An overview of effective and potential new conservative interventions in patients with frozen shoulder

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Introduction

Frozen shoulder (FS) or adhesive capsulitis is a pathology characterized by spontaneous onset of shoulder pain accompanied by gradual restrictions of both active and passive shoulder motion [1, 2]. The prevalence of primary FS in the general population is 2-5% [2, 3], while the prevalence of FS in patients with Diabetes Mellitus (DM) increases up to 39% [4, 5]. Additionally, in the last two decades there is an increase in the incidence and prevalence of patients with FS [6], although this might be a result of over diagnosis as well [7]. Frozen shoulder seems to be more common in patients with sedentary jobs, which might be explained by the fact that the evolutionary design of the shoulder is not sufficiently used by these jobs anymore. Combined with accentuation of age-related oxidative stress and pro-inflammatory cytokine production this might result in extracellular matrix alterations [8]. Frozen shoulder develops between the age of 40 and 60 years [9] and affects more women (50-70%) than men [9, 10]. Out of all FS patients 6-34% develop a FS on the contralateral shoulder [9, 10] and in 14% of the patients there is even a simultaneous bilateral FS [11]. Additionally, patients with DM or thyroid disorders have a 5 to 7 times higher risk of developing a FS [3].

Despite its common occurrence, FS remains a medical enigma; difficult to understand and difficult to manage. It is thought to be 'self-limiting' and therefore appears to resolve in most patients without the application of any intervention [9, 12]. However, patients with severe complaints, more movement restriction, less muscle force and more co-morbidities have a worse prognosis for recovery [9, 13]. Furthermore, the evidence in literature for the "self-limiting" and "3-phase" theory appears to be debatable [14]. It is suggested that there is an early improvement in disabilities (with the greatest gain in the early disease process) that slows with time [14]. As a consequence, prolonged limitations in active and passive range of motion (ROM) and functionality can last for multiple years [14]. Moreover, there is no evidence for complete recovery without supervised treatment [14], which is contradictory with the "self-limiting"-theory. In addition, from a clinical point of view there is an incomplete

recovery in a subset of patients [9]: some patients maintain a slight painful and restricted shoulder (in terms of mobility and functionality) after a certain treatment period [9, 11]. On the contrary, there is no sound evidence that patients (who have slight functional limitations and pain) years after suffering from a FS, still seek medical attendance. They are likely to adapt themselves to this situation.

The characteristic pain (also radiating to the upper arm) and gradual movement restriction of FS are consequences of diffuse inflammation of the synovial membrane and a progressive fibrosing that leads to a contracture of the total glenohumeral joint capsule within 1 to 9 months [15-17]. The loss of active and passive ROM applies to all movement directions, but especially external rotation [3]. All these may lead to functional restrictions in work or sport, sometimes for longer periods.

For clinical application it might be relevant to divide the FS into two stages: more pain than stiff and more stiff than pain [18]. In this first stage, patients complain about pain in the deltoid region, which is also present at night. In addition, there is an increase in loss of passive and active ROM [10, 19]. Around the capsule, inflammatory changes can be seen with synovial hyperplasia and a subsynovial hypervascularity and neurogenesis [20]. In a later stage there will be a decrease in pain, while the movement restriction remains and in the end active and passive ROM will recover in a slow and sustained manner [10, 19]. During this phase, the inflammation disappears gradually and tissue fibrosis occurs with a high number of fibroblasts within an extracellular matrix of densely packed collagen [20]. Total disease duration varies between 1 and 3 years [9, 11, 12].

Especially in the beginning of the disease when the shoulder pain mimics other shoulder pathologies there appears to be some misdiagnosis. This leads to unnecessary imaging, supplementary examinations, and accelerated interventions [21]. In addition, incorrect and aggressive treatment techniques may be applied, having a negative effect on the patients' complaints.

