

Pain in systemic sclerosis

S. Stisi¹, P. Sarzi-Puttini², M. Benucci³, G. Biasi⁴, S. Bellissimo¹,
R. Talotta², F. Atzeni²

¹Unit of Rheumatology, A.O. G. Rummo, Benevento;

²Unit of Rheumatology, L. Sacco University Hospital, Milan;

³Unit of Rheumatology, Ospedale San Giovanni di Dio, Florence;

⁴Unit of Rheumatology, University of Siena, Italy

SUMMARY

Chronic pain is a healthcare problem that significantly affects the mental health, and the professional and private life of patients. It can complicate many disorders and represents a common symptom of rheumatologic diseases, but the data on its prevalence is still limited. Pain is a ubiquitous problem in systemic sclerosis (SSc). SSc-related pain has been studied on the basis of biomedical models and is considered a symptom caused by the disease activity or previous tissue damage. Effective pain management is a primary goal of the treatment strategy, although this symptom in SSc has not yet been investigated in detail. However, these patients do not all respond adequately to pharmacological pain therapies, therefore in these cases a multimodal approach needs to be adopted.

Key words: Spondyloarthritis, fibromyalgia, Prevalence, Disease activity, Ankylosing spondylitis disease activity score, Bath ankylosing spondylitis disease activity index.

Reumatismo, 2014; 66 (1): 44-47

■ INTRODUCTION

Systemic sclerosis (SSc) is a rheumatic disease characterized by skin thickening and fibrosis of internal organs due to a build-up of collagen and other extracellular matrix proteins (1). There are two general classifications: limited cutaneous SSc (l-SSc) in which the skin involvement is only distal to the elbows and knees, the development of fibrosis is slow, and the internal organ involvement is milder; and diffuse cutaneous SSc (d-SSc), which has a worse prognosis, extensively affects the skin and internal organs, and is characterized by rapidly progressing fibrosis (1, 2). The clinical approach to SSc is complicated by a lack of effective treatments for many disease manifestations, therefore the primary goals are to preserve functioning, relieve symptoms such as pain, and improve the quality of life.

■ PREVALENCE AND CAUSE OF PAIN

Pain is virtually ubiquitous in SSc. In a recent study conducted on a large sample,

83% of patients reported moderate pain (3), confirming the results of previous observations (4-6). Early in the disease process, patients report non-specific muscle pain and stiffness (1), whereas other symptoms (e.g. difficulty in swallowing and gastrointestinal discomfort) emerge as the disease progresses (7). SSc-related pain has been generally associated to the disease activity or previously sustained tissue damage, on the basis of a biomedical model (8). However, the level of pain is not always related to disease severity (4, 9) because, although l-SSc patients typically report less pain than dcSSc patients, the differences are generally small and not clinically meaningful (3, 4, 10-12).

Some of the limited published data concerning SSc-related pain was collected from a large sample of 242 scleroderma patients. These findings show a generally mild pain and an expected correlation between pain and distress, but the authors did not provide any indication as to the frequency of pain or the impact, if any, of these mild pain levels on function (11).

An alternative approach to explain the genesis of pain is the bio-psychosocial model,

Corresponding author:
Stefano Stisi

Unit of Rheumatology
A.O. G. Rummo
Benevento, Italy

E-mail: stefano.stisi@ao-rummo.it

which has been widely accepted to understand many other diseases and suggests that SSc pain is not a purely physical phenomenon (13). This model highlights the presence of interconnections between the disease, the patients and the environment, but it postulates that none of these variables can independently explain pain, because biological, psychological, and social factors interact in complex ways to shape pain perceptions (13).

In general, emotional health and pain are closely correlated, thus potentially explaining the reason why half of chronic pain patients also have depression and/or anxiety (13). In SSc patients, symptoms of depression (14) and anxiety (15) are common, and closely correlated to the perception of pain (3-5, 10, 16, 17). For example, symptoms of depression (3) and anxiety (17), and the mental health-related quality of life (10) are correlated to pain, even when other disease and psychosocial variables are taken into account.

The way a person thinks about his/her health has also been linked with pain perception in clinical (13) and rheumatic populations (9, 18). The awareness of the disease can vary depending on the patients and for some of them it can even become a continuous source of major concern. Some studies suggest that thinking about the serious consequences of SSc (12), catastrophizing (6), and maladaptive disease cognitions (19) are all associated with greater pain. Other variables have also shown to influence pain perception. For instance, patients with a lower level of education and social support who develop catastrophic cognitions report greater pain (6).

