Frozen shoulder

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Abstract

Frozen shoulder is a common debilitating disorder characterized by shoulder pain and progressive loss of shoulder movement. Frozen shoulder is frequently associated with other systemic conditions or occurs following periods of immobilization, and has a protracted clinical course, which can be frustrating for patients as well as health care professionals. FS is characterised by fibroproliferative tissue fibrosis, whereby fibroblasts, producing predominantly type I and type III collagen, transform into myofibroblasts (a smooth muscle phenotype), which are accompanied by inflammation, neoangiogenesis and neoinnervation, resulting in shoulder capsular fibrotic contractures and the associated clinical stiffness. Diagnosis is heavily based on physical examination and can be difficult depending on the stage of disease or if concomitant shoulder pathology is present. Management consists of physiotherapy, therapeutic modalities such as steroid injections, anti-inflammatory medications, hydrodilation and surgical interventions; however, their effectiveness remains unclear. Facilitating translational science should aid in development of novel therapies to improve outcomes among individuals with this debilitating condition.

[H1] Introduction

Frozen shoulder[1], also known as adhesive capsulitis, is a common shoulder disorder manifesting as pain and progressive loss of shoulder movement. FS can be either primary or secondary, which refers to whether the condition has come on spontaneously, with no known cause or trauma (primary FS), or whether it is associated with trauma, surgery or other pathology, such as subacromial pain (secondary FS). FS typically progresses through three overlapping stages, with the predominate symptoms of pain and loss of motion (stage I: inflammation/'freezing'), stiffness (stage II: 'frozen'), and then resolution of symptoms (stage III: 'thawing'). However, this classification remains contentious, as many patients still experience symptoms and functional restrictions long after this period.

FS is characterised by fibroproliferative tissue fibrosis **(Figure 1**) of the shoulder capsule, which is thought to be modulated by mediators that include cytokines, growth factors, and enzymes, in particular, matrix metalloproteinases (MMPs), with increasing evidence of the involvement of inflammatory mediators and various immune cells. The histological characteristic of FS is a matrix of type I and type III collagen containing fibroblasts and myofibroblasts, resulting in an imbalance between tissue extracellular matrix (ECM) degradation, remodelling and regeneration.Although knowledge of risk factors of FS, pathophysiology, and enhanced treatments are still emerging, both basic and clinical research (and consequently therapeutic advances) lag behind that in other musculoskeletal conditions, such as inflammatory arthritis and osteoarthritis.

A true evidence-based model for the management of FS has yet to be defined, with a wide spectrum of treatments available. Management varies according to the stage of the disease and range from early pharmacotherapy and associated physiotherapy versus later approaches such as surgery (manipulation under anaesthesia (MUA) and arthroscopic capsular release (ACR)), extracorporeal shockwave therapy, hydrodilation, injections (sodium hyaluronate injection, collagenase treatment, and experimental approaches that require validation in clinical trials. FS therefore remains a challenge to treat, with a large proportion of patients still failing to attain complete resolution of symptomology. Indeed, while FS is often regarded as a self-limiting disease (1–2 year recovery), various studies have shown that many of the symptoms associated with FS, such as stiffness and pain, persist in 20–50% of patients[2-4]. Thus, further work is required to identify more effective treatment options for these patients. This Primer presents the current knowledge of the basic and clinical science of FS and highlights its clinical presentation, natural history, risk factors, pathoanatomy and pathogenesis. Furthermore, we provide evidence-based treatment guidelines in the form of a proposed treatment algorithm. In addition, we aim to consolidate and interpret the unmet needs in the field and discuss the barriers that need to be overcome to attain better outcomes for all patients with FS.

[H1] Epidemiology

[H2] Prevalence

The lifetime prevalence of FS is estimated to be 2–5% of the general population, and FS affects ~8% of men and ~10% of women[5,6]. FS is most common in the fifth and sixth decades of life, with the peak age in the mid-50s[7]. In up to 17% of patients with FS, the other shoulder becomes affected within five years[4,8].

It is debatable whether FS as a condition is truly unique to the shoulder. Indeed, there are case reports of occurrences of adhesive capsulitis in the knee, hip and ankle[9,10], although they are exceptionally rare. Contractures and fibrosis do frequently occur in the knee and elbow, although without the potential for the spontaneous resolution seen in the shoulder[83,84].

[H2] Risk factors

FS has been linked to a range of comorbidities, including cardiovascular disease[11], Parkinson disease, stroke[12], hyperthyroidism and, in particular, diabetes mellitus, where the incidence of FS can reach close to 60%[13-16]. FS has also been linked to hypothyroidism[17], hyperlipidaemia[18] and autoimmune diseases[19]. These comorbidities are found in more than 80% of individuals diagnosed with FS, with over 35% of affected individuals having more than three associated conditions[13]. Other risk factors (Box 1) associated with FS are smoking[20], obesity[7] and low levels of physical activity[21]. In addition, FS risk is increased in individuals with Dupuytren's disease, a fibrotic disorder of the palmar fascia that has a very similar pathophysiology to FS[22-24]. In addition to an association with metabolic and hormonal changes, FS has also been associated with abnormal shoulder mechanics and nerve dysfunction. This link between primary nerve dysfunction and FS was first proposed in 1959 by Thompson and Kopell[25], who proposed that reduced glenohumeral motion could result in exacerbated scapulothoracic motion, thereby stretching the suprascapular nerve, leading to a cycle of pain and shoulder dysfunction. Since then, FS has been identified in patients with a variety of primary neurological conditions. FS is a cause of shoulder pain and dysfunction in patients after radical neck dissection[26], acute cerebrovascular aneurysm surger and subarachnoid haemorrhage[27] and in individuals with Parkinson disease[28]. Furthermore, FS, as identified by shoulder capsule volume on arthrography, is the leading cause of hemiplegic shoulder pain after stroke[29].

[H1] Mechanisms/pathophysiology

[H2] From homeostasis to disease

The shoulder joint capsule is a lax fibrous sheath that encloses the joint. The healthy capsule is collagenous in structure, composed primarily of dense type I collagen and elastic fibre bundles with limited vessels and nerve fibres. The main cell type within this membrane are fibroblasts, which maintain capsule health by producing ECM proteins that provide a supportive yet flexible structure.