The purpose was to provide a short summary and update of the frozen shoulder diagnosis and conservative treatment, corresponding with the irritability levels based on the FS guideline [3]. Additionally, clinically relevant information regarding new treatment options and ongoing research will be discussed more thoroughly to provide new insights for more accurate diagnosis in order to increase treatment efficiency.

Search strategy

PubMed, Web of Science and Cochrane Database of systematic reviews were searched for relevant studies regarding diagnosis and conservative treatment of patients with frozen shoulder, additionally reference lists of relevant studies were screened for additional studies. The following key words and a combination of them was

used: frozen shoulder, adhesive capsulitis, pathophysiology, diagnosis, tissue irritability, conservative treatment, pharmacotherapy, physical therapy, corticosteroid injection, pain neuroscience education, patient education, hyperglycemia, chronic low-grade inflammation, myofibroblasts and matrix metalloproteinases. Studies regarding surgical interventions and neurologic secondary FS were excluded. The last update of the search was 17 August 2021.

The strength of the evidence was based on the conclusion of the included studies; no additional method was used to determine the strength of the evidence.

Diagnosis

Diagnosis of FS in the early stage is difficult and mainly based on pattern recognition and clinical criteria. Therefore, history, physical examination, and exclusion of other pathologies are crucial [3, 11, 22]. In this stage, the diagnosis can easily be confused with several differential diagnosis, such as (osteo)arthritis, posterior dislocation of the humeral head, subacromial shoulder pain with calcifying tendinitis in the resorption phase and post-operative shoulder stiffness [22, 23]. Although there is no direct evidence that a trauma is a cause of FS, most patients associate the start of FS with a previous every day or banal event. The diagnosis will become more obvious from later stages, when the FS becomes more characterized by both the active and passive ROM restriction. For the diagnosis of FS, the characteristic course described above together with a ROM restriction of at least 25% in at least 2 movement planes and more than 50% in external rotation (arm in 0° of abduction) compared to the non-involved side are used [3]. In addition, the complaints must be stable for at least 1 month or worsening [3]. Additionally, 'rule in' and 'rule-out' criteria (Table 1, translated with permission) can be used to prevent incorrect diagnoses of FS [24]. Furthermore, imaging can be used to exclude other pathologies (e.g. osteoarthritis, posterior dislocation) when suspected [3, 11, 21]. It seems that the coracohumeral ligament has a pivotal role in the development of FS [20] and therefore there might be an important role for palpation in the diagnosis of FS [25]. Inflammation and fibrosis are seen in the rotator interval, including the coracohumeral ligament and a thickened coracohumeral ligament was found with intra-operative visualization and various forms of imaging [17, 26, 27]. A thickened and tightened coracohumeral ligament results in an external rotation ROM restriction, which is a main characteristic of FS [11, 27, 28]. The origin of the coracohumeral ligament is the base of the coracoid process [17]. If palpation of the coracoid area results in a significant higher pain severity compared to the acromioclavicular and anterolateral subacromial region the diagnosis FS might be more likely [25].

Tissue irritability

Originally, recognition of the different phases of FS was important to apply a suitable treatment plan [19]. This was mainly done clinically based on the symptoms described in history taking and physical examination. However, there is an alternative method available to determine a suitable treatment, based on the irritability level of the patient's affected shoulder [3, 24, 29]. Irritability levels reflect the ability of the affected tissue to cope with physical stress and theoretically relates to the degree of present inflammatory activity [3]. Three different levels can be distinguished: high, moderate and low. The determination of the irritability levels is based on the examination of the intensity of pain, presence of night pain, presence of pain in a movement trajectory and whether there is a difference in active and passive ROM (Figure 1). Because the progress of FS runs in a continuum, there is a possibility that not all the elements of a level are present, but elements of a higher or lower level are present as well. The determination is then performed based on the dominant elements that are present. For example, a patient indicates to have frequent night pain with a numeric pain rating scale (NPRS) of 5/10 and severe movement restriction with moderate pain in all directions. Examination of this patient shows a larger passive than active ROM (e.g. as a consequence of pain). In this case, we classify the patient as one with high irritability: moderate pain level, but pain in all movement directions, night pain and a difference in passive and active ROM.

