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Pain without inflammation in rheumatic diseases

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A B S T R A C T

Chronic pain is a common symptom in rheumatic diseases, and the patient with pain and no signs of inflammation poses a challenge to the physician.

Notably, all rheumatic diseases have components of non-inflammatory pain and a higher prevalence of fibromyalgia compared to the overall population.

Hypothetically, a chronic pain stimulus may have stronger impact in a chronic inflammatory state, and the process towards a pain condition may be influenced by individual predisposition for development of chronic pain. In addition, the features of peripheral and central pain processing may be exacerbated by inflammation, and disturbed pain processing may be a feature contributing to widespread pain.

We herein review and describe the prevalence of chronic pain and different pain modalities in the most common rheumatic diseases. In addition, the background mechanisms of non-inflammatory pain in rheumatic diseases are discussed.

Finally, we here review the current strategies for pain management, with a special focus on non-inflammatory pain. The key message is that pain management should be individualized and based on a thorough pain analysis with investigation of the pain modality, localization and pain intensity. Other factors to consider are the underlying rheumatic disease and treatment, the patient's mental and physical health status and psychological factors.

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Introduction

Chronic pain accompanying a rheumatic disease is common, and relief of pain is one of the primary goals with all anti-rheumatic therapies. The prevalence of widespread pain is higher in most rheumatic conditions than the normal population [1].

In arthritis, pain is the most common presenting symptom [2] and central nervous system (CNS) mechanisms have been implicated in the pain experience by arthritis patients, for example, a generalized increase in pain sensitivity in rheumatoid arthritis (RA) patients [1]. The importance of CNS changes in endogenous pain modulation (i.e., facilitation, central sensitization/disinhibition) is further underscored by the high co-morbidity between rheumatic diseases and generalized pain syndromes such as fibromyalgia (FM) [5], where specific dysfunctions of endogenous pain modulation have been shown [3].

The recognition of chronic pain as a "disease itself" has emerged during the last decade, and implicates a condition where pain is the major problem, and other symptoms are of lower impact to the patient. In rheumatic diseases, this may depict the state where the inflammatory disease is adequately controlled, with or without powerful immune suppressive therapy. Although the patient displays no inflammatory joints, no inflammation in other organs and no inflammation systemically, the pain is still evident. This condition is challenging and may result in despair and escalation of ineffective therapies. For example, fibromyalgic RA patients were shown to be treated to a higher extent with biologic agents [4], although presumably these agents do not help the pain problem. Moreover, recent investigations give at hand the insufficiency of current anti-rheumatic pharmacological treatments to improve mental health, which is closely related to pain [5].

Altogether it is important to acknowledge pain with no inflammation in rheumatic diseases and specifically identify the origin of the pain, in order to avoid overtreatment, which may lead to escalation of the pain problem.

This review article will first describe the prevalence of chronic pain and different pain modalities in the most common rheumatic diseases. Then will follow a background of the mechanisms and key features of clinical chronic pain, and finally practical suggestions of management of non-inflammatory pain in the rheumatic patient.

Chronic and non-inflammatory pain in rheumatic diseases

In a similar way that the inflammation patterns differ between different rheumatic diseases, also pain symptoms and pain localizations may differ substantially. Pain may be accompanied with inflammatory actions and processes in several organs, but pain may also exist without any apparent signs of inflammation [6]. The following section will describe pain modalities in different rheumatic diseases.

Rheumatoid arthritis

Patients with RA commonly report pain as their most important problem [2], often deeply affecting disability and quality of life.

It is now well agreed that pain in RA is dependent on many factors, among which is inflammation in the joints, and pain sensitization, bone destructions, and other factors may also contribute to pain. Moreover, pain progress in RA is dynamic and may display in different forms and severity during the disease course.

In the early stage of the disease, pain is often prominent before the development of visual joint swelling. This arthralgia may be intermittent and may affect both small and large joints. In the synovium, not only inflammatory mediators act directly on the nociceptors, but also the distension of the joint will activate pressure-sensitive receptors and cause pain transmission. Morning stiffness may represent a clinical feature of active synovitis, but comprise another modality that may be difficult to distinguish from pain [7].

Treatment of RA with nonsteroidal anti-inflammatory drugs (NSAIDs) and biological and nonbiological disease-modifying antirheumatic drugs (DMARDs) are usually effective to relieve from inflammatory pain symptoms [8]. However, disabling pain may persist even when the inflammatory

disease is controlled [9]. In a previous study, we report that over half of the patients with early RA continue to have significant pain in the early stage after initiation of methotrexate treatment [10]. There is also a documented discrepancy between degree of systemic inflammation and pain experience [11]. In a subset of patients, the initial joint pain may persist although the inflammation resolve, and subsequently develop widespread pain, which is also known as "fibromyalgic-RA" [12]. The symptom burden of this "secondary" FM does not differ from primary FM [13]. The chronic widespread pain in RA may acquire typical neuropathic features, for example, has the pain experience in established RA without arthritis been described as a "burning pain" and sudden attacks similar to electric shocks, that are well-documented symptoms of neuropathic pain [14]. These and other clinical findings support a key role of neuro-sensitization mechanisms of nociceptive pathways in the CNS in the establishment of chronic arthritic pain.

In addition, the prevalence of FM is higher in RA than in the population [1]. The pronounced co-morbidity between FM and rheumatic inflammatory diseases, and the fact that a generalized increase in pain sensitivity has been reported in patients with long (>5 years) but not short (<1 year) duration of RA [6] suggest that disturbances in pain modulation can also be important for pain perception in many patients with RA.

Several investigations have indicated that RA is associated with an altered state of central pain processing. In a study of structural brain components, RA patients compared to healthy controls displayed increased grey matter (GM) density in the basal ganglia, which are involved in pain processing and motor control [15]. Moreover, using positron-emission tomography (PET), Jones et al. found that RA patients compared with controls displayed reduced activity to heat induced pain in the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (dlPFC), with an additional decrease in inferior parietal lobe (IPL) and posterior insula (pIns) [16]. In line with these data, we have earlier shown increased resting-state connectivity in RA patients compared to healthy controls between frontal midline regions such as mid cingulate cortex and supplementary motor areas and bilateral primary sensorimotor cortices [17].