In FS, the typical collagen structure is disrupted by gradual fibrosis of this connective tissue membrane and thickening of the adjacent synovial membrane[30]. These fibrotic changes are accompanied by inflammation, neoangiogenesis and neoinnervation [31,32,33,34]. The consequence is a reduced joint volume and increased stiffness of the capsule, causing restricted movement and pain. In the following sections we describe how the shoulder capsule and associated structures progress from lax fibrous membrane to a fibrotic hypervascular structure that drives the clinical course of FS.

[H2] Stages of FS

FS progresses through three characteristic stages,[1] each with associated arthroscopic and histological changes.[6] Neviaser et al. initially described four stages of disease (stage I–IV) in 1987[1], which was modified in 2010 to three clinically-based stages (stage I–III)[35] (**Figure 2**). Stage I is characterized by pain without appreciable limitation in motion, and is associated with an inflammatory synovial reaction on arthroscopy, and with hypervascular synovitis with rare inflammatory cell infiltrates and normal capsular tissue on biopsy. Clinically, stage II involves ongoing pain with progressive limitation in motion. Intra-articularly, there is ongoing synovitis and progressive capsular contracture. On arthroscopy, there is hypervascular synovitis and loss of axillary folding. Histology shows hypertrophic, hypervascular synovitis now with perivascular and subsynovial scar formation. Stage III is marked by ongoing stiffness clinically, and is associated with loss of the axillary recess, fibrosis, and minimal synovitis on arthroscopy. Biopsy of patients with stage III FS reveals dense, hypercellular collagenous tissue to mature fibrosis with a thin synovial layer, similar to other fibrosing conditions.

[H2] Inflammation

Recent years have seen the musculoskeletal scientific community direct its attention to investigating the mechanisms underlying the inflammatory and fibrotic changes associated with FS to elucidate the aetiological, cellular and molecular pathways. Although a single unifying cause is yet to be identified, several key mechanisms have been implicated in the pathogenesis of FS. One of these is chronic, unresolved inflammation. Histological analyses of tissue biopsy samples from affected patients consistently reveal chronic inflammation, which is associated with increased vascularity, fibroblast proliferation, synovial membrane thickening and increased ECM deposition.[7–10] Various immune cells have been identified in

capsular tissue from patients with FS, including B cells, macrophages, mast cells and T cells[36-38]. There is growing evidence indicating a reciprocal homeostatic relationship between immune cells and stromal cells within soft tissue, in both health and disease, and as we enter the single-cell genomic age, there are emerging data of the presence of discrete subtypes of immune cells in the capsule of patients with FS, including several subpopulations of dendritic and T cells[39]. Immune cells and their mediators have been implicated in driving the progression of many fibrotic disorders, and there are now the beginnings of a greater appreciation for their role in soft tissue diseases. While it is simple to explain the presence of immune cells in a purely pathological context, their homeostatic and inflammation-resolving role in soft tissues is now evident. For example, a subtype of macrophage (those expressing *LYVE1* and *MERTK*) that has been identified in patients with rheumatoid arthritis (RA) who are in remission[40] are phenotypically similar to a population of macrophages that are present in healthy shoulder capsule but are reduced in the capsule of patients with FS[39]. Loss of these homeostatic or resolutory cells could indicate a function for these macrophages in maintaining healthy tissue.

[H2] Pro-inflammatory cytokines

As FS has been historically described as a chronic fibrotic disease of the shoulder capsule, the main emphasis of cytokine studies has been on the role of TGFß. Many studies have unequivocally implicated TGFβ in fibrotic disease, and FS is no exception. TGFß is highly expressed in FS tissue[41] and can induce numerous cellular fibrotic responses, including ECM protein production, fibroblast proliferation, increased myofibroblast differentiation and collagen gel contractility[42]. The link to fibrosis will be discussed later in this section. Other inflammatory mediators, including IL-1, IL-6, IL-10, GM-CSF, M-CSF, PGDF and TNF, are also dysregulated in diseased capsule[43,37] and may drive inflammatory and matrix responses. Fibroblasts cultured from diseased capsule produced elevated levels of pro-inflammatory cytokines (such as IL-6, IL-8 and CCL-20) in comparison to healthy capsular fibroblasts[44].

Evidence suggests a prominent role for IL-17A in FS. FS tissue contains T cells ($CD4^+$ and $CD8^+$ T cells, among other subtypes), which produce IL-17A, whereas T cells are predominantly absent from healthy shoulder capsule[39]. In this study, IL-17A induced greater pro-fibrotic and inflammatory responses in FS fibroblasts compared with fibroblasts from healthy tissue as a result of greater levels of the IL-17A signalling receptor (IL-17RA) on fibroblasts from diseased shoulders. The potential pathological effects of IL-17A are notable due to its similar effect observed in tendinopathy[45], where anti-IL-17A treatment (secukinumab) which is currently under clinical trial for this soft tissue disease[46].

The levels of IL-33, which can also act as an alarmin (also known as a damage-associated molecular pattern (DAMP)), are also elevated in FS tissue[47]. Alarmin release has

been described in other chronic musculoskeletal conditions, such as RA and osteoarthritis [48,49,50]. A study examined H&E-stained capsular tissue from patients with FS and found fibroblastic hypercellularity and increased vascularity as well as high levels of the alarmins IL-33, high-mobility group protein B1 (HMGB1), S100A8 and S100A9; the levels of these alarmins were correlated with the severity of patient-reported pain[47]. These alarmins can be released from immune and stromal cells and may mediate crosstalk between the two compartments.

Advanced glycation end products (AGEs) have been associated with inflammation, and these increased production and accumulation of which is seen in diabetes and routine ageing. AGEs can act as immune modulators by attracting cells that release pro-inflammatory cytokines to coordinate degradation and renewal of ECM. Capsular tissue of patients with FS had higher immunoreactivity, blood vessel formation and perivascular adipocytes compared with that in healthy capsule tissue[51].

