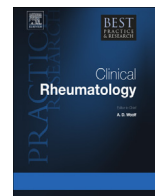




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Pain in systemic connective tissue diseases



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abstract

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SSc

Pain is frequent in patients with connective tissue diseases (CTDs), particularly those affected by systemic sclerosis (SSc) and systemic lupus erythematosus (SLE) in which it is virtually ubiquitous and can have different causes. The SLE classification criteria include pain associated with musculoskeletal involvement, which are frequently the initial symptom of SLE and can include arthralgia, arthritis and/or myalgia. Chronic widespread pain, the cornerstone of fibromyalgia (FM), is also frequently associated with CTDs.

Chronic pain has a considerable impact on mental health, and the professional and family lives of patients. It can be due to many disorders, but there are few reports concerning its prevalence during the course of other diseases.

It is essential to identify the origin of pain in CTDs in order to avoid dangerous over-treatment in patients with co-existing widespread pain. Effective pain management is a primary goal of patient care, although it has not been investigated in detail in patients with SSc.

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Introduction

Connective tissue diseases (CTDs) are characterised by multiple symptoms generally related to organ injury. One of the most frequent is pain, the perception and threshold of which may be influenced by many biological, psychological and social factors interacting with the central and peripheral nervous systems. It may be acute or chronic: acute pain is often primarily attributable to inflammation and/or damage to peripheral structures (i.e. nociceptive input), whereas chronic pain (generally defined as lasting \geq 3 months) is more likely to be due to input from the central nervous system (CNS). The chronic nature of CTDs such as systemic lupus erythematosus (SLE) and systemic sclerosis (SSc), which are often associated with pain and stress, can also trigger widespread chronic pain conditions such as fibromyalgia (FM).

Pain in systemic sclerosis

Systemic sclerosis (SSc, also known as scleroderma) is a severe rheumatic condition characterised by skin thickening and internal organ fibrosis [1] that is classically classified as limited cutaneous SSc (lcSSc), which has rare organ involvement, and diffuse cutaneous SSc (dcSSc), which has a worse prognosis and is characterised by rapid fibrosis [1,2].

Pain is a ubiquitous problem in SSc, and may be caused by digital ulcers, Raynaud's phenomenon, skin breakdown, joint contractures and/or gastrointestinal (GI) disorders [3]. However, despite its impact on the patients' quality of life, it has not been widely studied. In a large study published by the Canadian Scleroderma Research Group, 85% of the 585 patients reported pain, which is correlated with more frequent episodes of Raynaud's phenomenon, active ulcers, worse synovitis, and gastrointestinal symptoms [4]; other authors have reported similar findings and that they correlate with a poor quality of life [5e7].

SSc and Raynaud's phenomenon

Raynaud's phenomenon (RP) is the most frequent and earliest manifestation of SSc. It is caused by digital vasospasms usually triggered by exposure to cold or stress, which lead to the three phases of the classical colour change from white to blue (cyanosis) and then red (erythema), and is frequently associated with pain and sometimes with paresthesia, numbness and impaired hand function. It can be effectively treated by various classes of drugs, whose benefits include a reduction in the frequency and severity of attacks, and the prevention and/or healing of digital ulcers. The first-line non-pharmacological treatment of Raynaud's phenomenon involves avoiding or minimising exposure to cold, the use of warm gloves, and avoiding aggravating factors such as smoking and certain drugs, although these measures are more effective in the case of primary rather than secondary Raynaud's phenomenon. Pharmacological measures usually start with calcium channel blockers but, if these are ineffective, other options include topical nitroglycerin, and alpha adrenergic or angiotensin receptor antagonists. Intravenous prostacyclin analogues are warranted in severe cases, particularly if there is a threat of digital ischaemia, but they are expensive and, as they are burdened by substantial risks (including the induction of severe hypotension), close monitoring is required during their administration. Novel approaches include the use of endothelin receptor antagonists, phosphodiesterase inhibitors and statins, although their place in the therapeutic armamentarium remains to be established, and it may also be possible to combine drugs acting on different target mechanisms, although this may be limited by questions of cost.