Other factors that may affect chronic pain in RA are joint damage and destructions.

In advanced RA, pain is markedly improved following joint replacement surgery, and it is believed that the mechanisms for arthroplasty effects on pain may be multiple in a pain relieving context. Thus, surgery may permit increased exercise of the joint and overall physical activity, which may act in a pain relieving way. However, at a group level, there are no clear associations between increased radiological progression and pain in RA patients [18,19]. Notably, RA pain might also in some elderly patients be due to osteoarthritis (OA), although OA is usually affecting other joint areas [20].

Ankylosing spondylitis

Ankylosing Spondylitis (AS) is characterized by recurrent pain mainly in the lumbar and thoracic back, and sacroiliac joints, and manifestations of peripheral arthritis, enthesitis, and ocular manifestations in some patients. NSAIDs and biological agents are usually very effective in the immune suppression and the pain of many patients is nociceptive and decreases during the course of treatment.

However, the prevalence of FM in AS is higher than in the general population; recent data display a FM prevalence of between 12 and 25% [21–23]. A higher prevalence of FM in women with AS was also detected [22]. Interestingly, a comparison between AS and non-radiographic axial spondyloarthritis (NrAxSpa) revealed a higher FM prevalence in the latter, 14% compared with 6% for AS [24]. Several investigations have indicated a neuropathic pain component of AS. Thus, Wu et al. showed, using painDETECT questionnaire and neuroimaging in 17 patients with AS compared with healthy controls, that 11 of the AS patients had painDETECT scores of at least 12, considered to be consistent with presence of neuropathic pain [25]. Moreover, brain MRI showed that AS patients compared with controls displayed cortical thinning in the primary somatosensory, anterior cingulate and anterior mid-cingulate cortices, insular area as well as the supplemental motor cortex. There was also an increased gray matter volume in the thalamus and putamen in AS [25]. Interestingly, PainDETECT scores were correlated with thinning in the primary somatosensory cortex and increased gray matter in the motor cortex, the ACC, prefrontal cortex, thalamus, and striatum. These results are in line with a central pain process in some patients with AS [25].

Psoriatic arthritis

Psoriatic arthritis (PsA) is a chronic arthritis disease affecting almost a third of patients with skin psoriasis [26]. In PsA, pain is elicited both by joint inflammation, but also to a great extent by enthesitis [27]. According to a recent statement from the group of outcome measures in rheumatology (OMERACT), pain has been considered a core outcome in trials and observational studies [28]. A recent retrospective investigation depicts entheseal PsA as comparable to dactylitis concerning impact on quality of life and disability [29]. Persistent pain has been reported in more than half of PsA patients in spite of inflammation control on conventional/biologic disease-modifying therapy [30] and patients often report allodynia and hyperalgesia, indicative of non-inflammatory pain. The prevalence of FM in PsA is 16–22%, and is a significant factor in the evaluation of PsA disease activity [31,32]. For example, in a recent study of 63 PsA patients, Hojgaard et al. detected a presence of Widespread pain (WSP) in 35%, and the presence of WSP decreased the chance of reaching minimal disease activity (MDA) [33]. Moreover, FM was shown to contribute significantly to decreased quality of life in PsA [34]. One important question has been whether enthesitis and FM tender points may be mis-judged, which has been thoroughly discussed [35]. This notion was partly confirmed in a study involving 60 patients with PsA, including 13 (17.8%) with FM [32]. The FM group displayed an increase in Leeds Enthesitis score, Health assessment questionnaire (HAQ) and Bath Ankylosing Spondylitis Disease activity index (BASDAI) score, whereas objective measures such as swollen joint count, psoriasis severity index and c-reactive protein displayed no differences. Thus, FM may negatively impact both the patient-reported disease activity measures and clinical investigation of enthesitis, which should be taken into account when considering disease activity in patients with a FM component. There are so far no reliable data on if Musculoskeletal ultrasound (MSUS) may improve the diagnosis of "true" and reversible enthesitis in this context.

Juvenile chronic arthritis

Juvenile Chronic arthritis (JCA) is a multifaceted disease with a reported incidence of 0.50 cases per 1000 children [36]. Approximately two-thirds of patients have a self-limiting disease, but a significant amount of children experience painful complications, including joint destruction and deformities, osteoporosis and growth abnormalities, potentially resulting in impairment of psychological development and difficulty with daily activities [36]. Chronic pain syndromes are common in children. Earlier investigations have reported that 25% of JCA patients report pain intensity in the middle or higher range of the pain measurement scales [37]. Since the development of more efficient biological DMARDs, the number of patients with severe pain has decreased; however, the pain problem in JCA remains significant for some patients in spite of inflammation control. There is insufficient data on the pain mechanisms in JCA, but the pain pathogenesis and progression to widespread pain in some patients is likely similar to the mechanisms in RA and PsA.

Systemic inflammatory diseases

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterized by focal lymphocytic infiltration in the major and minor salivary glands leading to progressive loss of glandular function and symptoms of dry eye and dry mouth [38]. Pain is common in pSS, and may evolve as a consequence of arthritis, arthralgia, peripheral neuropathy or other musculoskeletal disease manifestations. In addition, a common symptom in pSS is fatigue, with a prevalence of 60–80% [39]. Pain may augment fatigue and there is also evidence that fatigue can enhance pain [40]. A specific feature of pSS is the polyneuropathy, which comprises the most common neurological complication of the disease [41,42]. While the majority of these patients present with paresthesias, sensory loss, ataxia, motor deficits, and disturbances in the autonomic nervous system [43], a smaller group may develop a form of neuropathic pain that comprises small-fiber neuropathy (SFN) [44]. SFN has been defined as a dysfunction and degeneration of the distal terminals of small fibers. The condition involves Aδ and unmyelinated (C) nerve fibers that are responsible for the transmission of cold and nociceptive

signaling, innocuous warm and cold sensations, as well as high threshold mechanical, thermal and chemical stimuli (C fibers) [44].