Treatment

The effect of different interventions is unclear, because various studies do not show a difference in disease duration as a consequence of treatment [19]. It seems that we cannot influence the disease duration with treatment [30, 31]. Therefore, the aim of treatment of patients with FS focuses mainly on symptom reduction (like pain relief), informing, explaining and restoring mobility and daily functions. Without adequate and appropriate management, biomechanical changes might occur, resulting in altered limb use with muscle atrophy, osteopenia, and tendinopathy as consequence [32]. In some studies, patients show a large increase in shoulder mobility and report improvement in pain and function after the start of conservative treatment [33].

There is no superior conservative intervention, but a multidisciplinary approach (cooperation with e.g. general practitioner or orthopedic surgeon) is preferred in patients with negative psychosocial factors [24] and has shown to improve outcomes [34]. The treatment should be adjusted to the disease phase and tissue irritability level. Conservative interventions that can be applied in the treatment of FS include patient education [35], pharmacotherapy [19, 36, 37] and physical therapy [19, 36, 37].

Patient education

Based on moderate evidence, patient education is recommended [3] as one of the most important interventions. Informing the patient about the course of the FS seems to bring relief to the patient and will contribute to a gradual improvement in most patients [35]. By informing patients, recovery-inhibiting factors (e.g. detrimental stress, comorbidities, inappropriate posture and movement behavior) can be removed or prevented from occurring. To prevent the occurrence of negative illness beliefs and unnecessary stress and to guide patients towards an optimal recovery, they need answers to the following questions:

- *What is this pain and movement restriction (identity)?*

  An explanation of the process of inflammation and fibrosis that occurs during the course of FS.

- *What causes this pain and movement restriction (cause)?*

  The actual cause and what triggers the onset of FS is unknown, however, several risk factors are known to increase the probability of FS.

- *How long will this pain and movement restriction last (timeline)?*

  Disease course varies between 1 and 3 years. In the early stage, pain will predominate, while in the later stage stiffness will predominate.

- *What can I (or a caregiver) do about this pain and movement restriction?*

  Follow the guidelines regarding tissue irritability, education about the disease process, modify activities if necessary and stay generally active. In later stages manual and exercise, therapy can be applied.

- *What are the consequences (for my work and sport)?*

  Especially in the early stage, work and sport will be restricted and can be resumed gradually when irritability decreases. However, there might be a possibility that high demand work or sport activities might not be resumed in few cases.

These questions are part of the common-sense model of Leventhal [38]. The answers (often implicitly) determine partly the physical behavior of the patient. By answering these questions, the patient gets clarity about the cause, prognosis and own role in recovery (with an emphasis on self-efficacy and if appropriate on behavioral change). As a consequence, the patient will not develop negative illness beliefs and set treatment goals for self-management in consultation with healthcare professionals, such as physical therapists, more easily. It is important that all healthcare providers proclaim the same message to decrease detrimental and negative stress factors. Cooperation, communication and discussion with all the people who are part of the social environment of the patient and other healthcare professionals is therefore essential [35].

Another important factor in patient education is the evaluation of tissue response to interventions or activities, which is different for each irritability level. In case of high irritability, no increase in pain or restricted function will be allowed. It is recommended to allow a maximum of 4 hours of tissue response during moderate irritability and a response is accepted up to a maximum of 24 hours during low irritability [24].

Pharmacotherapy

Medication applied in the treatment of FS are paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids.