[H2] Neural and vascular changes

The hypervascularity that is associated with inflammation has also been proposed to play a key role in the development of FS symptoms.[20] Hypervascularity is prominent across histological studies on FS, particularly in the rotator interval.[7,8] This is the result of neoangiogenesis, which is demonstrated by overexpression of the haematopoietic cell surface marker CD34[9,21] and vascular endothelial growth factor (VEGF) in both diabetic[22] and non-diabetic[23] patients with FS. Neoangiogenesis is accompanied by neurogenesis, which is likely driven by increased expression of the nerve growth factor receptor p75.[9] In patients with FS, the degree of neo-innervation is correlated with the frequency of night pain and expression of HMGB1.[24] In addition to an increase in the density of nerves, there is also an increase in acid-sensing ion channels (ASICs), calcitonin gene-related peptide (CGRP) and substance P[13,25], which are upregulated in hyperalgesia and chronic pain. CGRP in particular is a key connection between the nervous and immune systems. CGRP is released by the synaptic terminals of pain sensing neurons and acts on lymphocytes, macrophages and mast cells, among others,[26] resulting in increased production of pro-inflammatory mediators and further immune cell recruitment. In addition, expression of the melatonin receptors MTNR1A and MTNR1B is upregulated in FS in response to the pro-inflammatory cytokines TNF and IL-1B[27], which in turn induces ASIC3 and IL-6 expression, leading to further pain and inflammation. Combined, these features might explain why pain, particularly night pain, is such a prominent feature of FS. Central sensitization in FS has not been comprehensively studied and so remains speculative, but could explain why some patients are resistant to current interventions and may benefit from a different approach.

[H2] Matrix changes

Fibrosis is the fundamental process manifesting in FS. Fibroblasts are the resident cell within the joint capsule and are responsible for producing the ECM that forms the structure of the tissue. In normal homeostatic conditions, type I collagen is the primary matrix protein produced, whereas the more immature and disorganised type III collagen[52] is deposited under pathological conditions, owing to the requirement for accelerated ECM turnover. In addition, the production of several other structural matrix proteins is increased in FS, including vimentin, fibronectin and tenascin C[53]. Both matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), which regulate matrix remodelling, are dysregulated in FS. MMP1–4, MMP7–9, MMP12–14 and TIMP1 and TIMP2 are implicated in FS[53]. These proteinases have a vital role in ECM turnover, with the balance between MMPs and TIMPS crucial in matrix remodelling and homeostasis, as highlighted by the development of FS in 50% of recruited patients in an anti-cancer treatment trial using a TIMP analogue[54].

Interestingly, many of the fibrotic facets of FS fibroblasts have been attributed to the effects of increased TGFß production. TGFß has long been known to induce transdifferentiation of fibroblasts to myofibroblasts, and myofibroblasts are a hallmark of FS and other fibrotic conditions[55 56 57]. In addition, there is now a greater appreciation of the potential role of other cytokines, including IL-1, IL-4, IL-13, and IL-17A, in fibrosis. One such aspect of fibrotic disorders that may be under cytokine regulation is the phenomenon of fibroblast activation. Activated fibroblasts show higher expression of CD44, CD55, CD90 (THY1), CD106 (also known as VCAM1), CD248 (also known as endosialin), podoplanin, uridine diphosphoglucose dehydrogenase, prolyl-4-hydroxylase and prolyl endopeptidase FAP (also known as fibroblast activation protein) compared with control healthy fibroblasts, which are associated with inflammatory cytokine and matrix dysregulation[46]. Elevated expression of these proteins by fibroblasts is a phenotype of several musculoskeletal diseases including frozen shoulder, and activated pathogenic fibroblasts produce more pro-inflammatory proteins compared with healthy fibroblasts[44]. However, whether the increased expression of these proteins is itself directly responsible for the pathological effects of activated fibroblasts or whether it is just an epiphenomenon of fibroblast activation remains unclear[58].

[H2] Metabolic factors

Multiple researchers have proposed that certain conditions, such as hyperlipidaemia and hyperglycaemia, predispose patients with FS to propagation of pro-inflammatory and pro-fibrotic signalling cascades. Multiple studies have found a strong association between diabetes mellitus and FS,[45–47] particularly in the setting of long-term hyperglycaemia.[48–51] In addition, FS in diabetic individuals tends to be prolonged and refractory to non-operative treatment compared with that in non-diabetic individuals.[52] This association is likely multifactorial, resulting from chronic low-level inflammation in diabetic individuals as well as

the presence of AGEs. Pro-inflammatory cytokines that are consistently elevated in diabetic patients, including TNF, IL-6 and IL-1B,[53] are also present at high levels in the capsule and synovium of patients with FS.[8] Furthermore, AGEs show increased immunoreactivity in both diabetic and non-diabetic patients with FS.[54] AGEs contribute to fibrosis and inflammation across other organ systems in diabetic individuals through multiple mechanisms.[55] Firstly, AGEs form cross-links between collagen molecules, leading to resistance to proteolysis and reduced tissue compliance.[56] Second, AGEs stimulate the production of pro-inflammatory and pro-fibrotic cytokines and growth factors in stromal and immune cells through activation of the receptor for AGEs.[57] Finally, AGEs may also contribute to the imbalanced MMP and/or TIMP activity that is found across diabetic organ systems.[58]

Elevation in serum lipids and cholesterol is also associated with the development of FS, both in conjunction with diabetes and separate from it.[47,59,60] Inflammatory lipoproteins, which are associated with vascular inflammation and immune reaction, are independent risk factors for the development of FS.[61] Furthermore, the level of increase in serum lipids and glucose is inversely correlated with the Constant score (a measure of patient-reported pain and shoulder function) in patients with early FS,[62] supporting the role of these blood markers in disease progression. Transcriptional profiling of samples from patients with FS (using RNA sequencing) revealed that the greatest differential gene expression was in the peroxisome proliferator-activated receptor-γ (PPARγ) pathway,[63] suggesting a central role for altered lipid metabolism in the pathogenesis of FS. Interestingly, patients taking lipid-lowering medications (such as statins) are not at an increased risk of developing FS, unlike those taking anti-hyperglycaemic medications.[47] This observation suggests that either a reduction in serum lipids or lipid-lowering medications might be protective, which is consistent with the known anti-inflammatory and anti-fibrotic effects of statins in other conditions[59, 60].

In addition to hyperlipidaemia and hyperglycaemia, both hyperthyroidism and hypothyroidism are associated with increased risk of developing FS.[46,64,65] Calcitonin is likely the connection between thyroid dysfunction and FS, as calcitonin deficiency is a feature of both disorders.[66,67] The connection between calcitonin and FS was first noted when postmenopausal women being treated for osteoporosis with salmon calcitonin showed improvements in their FS symptoms.[68] Salmon calcitonin reduces TGFβ, type I collagen and type III collagen synthesis as well as fibroblast adhesion in cultured cells,[69] all of which are key mediators of fibrosis in FS. These results were confirmed in a double-blind, randomized, controlled trial in which intranasal calcitonin treatment improved shoulder pain and function faster than placebo in patients with FS.[70]

In summary, the pathophysiology of FS is not yet clear but accumulating evidence is starting to clarify the roles of inflammation, angiogenesis, neuromodulation, and fibrosis in this disease (Figure 3).