The pain can be spontaneous, but in some cases may also present as allodynia or hyperalgesia. SFN pain is usually severe, and typically begins in the feet, whereas the hands are rarely involved [45]. The modality of the pain is often described by the patient as burning sensation, sometimes with added itching. Routine clinical nerve conduction studies do not measure alterations in thermal sensitivity, so for diagnosis of SFN a more comprehensive quantitative sensory testing (QST) is needed, although also this method is not perfectly reliable [46]. Treatment of SFN includes common agents for neuropathic pain, although the results are mostly marginal and seldom lead to strong improvement.

Similar to inflammatory arthritis there is comorbidity with FM and widespread pain in pSS. The prevalence of widespread pain in pSS is 35–50% according to different reports [47]. FM in pSS has been strongly related to the presence of fatigue and mood disorder [48]. Interestingly, other reports have shown a higher frequency of FM in seronegative patients and patients without extra-glandular involvement [49], the latter suggesting that other mechanisms than immune activation are involved in the induction of widespread pain in pSS.

Systemic lupus erythematosus (SLE) commonly involves arthritis and arthralgia, and pain, especially in earlier stages, may be closely related to inflammatory joint disease [50]. The arthritis is non-erosive, seldom causes joint deformities and often precedes other manifestations of the disease. A specific reversible joint manifestation is Jaccoud's arthropathy, which despite severe deformations of small joints in hands, normally causes little or no pain [51]. Other manifestations of SLE, such as pleuritis, pericarditis may be painful, but may also remain painless. Abdominal pain is reported in about one third of the SLE patients, and besides serositis and ascitis also mesenteric vasculitis and pancreatitis are conditions underlying this symptomatology. Central and peripheral nervous system involvement is a feature of SLE and headache and migraine have been reported in a majority of SLE patients [52]. These symptoms may also be a component in a more extensive involvement of the CNS, i.e., neuropsychiatric SLE (NPSLE), often also characterized by cognitive impairment, memory loss, and, in severe cases, seizures and stroke [53]. Moreover, peripheral neuropathy is another feature of SLE, often characterized by sensory and sensorimotor loss. Like pSS (see above) some SLE patients may also present with SFN [54]. FM has been reported to affect up to 33% of SLE patients [55,56].

Pain in systemic sclerosis (SSc) is mainly caused by digital ulcers, Raynaud's phenomenon, joint contractures and gastrointestinal (GI) disorders [57]. The most severe pain is caused be digital ulcers, which may lead to chronic pain and loss of function [58]. Moreover, tendinitis [59] and polyarthralgia [60] may cause significant pain, especially in early diffuse SSc. There are no population-based studies of prevalence of FM in SSc, but a recent investigation that used screening questionnaires for FM estimated the prevalence to 27.8% in SSc as compared with 22.6% in RA [61].

In vasculitis, such as granulomatous polyangiitis, pain is usually accompanying clinical inflammatory manifestations, such as musculoskeletal pain with commonly arthritis, ear-nose and throat involvement and affection of the eye [62]. In addition, peripheral neuropathy is common, and may be painful also after immunosuppressive treatment [63]. FM is probably as common in vasculitis as in SSc; however, there are only few reports that have investigated this [23].

Other rheumatic diseases

Crystal-induced joint pain, such as gout and arthritis caused by calcium pyrophosphate crystals, is characterized with an intense inflammatory reaction and severe pain [64]. The pain is most often directly related to the arthritis flare and typically resolves completely. However, the chronic forms of gout may display chronic pain in affected joints; however, the characteristics of this pain and/or potential pain sensitization have not been investigated.

In septic arthritis, the pain is usually severe in the affected joint [65]. After treatment with antibiotics, the pain may resolve, or there may be remaining destructions that causes pain. Reactive arthritis (ReA) is also transient in its nature. However, a significant part of patients reported problems with arthralgia 12 months after the initial episode in a small follow-up study of 21 patients with confirmed diagnosis of ReA [66].

Non-inflammatory pain mechanisms

Pain is acknowledged as a multidimensional entity, and has been defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage", which has been recently reviewed [67]. Previously, four main groups of pain have been identified; nociceptive, neuropathic, nociplastic and psychogenic pain [68]. Nociceptive pain normally depicts pain related to tissue damage, and could be the result, for example, of arthritis or enthesitis. Neuropathic pain is elicited by various forms of damage to the peripheral or CNS and often anatomically defined, corresponding to a dermatoma, for example, after nerve injury. The new term nociplastic pain depicts pain related to disturbances in the pain regulating systems, which is a prominent feature of FM. Psychogenic pain is uncommon, and only found in association with severe psychosis. Importantly, different groups of pain will respond to different treatments, so it is vital to make a thorough pain analysis identifying these conditions. Moreover, a certain extent of overlap of the pain groups is common, and should be considered. For example, systemic inflammatory diseases such as SLE may present both with arthritis, causing nociceptive input, and vasculitis that may lead to nerve injury and neuropathic pain. Another overlap may be chronic arthritis and nociplastic pain, i.e. concomitant FM. Inflammation or injury at the site of the affected nerve is the origin of inflammatory or neuropathic pain. Peripheral mediators of the pain process are neuropeptides and cytokines. On the CNS level, the pain transmission is affected by neuro-mediators released from astrocytes and microglia, which modulate the transmission of the pain signal. On the cerebral level is the recognition of pain and the pain experience.