The evidence for the use of *paracetamol* in patients with FS is *limited*, but useful when there are no co-morbidities [39]. Paracetamol (or acetaminophen) works both peripherally and centrally [39]. Peripherally acetaminophen inhibits cyclo-oxygenases (COXs) and herewith the synthesis of prostaglandins [40]. Prostaglandins are involved in the processes of inflammation and pain. Centrally it is presumed that acetaminophen activates the periaqueductal gray matter, which activates descending serotonergic and noradrenergic neurons. Consequently, these neurons activate the rostral ventromedial medulla and dorsolateral pons respectively [39]. These areas are important for controlling the balance between nociceptive inhibition and facilitation [39].

Like acetaminophen, oral *NSAIDs* have both peripheral and central effects [40]. They inhibit COXs and prostaglandins as well and consequently mask its nociceptive effect [40]. NSAIDs might therefore be used for pain relief as well, but the evidence is *limited* and they have no effect on the ROM [19]. Long-term and frequent use of NSAIDs are associated with hip and knee osteoarthritis and a delay in tissue healing and cardiovascular events, bleeds and renal dysfunction are reported as side effects [40]. *Steroids* oppose inflammation in several ways. One of these ways is to inhibit action of nuclear factor kB and AP-1 protein; as a consequence, the upregulation of pro-inflammatory molecules is inhibited [41]. *Oral steroids* provide quicker pain relief compared to placebo, but this effect is not retained in the long term [19, 36, 37, 42]. Based on *strong evidence corticosteroid injections* (CSI) are recommended in the early stage of FS, prior to the emergence of capsular contraction, they provide pain relief and reduce inflammation [3, 18, 24, 43]. They have an inhibiting effect on the inflammatory response and impedes the differentiation of fibroblasts into myofibroblasts [20]. Which is confirmed in a prospective clinical study [44]. Corticosteroid injections are more effective than placebo (mean difference (MD): -16.3 mm and -6.9 and -1.4 points (VAS)), but unfortunately do not change the long-term outcome [45-47]. Especially in the early phase of FS CSI are more effective than physical therapy in decreasing pain [11, 18, 19, 36, 37, 42, 47], but in the long term there is no difference between CSI and physical therapy [2, 47, 48]. For the ROM conflicting evidence of solely

CSI was found. One study found no effect of solely CSI [36], while other studies found only an effect in the short term [47, 48]. Another meta-analysis found an improvement in passive abduction (MD: 12.78° and 11.95°), flexion (MD: 13.80° and 12.07°) and external rotation (MD: 9.79° and 10.59°) in the short and long term with CSI compared to placebo [45]. Furthermore, a combination of CSI and physical therapy resulted in an improvement of ROM (MD: 4.6°) [36, 47] or greater improvements than either sole treatment [48]. A recent randomized controlled trial showed that CSI combined with physical therapy was less effective than shockwave therapy combined with physical therapy for flexion and abduction ROM and shoulder pain and disability in patients with both FS and DM [49]. In addition, early CSI show greater improvement in pain and function than late CSI [50]. Regarding different doses, conflicting evidence was found for the effectiveness on pain and ROM [18, 36, 51]. The same applies for anatomical injection sites, where several reviews did not find a difference [18, 36, 42, 47, 48], while a recent meta-analysis indicated differences in pain at 1 month, 2 months, and 3 months (weighted mean difference (WMD): 0.9, 0.8, and 1.1 respectively) favoring intra-articular site [52]. For ROM and function (Constant score) at 1 and 2 months, no difference was found between intra-articular and subacromial injections [52].

In addition to the positive effects of corticosteroids, there are some adverse effects as well. Adverse effects after a single injection might be post-injection pain, subcutaneous atrophy, depigmentation, facial flushing, and menstrual irregularities [51, 53]. In patients with DM there is found conflicting evidence regarding the increase in blood glucose levels after a single injection [54, 55]. After multiple injections an increase in glycosylated hemoglobin (HbA_{1c}) was found [49]. Possible complications of the prolonged use of corticosteroids are among others avascular necrosis, infection, muscle soreness, fractures and pain increase after injection [56-58]. There is no difference in adverse effects relative to injection site [52]. Furthermore, there are some contra-indications for the use of corticosteroids, like infectious arthritis, anti-coagulation therapy and uncontrolled DM [59]. The application of corticosteroids should therefore be carefully considered.