[H1] Diagnosis, screening and prevention

[H2] Diagnosis

The diagnosis of FS is fraught with ambiguity, inconsistency, and confusion for clinicians. Many patients can present with signs and symptoms of FS (pain, and global restriction in movement) but not have pathological changes of the joint capsule[61]. Despite the many diagnostic labels and familiar patterns of presentation with FS, there are currently no formally recognised diagnostic criteria. Consensus studies indicate that pain, particularly at night and with sudden or unexpected movements, along with a global loss of active and passive movement of the shoulder, are reliable clinical identifiers[62]. While these are all undoubtedly characteristic features of FS, they lack sufficient differential diagnostic capability to distinguish FS from other shoulder pathologies.

Pain in FS is often reported in a wide and diffuse pattern around the shoulder, scapula, chest and into the upper arm, usually above the elbow, which, in its early stages, can make FS indistinguishable from other shoulder pathologies, such as rotator cuff tendinopathy, joint arthrosis and pain from cervicogenic sources. Pain in FS is often described as constant, deep, and severe. Loss of shoulder range of motion (ROM) is a key feature of FS pathology but objective clinical markers that are deemed to constitute positive findings are rather nebulous.

[H3] Clinical assessment. Loss of passive and active ROM is inherently associated with FS but criteria are conflicting. Thresholds range from a reduction of 30% in two of three unspecified directions[63], to 50% loss of external rotation compared to the contralateral side[64]. However, there is a lack of reliability in differentiating movement loss from capsule pathology resulting from other potentially more serious pathologies or from self-limiting movement owing to kinesiophobia and protective pain guarding[61,65,66].

Reliably and accurately assessing shoulder movement in an individual with severe pain is a clinical challenge. Often, what appears to be an abnormal loss of range can be a patient self-limiting due to pain or fear. It is therefore recommended that movement is assessed in a variety of positions with differing levels of support. For example, the key movement of external rotation, if found to be reduced in standing position, should also be assessed in the supine or lying position with the arm and trunk supported (**Figure 5**). Similarly, assessing shoulder elevation by lifting the arm overhead could be compared with lowering the head and trunk below a supported arm. A noticeable disparity in ROM is more

likely to represent kinesiophobia and movement inhibition as opposed to true capsular restriction.

As capsular tissue is non-contractile, isometric muscle testing in the mid-range of movements should elicit little pain provocation in patients with FS (Figure 5). This can be a useful screening tool when considering other diagnoses such as rotator cuff tendinopathy. Assessment of the cervical spine is also essential to eliminate possible cervicogenic pathology such as nerve root irritation causing radicular pain.

***[H3] Imaging*.** Plain radiographs of the glenohumeral joint are often suggested to be taken to ensure that there is not substantial degenerative joint changes that could also present with pain and motion loss and therefore confound the diagnosis of FS. However, in practice, a working diagnosis can often be made on the basis of a good medical history and simple clinical examination, with X-rays not necessarily required in primary care environments[67]. It has been suggested that routine radiography may not confer superior diagnostic accuracy of serious pathology to good clinical questioning and physical examination[68].

The use of advanced imaging modalities such as ultrasonography and magnetic resonance imaging (MRI) to diagnose FS has been proposed. Findings such as axillary capsule thickening and/or obliteration of the axillary recess, coracohumeral ligament [66] and rotator interval (RI) thickening, and/or hypervascularity are considered indicative of FS pathology if the imaging results matches the clinical presentation[69,70]. Indeed, advanced imaging in refractory FS cases can be extremely important in detecting undiagnosed soft tissue tumours, although these undiagnosed tumours Are present in fewer than 1% of FS cases[66]. However, imaging does not offer superior diagnostic information beyond a medical history and physical examination and is therefore not recommended for routine workup[71] however MRI may be useful if there is a clinical suspicion of another serious pathology with similar symptomology to FS.

[H2] Screening and prevention

With new research and an associated understanding of the complex pathophysiology of FS, it is increasingly apparent that the lack of clarity surrounding diagnosis of FS is, in part, due to a historically oversimplified approach to this disease that does not consider the heterogeneity of individuals with FS.

As discussed above, FS has been associated with myriad systemic diseases, such as diabetes mellitus, cardiovascular disease and thyroid disorders. Although robust evidence of a causal relationship between these conditions and the development of FS is lacking, there are theories regarding the potential mechanisms that might underlie an increased risk of developing FS. These conditions are associated with chronic low-grade inflammation[21],

which has no mechanism of injury and is marked by elevated levels of active pro-inflammatory cytokines but the absence of the increased neutrophil abundance associated with acute inflammation[72]. The influence of hyperglycaemia on FS risk is mediated by pro-inflammatory cytokines, which are elevated in the capsule and synovium of patients with FS [73]. Raised levels of serum cholesterol and pro-inflammatory lipoproteins have also been detected in FS and are risk factors for cardiovascular disorders[74]. Thyroid-stimulating hormone (TSH) levels also seem to be correlated with severity of FS[17].

Routine haematological analyses and blood biochemical tests to assess for the presence of inflammatory or metabolic markers are not routinely performed in patients with FS. Although these markers have been shown to be risk factors, their prevalence across the FS population and the impact they may have on disease trajectory and their relation to causal mechanisms remains unknown.

A process that has received little attention to date is the role of chronic or persistent pain. Chronic pain is now viewed as a long-term condition in its own right and has been identified as a global health priority[48,75]. Central pain mechanisms are known to be present in long-standing shoulder pain and could potentially play a greater role in FS than previously considered[76,77]. Chronic pain could be compounded by low self-efficacy, pain perceptions and health behaviours such as fear avoidance and kinesiophobia, which can be associated with poor outcome[78].

Individuals with traits of anxiety and depression might be at higher risk of longer duration of symptoms and poorer prognosis[79]. The independent FS risk factors smoking and obesity have the potential to further exacerbate levels of disability, as their presence, along with sleep deprivation, lower pain thresholds[80-84].