Peripheral pain sensitization

In rheumatic diseases, the peripheral inflammation in joints and entheses may lead to activation of pain signaling from the nerve endings. These mechanisms are elicited by algogens, cytokines, chemokines and immediate, leading to the known symptoms of joint pain and also the inflammatory characteristics of swelling, redness, elevated temperature, pain and loss of function [7]. In addition to the acute effect, the inflammatory mediators may also sensitize the peripheral nerves, leading to high spontaneous activity, a low threshold of activation in nociceptive fibers and local release of neuropeptides [69]. The process of sensitization will subsequently lead to sensitized spinal neurons. Key cytokines involved in peripheral sensitization in arthritis include TNF-alpha, IL-1 beta, IL-6, and IL-17 [70].

Central pain sensitization

Chronic pain signaling leads to central sensitization of the spinal cord. Moreover, central pain processing is enhanced in several rheumatic diseases [71].

Central pain is affected by psychological components of pain perception [72] and may be accompanied with other symptoms that are centrally mediated, i.e. insomnia, cognitive deficiencies, memory disturbances, and fatigue [73,74]. The diffuse noxious inhibitory control (DNIC) is a physiologic regulation system with descending pathways normally modulating pain signaling. This pathway may be altered in its function when exposed to repeated painful stimuli, and DNIC is known to be dysfunctional in FM [3]. Moreover, at a group level, RA patients display increased pain sensitivity not only in the inflamed joints, but also in non-inflammatory sites [75]. Also reduced thresholds for pressure and thermal pain have been reported in RA patients [73]. Cerebral activity associated with evoked pain in RA has been shown to be modulated by the psychological state [76].

Lessons from animal models of arthritis

Several animal models of arthritis have also been investigated concerning pain mechanisms, and emerging data suggest the importance of arthritis-induced pain for development of pain sensitization.

The models previously used for arthritis studies in rats and mice are inflammation induced by adjuvants, such as Freund's complete adjuvant (CFA), collagen and also antigen-induced or serum-transfer arthritis. The most frequently used model of RA is collagen-induced arthritis (CIA) [77]. Briefly, immunization with CII in CFA leads to production of anti-CII antibodies directed to the same major CII epitopes as in patients with RA [78]. CIA arthritic mice display decreased climbing, locomotion and grooming behaviors [79]. Moreover, mice with CIA feature thermal hypersensitivity [79,80] and mechanical hypersensitivity that develops before onset of inflammation [81,82] and lasts for at least 28 days after the arthritis onset [79]. Antigen-induced arthritis (AIA) and streptococcal cell wall (SCW)-induced arthritis are monoarthritis models in mice and rats [82–84]. They are both characterized by an acute phase with severe joint swelling and infiltration of immune cells. Subsequently the arthritis transforms into a chronic stage with hyperplasia of the synovium, loss of cartilage and bone destruction of the affected joint. Mice affected by AIA display mechanical hypersensitivity of the inflamed knee joint in the acute stage [85]. Also, thermal hypersensitivity (up to 6 weeks), is a feature of the affected paw. Mechanical hypersensitivity has also been reported with SCW, and progress in line with inflammatory flares.

Models of transient arthritis and remaining pain behavior have been widely studied concerning mechanisms of pain in arthritis. The two most studied models for pain are collagen antibody induced arthritis (CAIA) model and K/BxN arthritis model [82]. In CAIA, a cocktail of anti-CII antibodies is injected i.v. or i.p. followed by a booster lipopolysaccharide injection after 3–5 days. The K/BxN model is based on transfer of serum. Both models develop swelling of the small joints in front and hind paws within a week of the injection. The arthritis is transient and visually resolves after two to four weeks after induction. Mechanical hypersensitivity precedes inflammation, is maintained during arthritis and persists after the joint inflammation has been resolved. In this phase, the mice usually display thermal hypersensitivity and reduced locomotion [82]. Another interesting observation is the responsiveness to analgesic agents. In the transient arthritis model, mice in the post-treatment phase did not respond to NSAID but to gabapentin. Furthermore, the responsiveness to biological agents has been investigated in several experimental arthritis models. Thus, TNF-blockade is efficient in joint pain behavior in the acute phase of both CAIA and AIA, and also maintained in the non-inflammatory phase [82].

Interestingly, transfer of RA-specific autoantibodies, anti-citrullinated peptide antibody (ACPA) IgG isolated from patients, to naive mice leads to pain behavior in the absence of joint inflammation within a week and lasts up to 28 days after injection. The pain behavior is accompanied by decreased locomotor activity and bone erosion and the mice display thermal hypersensitivity [86,87]. These findings suggest that arthralgia may involve ACPA associated mechanisms, and the definition of a “pre-RA” stage have been discussed [88].

Collectively, the results from experimental arthritis models have contributed important information concerning pathogenesis of inflammation-induced pain. First, there is massive evidence that a transient arthritis is associated with post-inflammatory increased mechanical hypersensitivity, which is comparable to the allodynia and hyperalgesia observed in human chronic arthritis, and which may persist when inflammation is under control. Second, the arthritis-induced neuropathic pain-like mechanisms are responsive only to centrally acting analgesics and not anti-inflammatory agents, suggesting that the pain suppression of the latter (for example, NSAIDs) is dependent on active inflammation. This finding supports the need for thorough pain analysis in rheumatic patients as to components of neuropathic pain in the pain problem, where anti-inflammatory treatment may be insufficient for pain relief.

Recently, there have also been several reports of sex differences in pain-like behavior as well as immunity processes in animal models of pain [89]. These data implicate that microglia are not required for mechanical pain hypersensitivity in female mice, which acquire the same hypersensitivity after adoptive transfer of T lymphocytes. These findings are of particular interest in arthritis pain research, with documented gender differences both in diagnoses of rheumatic diseases as well as in pain modalities [90]. Thus, further investigations on pain sensitization and microglial function in the context of gender may result in more targeted treatment approaches also for arthritis pain.

Finally, animal models of SLE may provide essential information on the relations between CNS-related symptoms and systemic inflammation. The MRL-model is characterized by clinical features of neuropsychiatric involvement, with a behavioral phenotype of depressive-like behavior and

visuospatial memory deficits along with increased neurodegeneration and cellular infiltration in the choroid plexus. Interestingly, all these features also remained in mice that were transplanted with healthy MRL/+ bone marrow, thereby showing absence of significant systemic autoimmunity [91]. These data show that neuropsychiatric symptoms may also remain when systemic inflammation is low, which is in line with the lack of correlation between disease activity and fatigue and other central mediated symptoms in SLE [92].