Finally, surgical approaches (particularly thoracic sympathectomy) have fallen out of favour, probably because of improvements in pharmacological treatments [8].

SSc and digital ulcers

Often persistent and recurrent digital ulcers are one of the most frequent and burdensome clinical manifestations, and occur in more than 50% of patients. They may simultaneously affect more than one

finger, and lead to severe pain and function limitations [9]. The lack of validated guidelines has prompted a number of researchers to seek the best treatment, and a very recent study published by Giuggioli et al. tested the initial use of local lidocaine and prilocaine (25 mg of both per gram of 5% EMLA cream), followed by local and oral morphine depending on the severity of the pain as measured by means of a 10 cm visual analogue scale (VAS), and found that the deep wound debridement crucial for healing was better tolerated [10].

SSc and synovitis

Between 40% and 80% of SSc patients complain of musculoskeletal pain, which is more problematic in patients with early diffuse SSc. The pain may not be sufficiently localised to attribute it to a particular anatomical location, but a number of pain syndromes have been identified.

1. **Tendinitis:** Tendon friction rubs mainly affect patients with early diffuse SSc. They have a frequency of 23e65%, but this tends to decline over time [11,12]. They are considered to be associated with more active disease and worse outcomes.
2. **Polyarthritits:** Between 36% and 80% of patients complain of polyarthralgias, which may be more frequent in those with early SSc, although some studies have found their occurrence more equally distributed between limited and diffuse SSc [13]. The wide range of articular and non-articular changes observed in radiographs of SSc patients go from juxta-articular osteoporosis and joint space narrowing to frank erosions in the metacarpophalangeal (MCP), proximal interphalangeal (PIP), and distal interphalangeal (DIP) joints, and wrist. It has been said that bony erosions (mainly in the hands) affect 4e57% of patients who have had SSc for seven years, and joint space narrowing affects 16e92% [14]; however, concern has been raised that some of the joint space narrowing may be related to concomitant osteoarthritis and not just SSc.
3. **Rheumatoid arthritis (RA):** The recent availability of anti-cyclicitrullinated peptide (CCP) assays has led to the finding that 1e15% of SSc patients have overlapping anti-CCP antibody-positive RA. However, it should be noted that anti-CCP antibodies alone do not define RA, and it is not known how many SSc patients without RA are anti-CCP positive.
4. **Fibromyalgia (FM):** Studies reported that 48% of patients had 11 or more tender points (TPs), whereas the mean TP count was 7 (of 18) in the Malcarne study [15]. Clinical experience suggests that FM is not uncommon in patients with SSc or other CTDs, and dedicated work is needed in this field, including studies using the 2010 fibromyalgia criteria.

SSc and gastrointestinal disorders

The gastrointestinal (GI) is the second most frequently involved organ system in SSc patients [16], who often experience complications such as gastro-esophageal symptoms, abdominal pain and distension, weight loss and nutritional deficiencies, diarrhea, incontinence, and constipation.

The esophagus is the most frequently affected part of the GI tract, and up to 90% of patients describe symptoms of heartburn, regurgitation and dysphagia. These dysfunctions are probably due to smooth muscle atrophy (particularly the inner circular layer of the muscularis propria) and fibrosis affecting the distal two-thirds of the esophagus but sparing the proximal part that causes the loss of normal neural function. Lifestyle modifications and the avoidance of exacerbating food groups are often suggested first, but patients often need intensive treatment with proton pump inhibitors to control their symptoms.

Up to 50% of SSc patients report early satiety, nausea, bloating, and abdominal discomfort. The pathophysiology is not clear but it is possible that lymphocyte activation plays an important role in causing smooth muscle atrophy and collagen deposition, leading to severe ultrastructural alterations in smooth muscle cells and nerve fibres. It is thought that gut dysfunction relates to a neuropathic process in SSc patients [16].