Physical therapy

Physical therapy is a commonly used intervention and recommended for FS [30]. It is mostly prescribed to treat capsular contraction [19] and maintain and improve the active and passive ROM [2, 19, 60, 61], but it is complementary to other interventions like pharmacotherapy [2]. Physical therapy results in early gain in ROM, but there has been insufficient evidence to suggest that physical therapy alters the long term outcome [30]. In the short term physical therapy is only more effective than no treatment and in the mid-term physical therapy combined with intra-articular CSI is the most effective treatment [47]. Physical therapists choose their interventions guided

by the level of irritability of the shoulder joint. Some physical therapy guidelines for this treatment strategy are available [3, 24], in which advice (such as patient education as described above) and interventions (such as manual mobilizations, capsular stretching, and exercise therapy) are described.

When the FS is in the high irritability stage, passive mobilization and capsular stretching are counterproductive (possibly due to activation of the inflammatory response) and adaptations of activities and pain relief are more appropriate [11]. For pain relief in the short term, based on weak evidence, some physical therapy modalities are recommended in this phase [3, 24, 43]. These modalities include low-level laser, electro-acupuncture, interferential therapy, deep heat, and continuous passive motion. The most important pain relief in the initial phases is a result of the fact that the patient is given a diagnosis, answers, explanation and therefore mental relief [38].

Several mobilization techniques are effective in the short and long term [36, 37] and based on weak [3, 24] and strong [43] evidence these interventions are recommended for pain relief and increasing ROM and functions [3, 24]. Recently a meta-analysis did not show a difference in various mobilization techniques used [62]. They found benefit of various mobilization techniques, either solely or in a treatment program compared to treatments without mobilization for reducing pain (MD: 1.2 cm on the VAS) and improving ROM (MD: 20.1°-26.8°) and function (MD: 13.9 with Constant Murley score) [62]. Contrary, another review indicates that uncertainty over clinically important differences and no differences for certain outcomes challenges the certainty of any recommendations about manual therapy in the management of FS [63]. Unfortunately, there is not enough evidence to provide information about the ideal dose of mobilization.

Based on moderate [3, 24] and strong [43] evidence exercises are recommended for reducing pain, and improving ROM and function. Regarding exercise therapy, various forms can be applied to patients with FS. Most exercises aim to improve ROM and restore functional ability of the shoulder. However, the remaining of the kinetic chain, like the elbow, lower arm, wrist, hand, fingers and spine needs attention [24]. The intensity of exercises should be adapted according to the irritability of the affected shoulder, as mentioned earlier. Many different forms of exercises are applied to patients with FS. Reported forms of exercise include Codman's pendulum exercise, active and passive ROM exercises (stretching), pulley exercises, and proprioceptive neuromuscular facilitation (PNF) either supervised or unsupervised [64]. A (supervised) home exercise program in addition to other interventions is recommended [63]. However, in the short term there is only little benefit of the exercise program on pain in combination with a CSI (MD: -0.5 VAS points), while only an exercise program is more beneficial than no treatment (MD: -1.4 VAS points) [47]. As part of this home exercise program, stretching of capsular tissue is an ideal exercise to be part of such a program since, based on moderate evidence, they are recommended for the