Arthralgia in the early phase of RA

The earliest stage of development of RA is pain with no objective inflammation or joint swelling, arthralgia. Recent years, it has become evident that individuals with arthralgia and positive for ACPA are of significant risk for development of RA within the next years [93].

The arthralgia phase has recently drawn much attention among rheumatology researches, and therefore a new nomenclature on the various phases preceding the diagnosis of RA was proposed by the Study Group for Risk Factors for RA [94,95].

Synovial biopsies at early stages of arthritis have shown that all features of chronic inflammation can be found as early as some weeks after the first clinical evidence of arthritis [96]. Moreover, asymptomatic joints have been shown to present with established synovial inflammation [97], but presence of inflammatory cells in the synovium is not associated with development of arthritis [98]. This has led to the hypothesis that systemic autoimmunity seems to precede synovitis, and a second hit is required for development of arthritis, for example, a trauma or a viral infection [99].

Based on the earlier data that autoantibodies such as ACPA may be present in the circulation several years before arthritis onset and also contribute to pain induction and inflammation through activation of osteoclasts, a study with B-cell blocking therapy (rituximab-treatment, single dose) vs placebo was performed including patients with ACPA-positive arthralgia. This study showed that the diagnosis of RA was delayed with 12 months; however, all patients eventually developed RA [100]. It remains to be elucidated whether this kind of strategy for early suppression of inflammation may also be beneficial for the pain course and peripheral pain sensitization.

Psychological aspects in pain and the role of pain catastrophizing

Pain is associated with an exacerbation of psychological distress, and stress can also increase pain [101]. In several rheumatic diseases, worse mental health and higher levels of depression and anxiety have been reported [102,103], and psychological factors may be of extra importance in the rheumatic patient with control of inflammation, where increased anti-inflammatory treatment is not expected to further decrease pain [6]. Both depression and anxiety may contribute to RA pain [72] and depression can be associated with inflammatory disease activity, poor treatment outcome, pain severity, and sensitivity to pain [102]. Furthermore, a history of depression is associated with reporting of worse pain in RA [104]. In SLE, disturbed sleep and depression has been shown to affect the relationship between augmented pain and reduced cognitive function [105]. Similarly, in AS, depression was shown to have a major impact on BASDAI, which is highly related to pain [106]. Also in PsA, depression is a significant contributor to augmented pain and decreased quality of life [107].

In addition to depression, there is massive evidence that catastrophizing is a key risk factor for poor pain outcome in rheumatic diseases [102,108]. This condition may also affect the response to treatment, which should be taken into account in further clinical trials. In RA, we showed earlier that the response to biologic agents was significantly decreased in patients with high baseline levels on catastrophizing assessments at baseline [109]. A recent study has shown that catastrophizing in RA may decrease after initiation of anti-rheumatic treatment, consistent with dynamic properties of these psychological factors [110]. These data are consistent with the potential of additive beneficial effects of cognitive behavioral therapies on catastrophizing and pain outcomes in rheumatic disease.

Moreover, pain has been shown to have significant impact on the patient's assessments of RA disease activity. In several studies, pain was the major predictor of patient's global assessment of disease activity (PGA) [72], whereas pain contributes less to physician's global assessment of disease activity [111]. Furthermore, the presence of FM or chronic widespread pain has significant impact on

the assessment of disease activity in RA [12,112]. Collectively, these data point to the fact that pain in the rheumatic patient may be significantly augmented by psychological factors, which also may influence the outcome of anti-rheumatic treatment. This strengthens the demand for better assessment of pain by physicians, and point to the fact that coexisting pain may need to be considered in the evaluation of disease activity.

Management of non-inflammatory pain in rheumatic disease

Pain analysis

Pain is recognized as an important warning signal that is necessary in order to protect the individual from harm and organ damage. Since the pain condition is usually multifactorial, it is recommended that the first action in pain management include a careful analysis of different factors contributing to the pain condition and severity. Moreover, at a general level, the correlation between pain and actual organ damage or inflammation is weak. It is vital to analyze the pain modalities involved, since this may affect the choice of treatment. Furthermore, the dimensions of pain, the severity, and location of pain are other modalities that are of interest in the first pain analysis.

The rheumatic patient with pain and no visual signs of inflammation represents a challenge to the physician. However, the fact that the patient displays no arthritis or skin lesions causing pain does not mean that there is no potential origin of pain. Enthesitis may be very diffuse and difficult to discern, and the help of MSUS may guide the rheumatologist in the search for causes of pain. In PsA, enthesitis may represent the major disease presentation and a cautious investigation is of particular value in this context. In AS, the differential diagnosis on inflammatory back pain, and pain remaining after adequate treatment may result in challenges. Here, a thorough anamnesis and the recognition of NSAID response are of value. In SLE and pSS, the arthritis is seldom prominent, and causes of non-inflammatory pain may be multiple, where the component of widespread pain may constitute a major part. In all rheumatic conditions, concomitant FM is overrepresented, and the pain analysis should always include a thorough clinical examination searching to find signs and symptoms of nociplastic pain, i.e. allodynia and hyperalgesia. Furthermore, assessment of potential sleep disturbances and the patient's mental health status are important components in the analysis. Finally, it is important to consider the balance between peripheral and central origin of the pain condition.

Pain management

There is no optimal way to manage non-inflammatory pain, and the individualization of treatment is a hallmark of pain management. However, it is agreed by most physicians that when a rheumatic disease is adequately treated with immunosuppressants, the pain condition remaining is best treated with non-pharmacological strategies. The advantages with this strategy are numerous. First, the pain is a multiple condition, and varies over time, meaning that it is very difficult for the physician to grasp the whole modality, and continuous follow-up is often necessary. Second, all medications may have side effects, and such disadvantages may prevent the patient from reaching a sufficient dose in effective drugs or the withdrawal of potentially beneficial agents.