Individuals with recalcitrant symptoms for whom traditional mechanically-driven treatments have been unsuccessful often require multi-specialty, multi-modal input to address the complex physical, emotional and social dimensions that are the consequences of chronic pain conditions. Like screening for existing comorbidities, validated screening measures for dimensions such as fear avoidance beliefs, pain self-efficacy, sleep disturbance and mood are not routinely used with this cohort of patients[85-88]. Further research in this area is needed to determine whether such screening tools would be of value when determining individual patient treatments and likely outcomes.

[H1] Management

The pathogenesis of FS remains incompletely understood. It is therefore unsurprising that well-defined, evidence-based management guidelines are lacking. In general, a patient with FS can seek non-surgical treatments, such as physiotherapy, medications, and

corticosteroid injections, or more invasive options, such as surgical interventions. Whether disease duration can be influenced with treatment, and the efficacy of each intervention, is unclear, as the evidence for most interventions is mixed[35]. Therefore, current treatment of FS focuses primarily on symptom reduction, that is, pain relief and restoring mobility and function.

[H2] Non-operative management

There is consensus that non-operative management is the initial treatment of choice for frozen shoulder[89]. Many non-operative management strategies have been suggested for use in patients with FS. One of the reasons for this is that patients present with a wide array of symptoms and varied levels of disability, which may relate to disease stage. Consequently, it is suggested to adopt a treatment intervention suitable for the disease stage and pain level of the patient and there is growing evidence for this approach[90,91]. In addition, as patients with FS often have high pain levels and functional limitation in combination with a long duration of symptoms, they are often motivated to try every possible intervention that might help them. As symptoms may improve with time in a large proportion of those with FS, it is easy to consider the intervention as the reason for improvement, when in fact this may not be the case.

[H3] Patient education. Informing the patient about FS and discussing the natural history is one of the most important initial interventions. The mysterious and uncertain nature of FS can be worrisome and perplexing. Good advice and education reduces patient anxiety and results in subjective improvement of symptoms[92]; therefore, clearly explaining the evidence-based knowledge of FS natural history, such as expected duration, can have substantial effects on pain and function. It is important to inform patients of the options available to manage FS themselves and to give them simple and clear strategies to modify their occupational or recreational activities as required. It is therefore paramount that all healthcare providers provide the same message to reduce confusion, contradiction, and negative stress factors. Another important factor in patient education is noting the response to interventions or activity, which differs for each stage; for example, in early FS, no increase in pain and inflammation should be allowed, whereas in the middle and late stages, 24 hours of pain increase could be allowed [93].

[H3] Physiotherapy.

Physiotherapy provides accelerated pain relief[94] and/or improvement in ROM[35,94-96] compared with no treatment. However, these improvements are mostly short-term, without demonstrated reduction in disease duration. It is suggested that the level of irritability of the patient be used to define the appropriate intensity of the chosen management strategy[93,97,98]. Irritability levels

are mainly based on the intensity of pain. For example, in patients with high irritability (pain level at least 7/10), the intervention should be at an intensity that is not inducing extra pain, while in patients with moderate irritability (pain level 4–6/10) the intervention will increase in duration and intensity, and patients with low irritability (pain <3/10) will be able to perform increased duration stretches, with allowance for some pain or discomfort[99].

Several mobilization and stretching techniques (for example, four-direction shoulder-stretching[100] and inferior capsular stretching[101]) are effective in early and late stages of FS for pain relief [102,103] and can be recommended for increasing ROM and function [93,97]. One of the proposed mechanisms that might explain pain reduction in patients with FS involves the sensory input that activates the endogenous pain inhibitory systems[104]. Further study is clearly warranted to determine if endogenous pain inhibitory systems are indeed involved in manual therapeutic interventions around the shoulder. However, for patients with FS who are in their first high irritability stage, the use of passive mobilization or capsular stretching can be counterproductive and can even increase the inflammatory response[105]. However, a study comparing a combination of manual mobilisations and shoulder exercises to a glucocorticoid injection found that the physiotherapeutic combination probably results in less improvement in the short term but a similar number of adverse events[106], although no clinically important differences were noted at 6 or 12 months. Other mobilization techniques, such as Codman's pendulum exercises (passive mobilization of the shoulder while bent over), do not show a substantial difference for pain or ROM[107] compared with other techniques. Unfortunately, there is insufficient evidence to quantify the ideal frequency of mobilization. The intensity of stretching exercises should be determined by the patient's irritability level, since stretching beyond painful limits in a highly irritable patient results in poorer outcomes [93,97]. In addition to a patient's irritability level, the Total End Range Time (TERT) can be used to report the dose applied to the patient and evaluate progression [108]. TERT is the total amount of time that the joint is positioned at its end range and is proportional to the increase in passive ROM [109]. The importance of the right treatment intensity is highlighted again by a prospective study that compared intensive passive stretching and manual mobilization to supportive therapy and exercises within the pain limits, which demonstrated better shoulder function in the supportive group at the end of the 2 years follow-up period[110]. However, currently there is little evidence to support joint mobilizations over other non-operative interventions [97]. As such, the exact effects of exercises, the extent to which they are effective, and the format of exercise therapy that is the most effective is uncertain[111]. Preliminary evidence shows that supervised exercise therapy is more effective than unsupervised exercise therapy at home[112].

Resistance-based exercise may also have an important role in patients with FS,

476 although this approach has been poorly researched. The addition of strengthening exercises
477 to a multimodal programme with mobilization and electrostimulation seems to result in
478 improvements on pain, ROM, function, and muscle strength [113,114]. These improvements were
479 not seen with the addition of scapulothoracic exercises, mobilization, and electromagnetic
480 therapy to a similar multimodal programme[115-117].

481 The role of extracorporeal shock wave therapy (ESWT) has been investigated in the
482 treatment of frozen shoulder. In a randomized, double-blind, placebo-controlled trial comparing
483 radial ESWT to placebo shockwave therapy in 106 participants[118], substantial improvement in
484 function, pain and ROM occurred in the group who received shockwave. In a trial of patients
485 with primary frozen shoulder[119], focused ESWT produced superior pain outcomes compared
486 with oral prednisolone. A systematic review of 20 randomized controlled trials found some
487 evidence in favour of ESWT for reduction of pain in frozen shoulder, although the authors of
488 the review highlighted issues around the quality of evidence and were unable to perform a
489 meta-analysis. For now, definitive conclusions about the efficacy of ESWT as an adjunct to
490 treatment in frozen shoulder cannot be made[120].