The clinical management of gastric motility disorders can be difficult because of their poor correlations with symptoms. Dietary modifications with the addition of a prokinetic agent is often the mainstay of treatment, and probiotics may be useful in some patients. The use of metoclopramide can improve gastric motility and motor activity, and somatostatin analogues such as octreotide have also been used to induce contractile activity throughout the bowel. It has been reported that up to 18% of patients with SSc are at high risk of malnutrition due to perioral sclerosis, esophageal dysmotility and abdominal discomfort; the management of weight loss and malnutrition requires a multidisciplinary team approach in which dietitians, nutrition specialists and ward nursing staff play a crucial role.

Diarrhea can affect up to 50% of patients, who need to be fully assessed because the cause is multifactorial. Once the contributory causes of malabsorption have been investigated, symptomatic approaches such as dietary measures to increase stool consistency and use of loperamide to inhibit peristalsis and secretion can be tried; however, caution is required in order to avoid pseudo-obstruction. Cholestyramine or other bile salt acid sequestrants may be helpful [16].

The colon and anorectum are the second most frequently affected parts of the GI tract, and it has been suggested that the anorectal dysfunction reported by 50e70% of SSc patients is due to neuronal dysfunction, smooth muscle atrophy and fibrosis affecting the internal anal sphincter. Fecal urgency can arise because of reduced rectal compliance and capacity due to collagen deposition, and fecal incontinence has a significantly negative impact on the patient's quality of life. Practical specialist management such as biofeedback and bowel and pelvic floor muscle training can be offered although the evidence is limited. Surgical repair of the anal sphincter has been attempted but the long-term outcomes suggest worsening of continence and so this approach is not generally advocated [16].

It has been reported that colonic involvement occurs in 20e50% of patients, who often lack the post-prandial gastrocolic response mediated by the cholinergic pathway, thus reducing colonic motility, prolonging colonic transit and leading to constipation. Unfortunately, laxatives frequently offer little benefit: stimulant laxatives rely on contact with the bowel mucosa, which is unpredictable, and osmotic laxatives can aggravate bloating and discomfort. It has been shown that the 5HT₄ receptor agonist prucalopride accelerates colonic transit but, although the results have been promising, they have only been published in case reports. Opioid antagonists such as methylnaltrexone do not seem to be very beneficial in patients with SSc because of the nature of their bowel dysmotility. Biofeedback training is useful in the case of idiopathic constipation, but it has not been studied in SSc. There are no published data concerning the effect of sacral nerve stimulation (SNS) on constipation in SSc patients, although it is useful in idiopathic constipation; however, the drawbacks of SNS are that it is an expensive invasive procedure associated with the risks of infection, lead migration and pain.

Intestinal pseudo-obstruction is a rare GI manifestation of SSc. The treatment algorithms mention professional patient counselling, and depressive symptoms have been reported to be associated with GI involvement in SSc patients. Treating gastroenterologists should take an overall holistic approach and their patients' quality of life, functional status and depressive symptoms, whereas treatment interventions for SSc are limited [16].

Pain in systemic lupus erythematosus

SLE and inflammatory pain

Inflammation is the most frequent cause of pain in SLE patients. It is generally due to inflammatory arthritis, which is included in the clinical set of the American College of Rheumatism (ARC) classification criteria [17,18]. The arthritis is typically not erosive, does not induce joint deformity, and frequently precedes the other manifestations of SLE. It is associated with morning stiffness for more than 30 min, can be evanescent or persistent, affects the knees and the small joints of hands (PIPs), and produces objective evidence of inflammation (tenderness, swelling and effusion). A minority of patients may show deforming reducible joint involvement of the hands (Jaccoud's arthropathy) [19]. The presence of synovitis is due to the production of cytokines such as interleukin (IL)-6, IL-17, interferon (INF) alpha, IL-18, tumour necrosis factor (TNF) and B cell stimulating factor (BSF)-2, which

main responsible for immune response activation and tissue damage [20]. The clinical set of the ACR criteria includes serositis, which may present as painful or painless pleural or pericardial effusion and ascitis as a result of inflammation of the lining of lung, heart, and abdominal structures. Abdominal pain is reported by 8e40% of SLE patients but may also be due to other causes, including mesenteric vasculitis and pancreatitis [21,22].