Third, physical activity and cognitive behavioral therapy are well-documented for pain suppression, and physiotherapists are often motivating with the important steps of self-controlling of pain, which is important.

In the following section, an introduction of pharmacological treatment for efficient immunosuppression will be followed by a presentation of various non-pharmacological methods in pain management.

Pharmacological treatment

In the patient with rheumatic disease and uncontrolled pain, one of the first goals is to fully optimize the effects of anti-rheumatic treatment. Conventional DMARDs as well as biologics and ts

DMARDs rapidly reduce joint pain while suppressing inflammation over several weeks, maintaining these effects over months [113]. Interestingly, csDMARDs and biologics have however not been shown to substantially improve mental health [5]. Glucocorticoids in different administrations (i.a., i.m., p.o.) provide pain relief in arthritis and also in systemic diseases (i.e. SLE) with inflammatory mediated pain [114]. For biological agents, including TNF-blockers, IL-1 blockers, IL-6-blockers, rituximab, abatacept and rituximab the pain relieving effect in arthritis is paralleled by inflammation suppression and may be fast, with an onset of less than a month [7]. In spondyloarthritis including AS and PsA, biological agents such as TNF-blockers, IL-17-blockers, IL-12/23 blockers and apremilast markedly reduce joint and back pain [115]. Janus Kinase inhibitors (JAKi) including the presently registered tofacitinib and baricitinib, have proven efficacious for fast-acting pain suppression in RA and PsA (tofacitinib) [116,117]. The documented involvement of JAK as a contributor in neuropathic pain mechanisms [118] suggests that these agents may have additional effects on pain than only mediated by their anti-inflammatory mode-of-action, which have been recently discussed [113]. Although optimization of inflammatory control is essential, it is vital to consider that pain outcomes, for example, in RA may be poor despite low disease activity [9]. Moreover, NSAIDs have shown little benefit as monotherapy in patients with centrally mediated pain, such as FM [119]. Directly acting analgesics, such as paracetamol and NSAIDs, have documented short-term effects in arthritis and OA, but there is a lack of evidence for long-term efficacy of these agents in rheumatic diseases, and adverse effects need to be considered [120] (REF). Besides from anti-rheumatic agents, and of potential use in the non-inflammatory pain patient, there are a range of pharmacological analgesics, immunomodulatory agents, and serotonin-norepinephrine reuptake inhibitors available to help relieve pain in rheumatic patients. The 3e initiative involving 17 nations include a literature-review and recommendations for the pharmacologic management of pain in inflammatory arthritis [121]. The main options for pain treatment include: NSAID and acetaminophen as the first-line therapy. As second-line, alternative NSAID is recommended. As the third alternative, weak opioids are suggested when NSAIDs and acetaminophen have failed or are contraindicated.

There are few studies that have specifically investigated the effects of pharmacological agents on non-inflammatory pain in rheumatic diseases. A small study investigated effects of milnacipran in RA with widespread pain [122]. The study came to the conclusion that milnacipran had no measurable effect on RA-associated widespread pain. No pharmacological studies on widespread pain have been done in other rheumatic diseases.

Antidepressants and neuroactive drugs are frequently used in neuropathic pain, and clinically utilized by many patients with rheumatic diseases and concomitant depression. The 3e initiative for pain management recommend use of antidepressants as adjuvant therapy, with the consideration that their analgesic role in inflammatory arthritis is controversial [123]. Other neuromodulators, such as nefopam and capsaicin, have proven to reduce RA pain in small studies, but a cochrane review have concluded that the overall effects were weak, and should be balanced to a significant side effect profile for both agents [124]. Agents registered for neuropathic pain, including gabapentin and pregabalin, are alternatives, but not specifically studied in the context of rheumatic diseases. For patients with chronic pain, there is also a growing interest for natural products. These include omega-3 polyunsaturated fatty acids (n-3 PUFA), theanin, thaflavin derivatives, a-lipoic acid, curcumin and resveratrol. Some of these agents, i.e. curcumin, have shown both anti-arthritic effects to improve the outcomes on neuropathic pain in animal models [113]. The role of these agents for pain suppression in rheumatic diseases remains to be elucidated. An earlier investigation found an association between dietary PUFA intake and decreased risk of persistent pain in early RA [125], but importantly, in this study there was no association between PUFA supplementation and long-term pain suppression.

Overall, pharmacologic effects on generalized pain in rheumatic diseases are controversial and it is highly recommended to take into account the pain phenotype and elucidate whether there is remaining inflammation, or if pain sensitization seem to have developed. Moreover, the 3e initiative conclude that the presence of comorbidities, the addictive potential of the medication and the patient's preference when choosing the most appropriate pain treatment are other essential issues to consider in this context [121].

Non-pharmacological treatment

In the patient with rheumatic disease and inflammation control, pain management should always include pain analysis and consideration of various forms of non-pharmacological actions. Recently, a multidisciplinary task force defined EULAR recommendations for health professional's approach to pain management in patients with arthritis and OA [126]. Overarching principles based on expert opinion included a focus on patient-centered care, the biopsychosocial model of pain and control of inflammation. It was also stated that validation of the patient's pain experience is considered a prerequisite for trust, communication and engagement in treatment. Moreover, the ability to differentiate between types of pain was considered essential to direct the optimal pain-management strategy [126] (for recommendations, see Table 1).

Effects of exercise

In the patient with inflammatory controlled rheumatic disease and remaining pain, exercise is one of the first options for pain management. Exercise for the inflamed joints can be painful, but has been shown beneficial for central pain processing, and reduction of pain. Interestingly, earlier data from nonarthritic populations show that aerobic exercise can increase pain-detection and tolerance thresholds, as well as reduce pain intensity to a nociceptive stimulus [127]. One of the discussed mechanisms underlying analgesia induced by exercise is increased levels of endorphins [128]. Moreover, intensive training was shown to be associated with increased circulating endorphin levels [129]. The intensity of exercise seems to be important for the level of analgesia, and RCTs of aerobic exercise in patients with RA (with stable disease control) have indicated reductions in reported pain [130]. In a recent study, long-term health-enhancing physical activity was also associated with reduced pain [131]. This study also found that neither pain sensitivity nor exercise-induced hypoalgesia was affected during the training [131].