491 Other physiotherapy modalities, such as cold, heat, electrical modalities such as
492 transcutaneous nerve stimulation, pulsed electromagnetic field therapy or low-level laser
493 therapy, are proposed to have positive effects on pain in patients with FS. However, as these
494 modalities are typically applied as adjunctive interventions, the individual effect of each
495 technique on the natural course of FS is difficult to define. Consequently, there is only weak
496 evidence in favour of techniques such as shockwave therapy, shortwave diathermy, pulsed
497 electromagnetic field therapy, low-level laser therapy, therapeutic ultrasound, or electrical
498 stimulation to reduce pain and improve shoulder ROM in patients with FS[97,121].

499 Mirror therapy is a promising mode of exercise therapy that seems to be effective in
500 the treatment of FS. This approach aims to restore the congruence between motor output and
501 sensory output [122] and has been beneficial for patients with FS for improving pain, function,
502 ROM in flexion and abduction and general health, although further research is needed [123].

503 Besides exercises that specifically target the shoulder, general physical activity is
504 recommended for general health, well-being[93], improving mood and sleep, [124] and the
505 prevention of depression [124]. Physical activity can help to reduce or reverse the effects of a
506 sedentary lifestyle, which is often associated with an increase in chronic low-grade
507 inflammation and the development of insulin resistance [125].

[H3] Pharmacotherapy. Common medications for patients with FS include paracetamol or acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. The evidence for the use of paracetamol in patients with FS is limited, but it may be useful when there are contraindications to other medications [126-128]. Paracetamol inhibits cyclo-oxygenase and is active both peripherally and centrally. FS has been shown to be an inflammatory process followed by fibrosis, and therefore theoretically NSAIDs should be more effective in the early inflammatory stage than in the later fibrotic stage [14]. However, this has not yet been shown clinically. NSAIDs might be used for pain relief, but do not have an effect on ROM[35]. In addition, NSAIDs influence the serotonergic system, which may provide some benefit in modulation of perceived pain in addition to their direct anti-inflammatory effect[126]. Oral corticosteroids provide quicker pain relief compared with placebo, but this effect has not been seen in the long term, and in some cases this treatment exacerbate symptoms owing to rebound pain after their discontinuation[35,90,102,103].

Intra-articular corticosteroid injections (CSIs) are recommended in the inflammatory or early stages of FS, prior to the emergence of capsular contraction, to provide pain relief and reduce inflammation [129-132]. Histologically, intra-articular CSIs have been associated with decreased fibrosis proliferation [132]. CSIs are more effective than placebo, but do not change the long-term (6- and 12-month) outcome[133]. CSIs are more effective than physical therapy in decreasing pain in the early stages of FS [35,90,102,103,134], but the difference is minimal in the long term [94]. CSI alone has no effect on ROM but a combination of CSI and physiotherapy improves ROM [102]. In general, CSI in early stage (stage I or II) FS results in greater improvement in pain and function than in late (stage III or IV) FS[135]. Although risks are low, there are potential complications with the use of intra-articular CSI, including avascular necrosis, infection, muscle complaints, and pain increase [136-138]. Intra-articular CSI can also lead to a transient increase in serum glucose, which may be relevant in diabetic patients with FS.

[H3] Alternative interventions. There is limited and mixed data for several other interventions, including sodium hyaluronate injection[139,140], suprascapular nerve block[141,142], collagenase treatment[143], botulinum toxin[144], and hydrodilatation[145,146] for use in FS, with the most supporting evidence for botulinum toxin and hydrodilatation.

Hydrodilatation therapy refers to intra-articular injection of a large volume of sterile saline with or without corticosteroid to distend the capsule. Hydrodilatation therapy is a promising intervention that is gaining in popularity over the past 10 years[147-149]. A meta-analysis found that both CSI and hydrodilatation with corticosteroids provided superior short-term pain relief, ROM improvement, and function compared with placebo, with ROM

improvements persisting to I beyond 24 months [149]. Hydrodilatation with corticosteroids was found to have a greater benefit than CSI[150].

Following its successful use in Dupuytren's disease, collagenase *clostridium histolyticum* (CCH) has also been utilized to treat FS. . CCH is typically given in a series of 3 injections over 6 weeks. A randomized study showed improvement in subjective function with CCH but no notable increase in ROM compared with placebo[151]. Another study found a greater improvement in ROM at 3 months with CCH than with exercise therapy alone[143]. Histological examination of capsular tissue in a rat model of FS revealed less fibrosis with CCH injection than with CSI or saline[152]. These data support a potential role for CCH in the management of FS.

In conclusion, while many interventions have been described, the most reliable benefits are from steroid injection and NSAIDs in stage I, physiotherapy in stage II/III, and advancement of physiotherapy to mirror or resistance exercises in Stage III (**Table 1**).

[H2] Operative management

After ruling out other causes of pain and stiffness of the shoulder, the patient should be informed that the natural history of the condition is eventual resolution in most patients. However, symptoms and disability persist in some cases, and surgical management may provide a faster, more complete recovery. The aim of surgical approaches in FS is to release the fibrous, thickened and tightened glenohumeral joint capsule and associated contracted ligaments to improve ROM of the glenohumeral joint, and to decrease pain.

[H3] MUA. The aim of MUA is to tear the shoulder joint capsule and thereby improve ROM. In an anaesthetized shoulder, the procedure involves applying a passive stretch to the glenohumeral joint, in all shoulder ROM directions. There are conflicting opinions as to the ideal time to perform MUA in patients with idiopathic FS, from as soon as FS is diagnosed [153,154] to up to 12 months of failed non-operative treatment [1,91,155]. Several studies have cited improved patient outcomes from MUA in more than 80% of subjects[103,154,156-158].

[H3] ACR with or without MUA manipulation. ACR involves cutting and removing the thickened, swollen, inflamed abnormal capsule under direct arthroscopic control. ACR is a safe and an effective modality in treating FS[155,156,159-163] and may offer distinct advantages when compared to other methods of treatment. For example, direct visualization of the affected joint allows for diagnostic confirmation and enables additional pathology to be ruled out. The effectiveness of ACR has been demonstrated in multiple studies, with a dramatic reduction in pain scores, increased ROM as well as overall increased shoulder function[163],[164].[161 165 160 162].