treatment of patients with FS [3, 24]. The intensity of capsular stretching exercises should be determined by the patient's irritability level, since stretching beyond painful limits results in poorer outcomes [3, 24]. In addition to the patients irritability level the Total End Range Time (TERT) can be used to report the dose applied to the patient and evaluate progression [65]. TERT is the total amount of time the joint is positioned at its end range and is proportional to the increase in passive ROM [66]. The TERT can be calculated by multiplying the duration the joint is held in the end position and the frequency [66]. The TERT should increase from moderate to low irritability to elongate the capsular tissue [24]. To increase the compliance of patients to the exercise program one can send mobile text messages, consequently the active ROM (MD: forward flexion: 2°; external rotation: 8.7°; internal rotation: 9.2°) will increase due to the higher exercise compliance [67]. Another form of exercise which seems to be effective for improving shoulder function, ROM, and pain relief is PNF [68]. PNF can be performed solely or in combination with other interventions and both seem to be effective [33, 68]. In a systematic review total effect sizes [95% confidence interval] of 0.59 [-0.12, 0.90], 0.41 [-0.02, 0.62], and -0.57 [-0.31, -0.87] for external rotation and abduction ROM and pain respectively were found [68]. PNF techniques that were used are contract-relax, hold-relax (with contract times of 5-10 seconds and relax times of 10-20 seconds), rhythmic initiation, and repeated contractions with a number of repetitions varying between 3 and 20. The frequency of treatment ranged from 2-5 times a week and the total treatment duration varied from 3-6 weeks, with a preference of 4 weeks. This intervention can be performed in all irritability levels, because the aim is to enhance mobility, movement control and joint coordination with various techniques [68]. Another study investigating proprioceptive training found that additional proprioceptive exercises results in improved functional activity and pain more compared to treatment without proprioceptive exercises [69]. Finally, an interesting mode of exercise therapy that seems to be effective in the treatment of patients with a FS is mirror therapy. Mirror therapy aims to restore the congruence between motor output and sensory output [70]. By creating a visual illusion in the form of increased ROM of the affected extremity by performing movements of the unaffected extremity and using mirrors to make patients see the reflection of their unaffected arm and make them realize that motor commands would not cause them pain. The mirror possibly influences the long-term cortical reorganization of brain maps and in addition, it might modulate current on-going pain in a certain area. Furthermore, there is evidence that visual feedback can reverse objective signs such as inflammation [70]. Mirror therapy seems to be beneficial for patients with FS for improving pain (VAS, MD: 1.5), function (University of California-Los Angeles score, MD: 6), ROM in flexion (MD: 24.1 (active) and 22.0 (passive)) and abduction (MD: 21.7 (active) and 19.1 (passive)) and physical role limitation (MD: 29.9) and emotional role limitation (MD: 20) of the 36-item Short Form Health Survey [71]. In this randomized

306 controlled trial, all patients received a standard physical therapy program (10 sessions about 60 minutes lasting)
307 including several modalities. After each session one group received exercises with the non-reflecting side of the
308 mirror, while the other group received the exercises with the reflecting side of the mirror. Exercises included active
309 flexion, abduction, internal, and external rotation in 2 stages. In the first stage only with the unaffected shoulder
310 and in the second stage with both shoulders [71].
311 Besides these specific and local exercises, general physical activity, like walking or cycling, is recommended for
312 general well-being [24], improving mood [72] and prevention of depression [72].
313 There is evidence for efficacy of above interventions, focusing on symptom reduction. However, a superior
314 intervention cannot be determined, because the comparison of the studies is difficult. Stages of FS are not always
315 clearly described or are not comparable across studies and there is a difference in follow-up time, which limits
316 comparison in the long term. Figure 1 shows the three irritability levels and an overview of recommended
317 interventions and Table 2 shows an overview of the strength of the different interventions discussed.
318
319 ***Ongoing research***
320 Table 3 provides an overview of possible hypothesis regarding the pathophysiology and new interventions in
321 patients with FS. Possible hypotheses that might explain the pathophysiology of a FS can be found in biochemical
322 processes like chronic low-grade inflammation, hyperglycemia, and involvement of myofibroblasts and matrix
323 metalloproteinases (MMPs). A chronic state of low-grade inflammation might predispose to the development of
324 FS [20]. DM, thyroid disorders, and cardiovascular disorders are conditions associated with chronic inflammation
325 and might (at least partly) explain why DM and thyroid disorders are risk factors for FS [20, 73]. As a consequence
326 of this inflammation, proliferation, activation and differentiation of fibroblasts might take place and the collagen
327 synthesis might be dysregulated [20]. Persistent activation of fibroblasts enhances the inflammatory response and
328 is a potential mechanism of symptoms of prolonged stiffness [20]. In patients with FS a high population of
329 myofibroblasts in the rotator interval area of the capsule was found, these cells are characteristic for contractile
330 scar tissue [74]. However, differences in the number of myofibroblasts were found between studies, which prevents
331 making a strong conclusion [74]. The differences in number of myofibroblasts may be a consequence of a lack of
332 information regarding the phase of FS, duration of symptoms since onset or the way tissue samples were managed
333 during histology [74]. In the freezing phase a low number of myofibroblasts was found [74], a high number of
334 myofibroblasts in the inflammation phase could explain the adverse reaction to passive mobilization and capsular
335 stretching during high irritability. Myofibroblasts will contract harder when subjected to greater stress as occurs