Moreover, the underlying diagnosis may affect how exercise can decrease pain. In SLE, kinesiotherapy was proven beneficial [132], but in a controlled study, high-intensity interval training could not reduce pain in PsA [133], although fatigue assessments improved. In AS, a recent systemic overview concluded significant effects of physical activity on disease activity and well-being [134].

Although most trials indicate beneficial effects of physical therapy in rheumatic diseases, it should also be noted that earlier studies depict the difficulty to maintain the recommended enhanced levels of physical activity [135]. Therefore, especially in the patient with a pain problem, continuous support and motivation by physiotherapists and other health professionals is needed.

Psychological treatment

For many patients with rheumatic diseases, complete resolving of pain is not a realistic goal. While these patients live with their chronic or intermittent pain, they develop psychological strategies that may facilitate or hinder their daily living. Notably, active coping strategies, including problem solving, reappraisal of unrealistic negative thoughts and also exercise may improve physical and psychological well-being in RA whereas more passive styles such as social isolation and avoidance tend to have deleterious effects on health and adjustment [108]. The aim of psychological interventions, such as cognitive behavioral therapy (CBT) is to improve well-being in the context of chronic pain. In detail, CBT focuses to motivate the patient in changing behavior, based on productive coping strategies and disregard unhelpful beliefs. Although CBT has well-documented effects on pain in FM [136], in rheumatic diseases the pain-relieving effects are not clearly convincing. In RA CBT has minor effects on reported pain severity, whereas the disability is improved [137–140]. In adolescents with SLE, a 6-month RCT could not detect better outcomes on pain and quality of life with CBT compared with placebo [141]. In AS, a small, un-controlled study indicated beneficial effects [142], whereas in PsA there are as yet no controlled studies of CBT on pain. Interestingly, low-grade inflammation in patients with chronic pain (without any rheumatic disease) was shown to associate with decreased CBT effects on pain and quality of life [143].

Table 1
EULAR recommendations for the health professional's approach to pain management, modified [126].

	Level of evidence	Strength of recommendation	Level of agreement task force: mean (SD)
1. Assessment by the health professional should include the following aspects (the assessments is brief or extensive depending on factors such as available time, whether it is a first or regular consultation, and the needs of the patient): Patient's needs, preferences and priorities regarding pain management and important activities, values and goals in daily life Patient's pain characteristics including severity, type, spread and quality Previous and ongoing pain treatments and the perceived efficacy Current inflammation and joint damage as sources of pain, and whether these are adequately treated Pain-related factors that might need attention: (a) the nature and extent of pain-related disability, (b) beliefs and emotions about pain and pain-related disability, (c) social influences related to pain and its consequences, (d) sleep problems and (e) obesity	4	D	9.3 (0.8)
2. The patient should receive a personalized management plan with the aim of reducing pain and pain-related distress and improving pain-related function and participation in daily life. This plan is guided by shared decision-making, the expressed needs of the patient, the health professional's assessment and evidence-based treatment options. A stepped-care approach may include, in step 1, education and self-management support (recommendation 3); in step 2, one or more treatment options by a specialist if indicated (recommendations 4 to 9); or in step 3, multidisciplinary treatment (recommendation 10).	4	D	9.0 (0.8)
3. The patient should receive education. *All patients have easy access to (1) educational materials (such as brochures or links to online resources with encouragement to stay active, sleep hygiene guidelines and so on), (2) psychoeducation by the health profession and (3) online or face-to-face self-management interventions.	1A	A	9.7 (0.6)
4. If indicated, the patient should receive physical activity and exercise. *The health professional and patient appraise whether advice to stay active, supervised physical exercise or multidisciplinary treatment is needed. *If the patient is not able to initiate physical activity and exercises without help, then consider the possibility for referral to a physiotherapist for individually tailored graded physical exercise or strength training.If psychosocial factors such as fear of movement or catastrophizing cognitions underlie a disabled, sedentary lifestyle, then consider a multidisciplinary intervention including cognitive − behavioral therapy.	1A	A	9.8 (0.8)
5. If indicated, the patient should receive orthotics. *If a patient has pain during activities of daily living which impedes functioning, orthotics (such as splints, braces, gloves, sleeves, insoles and shoes), daily living aids (such as tin opener), an assistive device (such as cane or rollator) or ergonomic adaptation (at home, workplace) can be offered. If the patient wants to use the assistive support, then consider referral to the occupational therapist, who can proceed with several actions: offer education about appropriate ways to use joints and ergonomic principles, appraise the need for the use of an orthotic or assistive device, give advice about how to acquire it, fit the customized aid to the patient, offer training in the use of it, refer to the appropriate specialist who will do this, eg. orthopedic shoe maker.	1A	A	8.6 (0.9)