SLE and neuropathic pain

SLE patients show a wide range of central nervous system (CNS) manifestations, including neuropsychiatric disorders and syndromes associated with the presence of auto-antibodies [23]. Although its relationship with SLE is not clear, headache and migraine are reported by 32e66% of SLE patients and may have various causes, including neuropsychiatric SLE (NPSLE) [24]. A recent study of 40 SLE patients found that 70% experienced headache (tension type headache in 37.5%, migraine in 30%, cluster headaches in 2.5%, and intracranial hypertension in 5%) but there was no association with disease activity [25,26]. A close association with cognitive impairment, depression, pain and fatigue has been found in NPSLE patients, but the underlying causes are unclear. Auto-antibodies cross-reacting with DNA, N-methyl-D-aspartate receptors, and anti-endothelial and anti-phospholipid antibodies are the most common factors associated with the pathogenesis of NPSLE [27].

It has been shown that peripheral neuropathies may be equally or even more frequent than some CNS syndromes in SLE patients [28,29], and therefore another source of pain. A recent long-term study of more than 2000 patients found that the prevalence of peripheral neuropathies was 5.9% and that 66.7% of these were peripheral neuropathies due to SLE, of which sensory and sensorimotor axonal polyneuropathies were the most frequent. Small-fibre neuropathies and demyelinating polyneuropathies are other causes of peripheral neuropathy in SLE [30].

Neuropathic pain can be also a consequence of herpes zoster (HZ) infection, a painful neurocutaneous disease caused by the reactivation of varicella zoster virus. Immunological studies of SLE patients have shown abnormal Tcell-mediated cytotoxicity, and the suppression of cellular immunity may be involved in the pathogenesis of virus reactivation [31]. It is known that disease activity and the use of corticosteroids and/or immunosuppressive therapies contribute to HZ infection, although a study of a large cohort of SLE patients showed an annual HZ incidence rate of 6.4 events/1000 patient-years without any association with disease activity (SLEDAI <8); post-herpetic neuralgia was detected in 19% of the patients [32].

SLE and central pain

Musculoskeletal pain is reported by 50e90% of SLE patients during the course of the disease [33] and chronic widespread pain, which affects 5e10% of the general population [34], by 65e80% of SLE patients [35,36]. Until a few years ago, the pain associated with many rheumatic diseases was considered to be peripheral in origin and induced by the well-known mechanisms of acute or chronic inflammation, or morpho-structural alterations in the involved joints [37,38]. However, the mechanisms underlying chronic widespread pain (the prototype of which is FM) have only recently been identified as neurophysiological modifications in the perception, transmission and, above all, processing of nociceptive afferents at the level of the CNS, which seem to be caused by what has come to be called "sensitisation": i.e. a permanent state of neuronal hyperexcitability that involves all of the peripheral and central structures of the nociceptive system and causes hyperalgesia and allodynia [39,40]. Immunological cascades may play a role in maintaining central sensitivity and chronic pain, which is increased when CNS glial cells release pro-inflammatory cytokines; the traditional dichotomy of inflammatory vs non-inflammatory pain may therefore be less appropriate than previously thought [41]. The neurophysiological mechanisms underlying central sensitisation syndromes may also play a role in causing the painful symptoms characterising CTDs. Patients with chronic pain conditions are generally female and have experienced an early-life trauma or have a personal or family history of chronic pain, or a personal history of other centrally mediated symptoms (insomnia, fatigue, cognitive alterations and mood disturbances) and cognitions such as catastrophising, all of which can predict the likelihood that acute pain will become chronic [42,43].

