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5

Pain in systemic connective tissue diseases

Manuela Di Franco [a, *, 1], Laura Bazzichi [b, 1], Roberto Casale [c], Piercarlo Sarzi-Puttini [d], Fabiola Atzeni [e]

[a] *Rheumatology Unit, Department of Internal Medicine and Medical Specialities, Sapienza University of Rome, Italy*
[b] *Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Italy*
[c] *Department of Clinical Neurophysiology and Pain Rehabilitation Unit (RC), Foundation Salvatore Maugeri IRCCS, Montescano, Italy*
[d] *Rheumatology Unit, L.Sacco University Hospital, Milan, Italy*
[e] *IRCCS Galeazzi Orthopedic Institute, Milan, Italy*

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A B S T R A C T

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.

* Corresponding author. Department of Internal Medicine and Medical Specialities, Rheumatology Unit, Sapienza University of Rome, 00161 Roma, Italy. Tel.: +39 02 39042489; fax: +39 02 39043454.
E-mail address: manuela.difranco@uniroma1.it (M. Di Franco).
[1] MDF and LB contributed equally to drafting the manuscript.

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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) disrorders [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 [5–7].

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 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