6. If indicated, the patient should receive psychological or social interventions. *If there are indication that social variables or psychological factors interfere with effective pain management and functional status, then consider (depending on the severity) providing basic social and psychological management support or referral to a psychologist, social worker, self-management support program, CBT or multidisciplinary treatment. *If psychopathology (eg. depression and anxiety) is present, discuss treatment options with the patient and the patient's primary care physician.	1A	A	9.5 (0.6)
7. If indicated, the patient should receive sleep interventions. *If sleep disturbance is reported, inquire about causes (eg. pain, persistent worrying, poor sleep habits) and offer basic education about good sleep hygiene practices. *If sleep remains (severely) disturbed, refer to a therapist or program aimed at restoring sleep, or to a specialized sleep clinic.	1B	B	8.4 (1.1)
8. If indicated, the patient should receive weight management. *If the patient is obese, explain to the patient that obesity can contribute to pain and disability. Discuss accessible weight management options with the patient or signpost appropriate specialized weight management support; for example dietitian, psychologist, community lifestyle services or bariatric clinic/surgery.	1A	A	9.1 (1.0)
9. If indicated, the patient should receive pharmacological and joint-specific pain treatment according to recent recommendations. *Ask about the patient's existing use of prescribed and over-the-counter pain relief including homeopathic remedies and consider if the frequency of use is safe (not over dosing) and appropriately regular. Ask or refer for further specialist or medical advice if there are concerns or if additional pharmacological treatment may be indicated.	For references, see Ref [126]		9.5 (0.8)
10. If indicated, the patient should receive multidisciplinary treatment. *If more than one treatment options are indicated, for example, to treat psychological distress in combination with a sedentary lifestyle, and if monotherapy fail, consider a multidisciplinary intervention.	4	D	8.8 (1.1)

"Level of evidence" and "Strength of recommendation" for treatment modalities refer to specific diseases in which uniform positive effects on pain (excluding studies with "very low" quality of evidence) were observed. Overarching principles and recommendations regarding assessment are based on expert opinion.
Level of evidence: 1A; from meta-analysis or randomized controlled trials; 1B, from at least one randomized controlled trial; 2A, from at least one controlled study without randomization; 2B, from at least one other type of quasi-experimental study; 3, from descriptive studies, such as comparative studies, correlation studies or case-control studies; 4, from expert committee reports or opinions and/or clinical experience of respected authorities.
Source: Geenen et al. EULAR recommendations for health professional's approach to pain management in inflammatory arthritis and OA. ARD 2018.

It is thus possible that CBT may have more significant effects on pain outcomes in rheumatic patients with controlled or very minor inflammation; however, this remains to be elucidated.

There are also alternative psychological approaches, such as mindfulness training, which give moderate improvements in pain in rheumatic diseases [137]. In addition, acceptance and commitment therapy (ACT) has proven beneficial in chronic pain [144], but there are as yet no trials in rheumatic diseases.

The difference between ACT, mindfulness, on the one hand, and CBT, on the other, is that the formers aim to prevent consequences of chronic pain, without changing negative and counteracting thoughts, whereas CBT directs its force to individual pain control.

Comparison has revealed that CBT was more efficient for pain-control than was mindfulness training, whereas the latter was helpful for decreasing catastrophizing and enhancing coping of pain, particularly in patients with a history of depression. Thus, the presence or absence of depression may decide which of these therapies should be used for treatment of chronic pain.

The magnitude of placebo effects is also essential influencing pain outcomes. Thus, effect sizes for placebos in OA, compared with baseline or usual care, are of the order 0.4–0.5 (moderate effect size) [145]. The influence of placebo is dependent on the context in which treatments are given, for example, psychological distress, beliefs, genes, and also interactions between patients and healthcare professionals and mode of treatment delivery [146]. Interestingly, neuro-anatomic and other neuro-chemical findings are biologically valid components of the placebo response (for review see Ref. [146]). Augmentation of the placebo effects in treatment delivery in rheumatic diseases might be almost as important as developing novel pharmacological treatments in improving patient well-being.

Conclusion and future directions

Chronic pain is a common symptom in rheumatic diseases, and the patient with pain and no signs of inflammation poses a challenge to the physician.

Notably, all rheumatic diseases have components of non-inflammatory pain, and a higher prevalence of FM compared to the overall population.

Hypothetically, a chronic pain stimulus may have a stronger impact in a chronic inflammatory state, and the process towards a pain condition may be influenced by individual predisposition for development of chronic pain. In addition, the features of peripheral and central pain processing may be exacerbated by inflammation, and disturbed pain processing may be a feature contributing to widespread pain.

Pain management in rheumatic patients with inflammation control should be based on a thorough pain analysis with investigation of the pain modality, localization, intensity among other features. This information will be important to guide further management, for example, the potential that additive anti-rheumatic treatment should be considered for further pain relief. It may also be concluded that the pain type is not treatable with immunosuppression, and then neuroactive drugs or non-pharmacological treatment, such as CBT, are of value. All these specific therapies should be combined with enhanced physical activity and patient-centered care.

Summary

Chronic pain is a common symptom in rheumatic diseases, and the patient with pain and no signs of inflammation poses a challenge to the physician.

Notably, all rheumatic diseases have components of non-inflammatory pain, and a higher prevalence of FM compared to the overall population.

Hypothetically, a chronic pain stimulus may have a stronger impact on a chronic inflammatory state, and the process towards a pain condition may be influenced by individual predisposition for development of chronic pain. In addition, the features of peripheral and central pain processing may be exacerbated by inflammation, and disturbed pain processing may be a feature contributing to widespread pain.

We herein review and describe the prevalence of chronic pain and different pain modalities in the most common rheumatic diseases. In addition, the background mechanisms of non-inflammatory pain in rheumatic diseases are discussed.

Finally, we review the current strategies for pain management, with a special focus on non-inflammatory pain. The key message is that pain management should be individualized and based on a thorough pain analysis with investigation of the pain modality, localization and pain intensity. Other factors to consider are the underlying rheumatic disease and treatment, the patient's mental and physical health status and psychological factors.

Practice points

- Chronic pain is a common symptom in rheumatic diseases, and the patient with pain and no signs of inflammation poses a challenge to the physician.
- The features of peripheral and central pain processing may be exacerbated by inflammation, and disturbed pain processing may be a feature contributing to widespread pain.
- Pain management in rheumatic diseases should be individualized and based on a thorough pain analysis with investigation of the pain modality, localization, and pain intensity.

Research agenda

- To define better different states of chronic pain in relation to rheumatic diseases.
- To define predictors for development of persisting pain, which will, in turn, lead to potential early interventions.
- To understand the determinants of persisting pain despite inflammatory control of the disease.
- To maintain collaborative national and international initiatives for the development of guidance and routine collection of clinical data to support both clinical practice and research.

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