[H3] Comparison of ACR and MUA. UK FROST [166] is the largest multicentre randomized trial in FS, which compared early structured physiotherapy [107], MUA and ACR. Early

structured physiotherapy and post-procedural physiotherapy programmes were standardized at 12 sessions over 12 weeks. At the 12-month primary endpoint, most participants improved to near full function, as determined by the Oxford Shoulder Score (43 out of 48), a quality of life outcome score. Oxford Shoulder Scores were significantly better in the ACR group than in the MUA and early structured physiotherapy groups (p <0.01), while Oxford Shoulder Scores were higher with MUA than with early structured physiotherapy alone. Economic analysis in the UK FROST study [166] showed that MUA is more costly (£276) than early structured physiotherapy, while ACR was substantially more expensive (£1,734) than early structured physiotherapy. All three treatments led to substantial patient recovery, with no clear superiority for any approach. ACR resulted in patients requiring the least further treatment, but is the most expensive, was associated with higher risks, suggesting it should only be utilised when less costly and less invasive interventions fail. Early structured physiotherapy was accessed faster, but more patients required further treatment.

In summary, the surgical options of MUA and ACR may provide an earlier, potentially more complete resolution of pain and restoration of ROM and function, although these interventions should be considered only after non-operative management approaches have failed.

[H1] Quality of life

FS results in significant functional disability and reduction of quality of life, as shown using various questionnaires and scores, such as the visual analogue scale [125], disabilities of the arm, shoulder and hand (DASH) score, the 36-item Short-Form (SF-36) health survey, and the Hamilton depression rating scale and anxiety scores[78]. It is not clear what factors predict the severity of pain and disability as well as quality of life in patients with FS[167]. The prolonged disease course in FS results in greatly impaired sleep and everyday activities and, therefore, markedly affects the physical, psychological and social quality of life of patients[168,169,167]. FS has been linked to anxiety and depression[169]. Comorbidities are associated with increased disability and reduced quality of life in these patients but not with the severity of pain. Psychiatric disorders can also affect pain, disability and quality of life as well as patients' characteristic and objective symptoms[170], but the effect of these parameters on FS requires further study.

The patient's perspective and experience has been largely overlooked in research of FS. This is startling, particularly when considering the vast numbers affected by this condition and the subsequent healthcare cost and implications of long-term symptoms and reduced quality of life as a result of FS. A study[72] exploring patients' perception of FS treatment highlighted the severe pain and loss of function that impacted the daily lives of patients with FS, alongside sleep disturbance and inability to perform work duties. Delay to diagnosis was

a cause of frustration and worry for the patients interviewed, as the severity of pain often led patients to suspect that a more sinister cause of pain might underlie the symptoms. Patients also highlighted a lack of a definitive diagnosis alongside unclear pathways for management of their condition and emphasized a mismatch between their perception of the impact of FS and that of clinician's. Although only involving a small number of patients, this study stresses the need for a better understanding of FS, for both clinicians and patients. To improve a patient's experience with FS, a prompt diagnosis, a clear understanding of the treatment options available and an explanation of the course of this painful condition are priorities. Aligning treatment goals with those of patients suffering with FS should underpin clinicians' interaction with patients who present with FS and future research into this condition. Clearly, the patient's voice has not been heard enough in studies thus far.

[H1] Outlook

Research in recent decades has provided improved understanding of known risk factors and disease progression, and, importantly, insight into the basic mechanisms driving the disease process, with the potential for new therapeutic targets. Despite affecting 5% of the world's population[156], research into FS lags behind that of other musculoskeletal conditions, and integration of new findings into a comprehensive treatment strategy that can be applied across the spectrum of disease (from early- through to late-stage disease) and medical practitioners (physiotherapists, primary care physicians, and surgeons) remains elusive. Of note, emerging basic science research needs to be assimilated into clinical practice to provide clinicians with a principal picture of the pathophysiological processes involved in FS.

[H2] Physiotherapy advances

The component of physiotherapy that includes mobilization techniques beyond the threshold of pain in early disease can be detrimental to patient engagement and is explained by the unique mechanosensitive properties of fibroblasts and the fact that the inflammatory response makes fibroblasts more sensitive to progressive mechanical stress[110]. However, progressive stretching exercises up to tolerable pain levels results in an increase in the MMP/TIMP ratio, thus favouring collagen remodelling, and importantly is superior to supervised neglect[171]. Therefore, some mechanical stress is advantageous in promoting remodelling of the ECM, especially in the later stage of the condition. Thus, further research is now required on the role of precision 'tailored' physiotherapy guidelines for the treatment of FS.

[H2] Translational advances

Novel bench to bedside treatment strategies have been suggested to intervene in the inflammation–fibrosis cascade in different ways. Given the dominant role of the TGFβ pathway in FS, gene silencing (with small interfering RNAs (siRNAs)) was utilized to knock down *SMAD4* (a central mediator of TGFβ signalling) in a rat model of FS induced by immobilization[172]. Suppression of the TGFβ pathway impaired the inflammatory response and myofibroblast differentiation and resulted in better shoulder ROM and an increased joint volume in FS mice than in control rats. In a placebo-controlled, double-blind, randomized trial, the thyroid hormone calcitonin (delivery by nasal spray) was moderately efficacious in improving pain and functional outcomes in FS[173]. Another study found an association between expression of alarmins (such as IL-33, IL-17A, and HMGB1) and pain levels[47], highlighting a potential role for anti-cytokine therapies in treating FS; however, additional preclinical work is required before progressing towards potential first in human FS trials.

[H2] Clinical advances

Clinically, knowledge about pain management and the association between pain and other psychological disorders, such as depression and anxiety, is expanding. In addition, the central element of night pain in FS has a major impact on patients' overall wellbeing owing to interruption of sleep, and the emotional and societal implications of these factors are not well understood. These issues may play an important role in the management of FS in the future as these associations are clarified.