SLE and fibromyalgia

The clinical hallmark of FM is chronic widespread pain and tenderness to palpation of at least 11/18 tender points (TPs) [44]. Various symptoms are characteristically associated with FM, such as sleep, mood and neurocognitive disorders, as indicated by the 2010 ACR classification criteria [45]. The estimated prevalence of FM in the general population is about 1e3% in different groups [46], and many studies have investigated its prevalence in SLE patients, and evaluated how concomitant FM can influence the symptoms and the activity of SLE. Morand et al. [47] found a 25.3% prevalence of FM in a cohort of 87 SLE patients; Middleton et al. [48] a 22% prevalence in a group of 102 patients; and Iannuccelli et al. [36] a prevalence of 33% in a cohort of 50 patients. The co-existence of FM may make it difficult to make a differential diagnosis with SLE flares.

The most widely used indices for objectively measuring SLE disease activity are the British Isles Lupus Assessment Group (BILAG) Index, the European Consensus Lupus Activity Measurement (ECLAM), and the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), but none of these rates pain as such [49]. The Systemic Lupus International Collaborating Clinics (SLICC) group has recently proposed a new set of criteria that includes the specific clinical manifestations frequently reported by SLE patients. The features of arthritis are specified because of the overlap between FM and SLE in some patients and it is necessary to confirm that there is joint line tenderness and not more diffuse allodynia. It is also necessary to point out that the cause of all the SLICC criteria is attributable to SLE and not to another disease process or condition [50]. Middleton et al. [48] found that SLE patients with concomitant FM had significantly more frequent and severe symptoms, but there were no significant difference in SLE activity measures between the patients with or without FM, and other authors have confirmed the absence of correlations between concomitant FM and disease activity, joint damage or organ dysfunction [50,51].

Fatigue is another symptom characterising FM and the most common constitutional and debilitating symptom associated with pain in SLE patients [52], with prevalence rates of 50e80% [53]. Many studies have failed to demonstrate a correlation between fatigue and SLE disease activity, and only a few have observed greater disease activity in patients reporting fatigue [36,53,54]. Moreover, SLE patients with overlapping FM report symptoms such as headache, morning stiffness, diffuse alopecia, and arthralgia significantly more often [55].

The health-related quality of life (HRQoL) of SLE patients can be evaluated by administering questionnaires such as the Short-form 36 (SF-36) [56], and the Patient Acceptable Symptom State (PASS) a simple questionnaire used to assess well-being in various rheumatic diseases including SLE [57].

Pain is associated with anxiety and depression, and perceptions of reduced physical functioning, and so SLE patients need psychosocial interventions to relieve their pain and distress and improve their coping skills [58]. Pain coping cognitions such as self-efficacy for pain control and pain catastrophising can influence symptoms such as pain, stiffness, fatigue, and psychological distress in SLE patients. Recent data demonstrate that patients with low levels of self-efficacy for pain control and/or high levels of pain catastrophising report more physical symptoms and psychological distress, and highlight the importance of assessing coping constructs in SLE patients [59]. Regardless of FM, pain influences the quality of life, and SLE patients who have higher pain levels also report stiffness and fatigue. SLE patients frequently report symptoms such as pain, fatigue and musculoskeletal distress, all of which are related to low HRQoL scores [60] and cause functional limitations that lead to a significant economic burden. The working productivity of SLE patients with the highest levels of pain is lower than that of SLE patients with less pain [61]. Consequently increased work absenteeism and work disability (WD) rates have been observed in numerous SLE studies. The reported WD rates range from 20% to 50% and vary widely among SLE population studies. The demographic factors associated with WD include age, a low educational level, low socio-economic status and race, and correlations have been found between WD and pain, fatigue, depressive symptoms, comorbidities, disease duration and activity, joint damage and cognitive dysfunction [62]. The differential diagnosis of SLE and FM may be difficult because the two diseases have some symptoms in common, and low antinuclear antibody (ANA) titres are frequently reported in the general population and FM patients, thus making it necessary to evaluate patients clinically in order to avoid misdiagnoses.

