicine at the Vrije Universiteit in Amsterdam and obtained his medical degree in 2009. He worked for two years as a resident at the emergency department in Haarlem (Kennemer Gasthuis). In 2011 he started working with professor R.G. Pöll at the Slotervaart hospital in Amsterdam and he started the orthopedic surgery training program under supervision of professor C.N. van Dijk and professor G.M.M.J. Kerkhoffs at the AMC in Amsterdam in 2012. His general surgery training was supervised by dr. H. Rijna at the Kennemer Gasthuis in Haarlem. His first orthopedic rotation was at the Slotervaart hospital in Amsterdam under supervision of dr. H.M. van der Vis. This is when he started working on the first projects of this thesis together with dr. L. Beimers. He continued his orthopedic training at the Amphia hospital Breda under supervision of professor D. Eygendaal. She was the one who gave him a gentle push in the right direction for this thesis. He completed his orthopedic training in 2018, after which he went to Vancouver – Canada for a fellowship in sports injuries of knees and shoulders under supervision of dr. W.D. Regan at the University of British Columbia. This was followed by a shoulder fellowship under supervision of dr. A. van Noort and dr. T.D.W. Alta at the Spaarne Gasthuis Hoofddorp. Tim lives in Haarlem together with his fiancee Diana Molenaar and their two sons Benjamin and Aron.



# HERCULES AND CACUS

**Baccio Bandinelli - Piazza della Signoria, Florence, Italy (1534).**

**Made out of white Carrara marble. Height 5.05m**

The statue depicts Hercules, taking a pause just before killing Cacus, for stealing cattle of Geryon that was herded by Hercules. The statue of Hercules, symbol of physical strength was placed opposite to Michelangelo's David, a symbol of spiritual strength.

The statue of Hercules was chosen for this thesis because of his massive shoulders, made with attention for the anatomy. And afterall, a statue is a 'frozen' representation of a human body.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