with passive mobilization and capsular stretching. In addition, it might explain the almost normal passive ROM under anesthesia in the inflammation phase as well. Further research is necessary to confirm this hypothesis.

In patients with FS a higher level of immunoreactivity of advanced glycation end products (AGEs) in the capsular tissue was found compared to control groups [75]. Under normal circumstances, AGEs are a result of non-enzymatic crosslinking of the collagen connective tissue in the shoulder joint capsule: there is an oxidative reaction between glucose and Amadori-products [76]. There is found an age-related accumulation of AGEs in different tissues and fluids and it is suggested that they rather act as a marker of the severity of various diseases developing with age than solely a result of ageing [77]. Advanced glycation end products form crosslinks throughout the collagen molecule, while normally crosslinks will only be formed on two discrete sites of the molecule [78]. It is assumed that non-enzymatic crosslinking results in changes of the biomechanics (e.g. stiffness, flexibility) of collagen tissue such as capsuloligamentary systems [76, 79]. In the process of hyperglycemia, when the level of HbA_{1c} is elevated for a longer period, there is an accelerated level of non-enzymatic cross-link formation. This results in elevated levels of AGEs and consequently this might result in an accelerated collagen crosslinking of the connective tissue in the joint capsule [78-80]. The involvement of HbA_{1c} is confirmed by Chan et al. [81], who found a correlation between accumulated HbA_{1c} and FS. Regarding the static, single measurement of HbA_{1c}, there was not found a correlation with FS [81-83]. This can be explained by the fact that the measurement only provides information about the last 3 months of the disease burden [84] and might not be long enough to establish the correlation. This accumulated glycemic level might be another explanation for the higher prevalence of FS in patients with DM.

It was found that AGEs also decrease the expression of MMPs and increase the tissue inhibitor metalloproteinases (TIMPs) expression in diabetic nephropathy [85]. Another factor that is thought to affect the MMP/TIMP ratio is transforming growth factor, a pro-inflammatory cytokine [73]. MMPs remodel the extracellular matrix and pathologically attack substrates as part of an inflammatory response [86]. When the level of MMPs is decreased (as a consequence of an imbalance between MMPs and TIMPs), degradation of extracellular matrix components is decreased and might result in overflowing cross-links. In both patients with FS and DM, lower levels of MMPs were found compared to controls [87-90]. The MMP/TIMP ratio can be restored by increasing the MMP level and decreasing the TIMP level by intensive stretching [88]. The relationship between AGEs and MMPs could be another explanation for the fact that FS is seen more often in patients with DM. In patients with cancer receiving medication with MMP inhibitor (TIMP), it was found that 50% of the patients using this medication longer than 1

month developed a bilateral FS [91]. Furthermore, a FS was found as a complication in several patients with malignant disease [92, 93] and this might be related to medication intake, resulting in changes of the MMP levels.