Although secondary FM is not associated with SLE disease activity, it may worsen the quality of life of patients with SLE, and requires appropriate treatment. It is necessary to assess whether pain in SLE

patients is localised or widespread, visceral or musculoskeletal. SLE activity should be measured, and treatment with immunosuppressive drugs and steroids should be optimised on the basis of the severity of the disease [63,64]. The correct interpretation of the FM symptoms is crucial to avoid over-treatment because concomitant FM can simulate SLE flares. Once it has been excluded that the pain is attributable to disease activity, the same treatment as that used for FM can be administered. Analgesic drugs such as acetaminophen or tramadol can be safely used in patients with widespread pain and SLE [65]. Anti-epileptic drugs such as gabapentin and pregabalin have been approved for the treatment of neuropathic pain: both drugs have favourable safety and tolerability profiles [66], and pregabalin has also been approved by the American Food and Drug Administration (FDA) for FM. Low doses of tricyclic antidepressants are useful in the case of musculoskeletal pain and headache. Selective serotonin and serotonin norepinephrine reuptake inhibitors such as duloxetine (approved by the FDA for FM) can be used in SLE patients with pain and depression [67].

Summary

Pain is frequently associated with CTDs. The pain in SLE can have various causes (e.g. inflammatory, neuropathic and central pain), but inflammatory joint pain is one of the most frequent. Chronic widespread pain is the cornerstone of FM, and many studies have investigated the prevalence of FM in SLE patients, and evaluated how concomitant FM has a bearing on SLE symptoms and disease activity. The treatment of pain in SLE patients requires a differential diagnosis; in particular, it is necessary to establish whether the pain is localised or widespread, visceral or musculoskeletal. The first step is to evaluate SLE activity, and optimise specific SLE treatment with immunosuppressive drugs and steroids. FM symptoms in an SLE patient may be misinterpreted as lupus disease activity and thus lead to over-treatment: when it has been excluded that SLE activity is the main cause of pain, the treatment is the same as that used for FM. Analgesic drugs such as acetaminophen or tramadol can be safely used in patients with widespread pain and SLE. In many cases, non-pharmacological treatments such as aerobic exercise and cognitive behavioural therapy may also be useful.

Pain is a virtually ubiquitous problem in SSc: 83% of patients in a recent large sample reported significant pain. Early in the disease process, patients report non-specific muscle pain and stiffness, whereas other symptoms (e.g. difficulty in swallowing and gastrointestinal discomfort) emerge as the disease progresses. Effective pain management is a primary goal of patient care, although it has not been investigated in detail in patients with SSc.

Disclosure of interest

The authors declare that they have no conflict of interest concerning this article.

Practice points

- Pain is a cornerstone of the definition of SLE and SSc, but it may be due to a mechanism related to central pain sensitisation (similar to that observed in FM) and inflammation.
- Inflammatory pain symptoms can be reduced by NSAIDs and DMARDs, but many patients continue to experience moderate pain due to alterations in central pain regulation mechanisms, as in the case of CWP.
- It is important to identify the symptoms of CWP in order to be able to manage and treat patients with CTDs appropriately.
- Effective pain management is a primary goal of patient care, although it has not been investigated in detail in patients with SSc and SLE.
- Researchers and clinicians should be encouraged to assess perceived physical health, health worries, mental health, and social support, in addition to routinely evaluating organ disease severity in SSc and SLE patients.

Research agenda

- To develop new laboratory and clinical indices for distinguishing CWP from inflammatory pain in CTDs in order to reduce misdiagnoses.
- To evaluate the adequacy and appropriateness of measures for diagnosing inflammatory and central pain.
- To determine whether new instrumental methods such as ultrasonography can distinguish CWP from other types of pain.
- To develop new recommendations for differentiating widespread pain in the context of CTDs.
- To promote future multicentre studies and registries of widespread pain in CTDs in order to reduce the overestimated disease activity.

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