The lack of well-conducted prospective longitudinal studies to adequately investigate prognostic risk factors for FS is a barrier to furthering our understanding of this pathology. Although none of the risk factors discussed earlier are known to have a direct causative role, their high prevalence in the FS population indicates that reducing or improving them would be useful. Therefore, clear, simple, and actionable health promotion advice regarding smoking cessation, physical activity, stress, and sleep levels, diet and weight management is recommended. Even slight increases in physical activity and exercise can substantially reduce the relative risks of both morbidity and mortality associated with many of the proposed risk factors for FS[174]. Increasing walking time to just 2 hours a week significantly reduces the risk of cardiovascular disease in individuals with diabetes[175] and both aerobic and resistance-based exercise demonstrably reduce morbidity risk[176-178]. In the near future, 'frozen shoulder' could be considered an umbrella term for emerging subgroups of this pathology, each with their own aetiology, disease progression, prognosis and management strategies. While novel therapeutic modalities to treat FS are evolving, there should also perhaps be a concomitant focus on preventing the important and avoidable risk factors involved. Population health messages delivered consistently by health care professionals across all sectors should be considered core tenets within musculoskeletal care. This should

include an honest, open yet compassionate discussion and acknowledgment that it may take weeks, months or years for the benefits of lifestyle changes to make any demonstrable impact on patient outcome[179].

Clinical trials in FS remain challenging, with inconsistencies in outcome measures, heterogeneity of patient stage at recruitment and the requirement for prolonged follow up. Although advances have been made toward a consensus in terms of a core set of outcome domains for use in shoulder trials[180], several important issues need to be addressed, including heterogeneity in study design, stage- or patient-specific treatment protocols, and how we classify response to any treatment regimens – specifically those altering specific physiotherapy regimes. Further research is now required to link the genetic, epigenetic, environmental and therapeutic factors together so that curative or preventive therapies for FS can be obtained. These findings should give impetus to the development of new diagnostic techniques, evidence-based screening methods and more targeted personalised interventions, which underscore the need for a multidisciplinary approach to the management of FS.

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Author contributions

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Table 1. Treatment approaches for frozen shoulder based on stage of the condition.

Stage	Characteristics	Treatment approaches		
		Pharmacological	**Physical**	**Other adjuncts**
Stage I	Inflammation	NSAIDs CSI	Home exercises	Patient education Hydrodilation TENS
Stage I	Freezing and frozen	NSAIDs	Physiotherapy: Mobilization	Patient education Hydrodilation Shockwave therapy
Stage III	Thawing	NA	Physiotherapy: Resistance-based	Surgical management if symptoms do not dissipate

NA, not applicable; NSAIDs, non-steroidal anti-inflammatory drugs; TENS, transcutaneous electrical nerve stimulation.

Figure legends

Figure 1. Structural changes during frozen shoulder. a | The healthy capsule is collagenous in structure, composed primarily of dense type I collagen and elastic fibre bundles with limited blood vessels and nerve fibres. The main cell type within this membrane is the fibroblast, which maintains capsule health by producing extracellular matrix (ECM) proteins that provide a supportive yet flexible structure. **b |** In FS, there is fibrosis and thickening of the connective tissue membrane as well as the adjacent synovial membrane[17]. **c |** Fibroproliferation results in an increased number of fibroblasts producing more ECM proteins, resulting in a dense and poorly organized fibrillar structure. These fibrotic changes are accompanied by inflammation, neoangiogenesis and neo-innervation [18,19,20,21]. The consequence is a reduced joint volume and increased stiffness of the capsule, causing restricted movement and pain.

Figure 2. The stages of frozen shoulder. Frozen shoulder is classified into three clinical stages based on pain level and the severity of range of motion (ROM) limitation. Stage I is the inflammatory stage and includes gradually worsening pain but limited effect on ROM. Stage II involves plateauing of shoulder pain levels but is mostly associated with increasing stiffness that results in considerable loss of shoulder function that particularly affects a patients' normal activities of daily living. Stage III is characterized by reduction of pain (particularly night pain), with pain usually at the end of ROM, and a very gradual improvement in stiffness over a number of months to years.

Figure 3. Molecular pathophysiology of frozen shoulder. A trigger, typically systemic (for example altered metabolic status), extrinsic (for example shoulder immobilization after trauma or surgery) or intrinsic (rotator cuff pathology) induces a pro-inflammatory, profibrotic environment in which various soluble factors influence cell behaviour. Substance P induces production and release of neuropeptides by mast cells, which affects fibroblast activation and matrix production. Pro-inflammatory cytokines, such as IL-1, IL-6, HMGB1 and IL-17A, and growth factors stimulate fibroblast activation, proliferation and positive feedback loops driving further cytokine and growth factor production. Cytokines also induce T cell activation and production of IL-17A, while the abundance of macrophage subsets, B cells and dendritic cells are all increased in FS human biopsy samples. All these factors, together with mechanical stress and matrix turnover imbalance, induce fibroblast transdifferentiation to myofibroblasts, which leads to tissue fibrosis and contracture.

Figure 4. Proposed algorithm for differential diagnosis of frozen shoulder. This algorithm may aid in differentiating frozen shoulder from other painful and/or motion-limiting conditions of the shoulder, such as glenohumeral joint (GHJ) osteoarthritis [48], subacromial pain and acromioclavicular joint (ACJ) pathology. Decisions are made based predominantly on physical examination (loss of passive external rotation) but other techniques and methods also provide useful diagnostic information. SLAP, superior labrum from anterior to posterior.

Figure 5. Key examination techniques for frozen shoulder. Various movements of the arm of the affected shoulder are used to assess pain and limitations of range of motion (ROM) in individuals with FS.

Box 1. Risk factors for frozen shoulder.

Systemic risk factors

[b1] Diabetes mellitus

[b1] Hypothyroidism

[b1] Hyperthyroidism

[b1] Hypoadrenalism

[b1] Hyperlipidaemia

Extrinsic risk factors

[b1] Cardiopulmonary disease

[b1] Cervical degenerative disc disease

[b1] Cerebrovascular disease

[b1] Humeral fracture

[b1] Parkinson’s disease

[b1] Post axillary surgery (breast carcinoma)

[b1] Radiotherapy

Intrinsic risk factors

[b1] Rotator cuff tendinopathy

[b1] Rotator cuff tears

[b1] Biceps tendinopathy

[b1] Calcific tendinopathy

[b1] Acromioclavicular arthritis

Frozen shoulder is a fibroproliferative disorder of the shoulder characterized by pain and progress loss of shoulder mobility. In this Primer, Millar et al. provide an overview of the epidemiology, pathophysiology, diagnosis and treatment of FS, as well as how it affects patients' quality of life.