Regarding optimal treatment options for patients with FS, there are some new possible treatment options available. These interventions proved to be effective in various disorders, but are not examined in patients with FS so far [94, 95]. These interventions are more focused on tackling of the (partial) cause and may be used as well. From other populations it is known there might be subgroups of patients [96-98], for example patients with central sensitization or DM. Therefore, in these subgroups it might be useful to focus on treatment that is more focused on (a part of) the cause. If these subgroups are present in patients with FS, the treatment should not only be directed to the local complaints of the shoulder. Depending on the presence of the other factor, treatment could direct to e.g. the central nervous system or the metabolic system. This might result in a more efficient treatment and more patients might achieve a favorable outcome. For patients with dominant central nervous system involvement a cognition-oriented approach, with pain neuroscience education and general activation, might be effective [99]. Although there is a lack of evidence for this approach in patients with FS, there is sufficient evidence in other musculoskeletal complaints that applying pain neuroscience education, in which neurophysiology of acute and chronic pain is explained, has positive effects on pain, functionality, psychosocial factors (including thoughts and emotions), movement and medical costs [100]. In addition, general activating patients with chronic pain syndrome like FS could activate central pain inhibiting mechanisms and consequently decrease pain [101-103]. Furthermore, general exercises may lead to increased levels of MMP [104] and possibly result in improvement of shoulder function.

In patients with a more metabolic issue, e.g. patients with DM, a form of high intensity interval training and lifestyle changes might be effective in addition to the local treatment of FS. In patients with a metabolic disorder, these interventions are found effective [105-107].

Clinical message

- Diagnosis of FS is based on clinical criteria and irritability levels are available for guiding interventions;
- Patient education, pharmacotherapy, manual therapy, and exercises are recommended in the various FS stages;
- New possible interventions for FS are pain neuroscience education, lifestyle changes, and aerobic training;

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Tables

Table 1 'rule-in' and 'rule-out' criteria for diagnosing frozen shoulder (translated with permission from Vermeulen et al.[24])

Rule in	*Rule out*
• Age 40 to 60 year	• External rotation restricted largely with hard end feeling
• Slow progression of increasing pain and stiffness	• Painful abduction restriction without restricted of external rotation
• Pain and stiffness restrict sleep, daily activities and reaching	• Glenohumeral external and internal rotation ROM increase gradually with increasing abduction
• Glenohumeral ROM restricted in all directions, but most restricted into external rotation	• Significant trauma
• Glenohumeral external and internal rotation decrease gradually with increasing abduction	
• Passive movements to the end position reproduce recognizable pain	

Table 2 Interventions applied in patients with frozen shoulder with their strength of evidence

Intervention	*Strength of evidence*
Patient education	Moderate
Pharmacotherapy	
Paracetamol	Limited
NSAID	Limited
Corticosteroid injection	Strong
Physical therapy	
Physical therapy modalities	Weak
Mobilization	Weak/strong
Exercise therapy	Moderate/strong

NSAID: non-steroidal and anti-inflammatory drugs

Table 3 Possible hypothesis regarding the pathophysiology and possible new interventions for the treatment of patients with frozen shoulder

Possible hypothesis	
Hypothesis	*explanation*
Chronic low-grade inflammation	DM & thyroid CV disorder associated with low-grade inflammation
Hyperglycemia	Accumulation of AGEs
MMP/TIMP ratio	Imbalance might result in overflowing cross-links
Possible new interventions	
Treatment	*Reason*
Cognition-oriented approach (General activation and pain neuroscience education)	Presence of central sensitization
High intensity interval training and lifestyle changes	Metabolic co-morbidity

DM: diabetes mellitus; CV: cardiovascular; AGEs: advanced glycation end products; MMP: matrix metalloproteinases; TIMP: tissue inhibitor metalloproteinases

Figure legends

Fig. 1 Different phases of frozen shoulder in a continuum and characteristics and treatment options in the different irritability levels