Some authors identify a direct relationship between the social context and the perception of pain, which also includes the influence of the mood (13). This notion is confirmed by other studies conducted on populations of rheumatic patients (9, 20). For example, a study of patients with rheumatoid arthritis (RA), osteoarthritis (OA) or ankylosing spondylitis (AS) found that less social support correlated to greater pain (20). The only study of SSc patients that investigated the relationship between

pain and social support in SSc demonstrated that patient with a poor level of social adjustment reported worse pain, even though this relationship was attributed to underlying depression (4).

■ MUSCULOSKELETAL PAIN SYNDROMES IN SYSTEMIC SCLEROSIS

Although the pain may not be localized well enough to attribute it to a particular anatomical location, various musculoskeletal pain syndromes can be seen in SSc patients:

- **Tendinitis:** tendon friction rubs are most frequent in patients with early diffuse SSc; their estimated frequency in such patients is 23-65%, but it tends to decrease over time (16, 17). Tendinitis is associated with a more active disease and worse outcomes (16, 17).
- **Polyarthritis:** the estimated frequency of polyarthralgias is 36-80%. Once again, they are more frequent in patients with early SSc, but some reports indicate similar rates in patients with limited and diffuse SSc (9, 15). X-rays show that SSc patients have a wide range of articular and non-articular damage ranging from juxta-articular osteoporosis and joint space narrowing to frank erosions throughout the metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints, as well as wrist joints. During the first seven years of the disease, the frequency of bony erosions (mainly in the hands) is 4-57%, while the frequency of joint space narrowing is 16-92% (18-24). These reports suggested that some of the joint space narrowing may be related to concomitant OA rather than SSc.
- **Rheumatoid arthritis:** the recent availability of anticyclic citrullinated peptide (CCP) assays has led to report anti-CCP-positive RA in 1-15% of SSc patients (8, 18, 25, 26). In one study, the frequency of anti-CCP2 antibodies was 14.8% (11/74), while the frequency of anti-CCP3 antibodies was 13.5% (10/74) (26). However, anti-CCP antibodies do

not in themselves define RA. Furthermore the prevalence of these antibodies has not yet been identified in SSc patients without arthritis.

- Fibromyalgia (FM) and chronic widespread pain (CWP): forty-eight percent of Johnson's case reports of SSc patients show 11 or more positive tender points, whereas in the study by Malcarne the mean tender point count was 7/18 (7, 27). Clinical experience suggests that, as in the case of other connective tissue diseases, FM is not uncommon in patients with SSc. However, none of the published studies assessed the prevalence of FM in SSc patients according to the 2010 ACR criteria for FM (28).

The prevalence of CWP without all of the complex fibromyalgic symptoms is different. In a recent Italian multi-centric study (29), the overall prevalence of CWP was 27.1%, therefore much higher than the expected prevalence in the general population. Its prevalence in patients with l-SSc and d-SSc was respectively 17.6% and 32.3%, but the difference was not statistically significant ($P=0.318$). There was no correlation between the prevalence of CWP and the degree of cutaneous involvement (according to the modified Rodnan skin score) or the erythrocyte sedimentation rate ($P=0.48$), but there was a correlation with older age ($P=0.0196$). No statistically significant difference was identified between d-SSc and l-SSc using the Kessler psychological distress scale, the Flinder's fatigue scale, or the pain catastrophizing scale. Logistic regression showed that the only variable associated with development of CWP was the presence of anti-centromeric antibodies (ACAs) [$P<0.0001$; $OR=8.1$ (3.3-19.8)]. The higher prevalence of CWP among patients with SSc does not correlate with the clinical manifestations of the disease, but it does correlate with advanced age. The presence of ACAs may be a risk factor for CWP.

- Bursitis and other musculoskeletal pain syndromes have been reported, yet their frequency is unknown.

Effective pain management is a primary

goal of treatment, although it has not been investigated in detail in patients with SSc. Since not all patients respond adequately to pharmacological pain therapies, other methods that target modifiable psychosocial factors (*i.e.* emotional health, cognition, social support) should be considered. Cognitive-behavioral therapy (which involves skill building in areas such as mindfulness, relaxation, coping, social support, and changing maladaptive beliefs) has been used in other pain populations and can therefore be used in pain associated to SSc. Although the outcomes of these treatments are less straightforward (*e.g.* successful treatment may mean a partial pain improvement, patients experience pain differently, and healthcare costs have decreased), they may be promising adjuncts for patients who cannot benefit from the pharmacological therapy.

However, before implementing these therapeutic strategies, it is important to identify patients that can actually respond to them. In conclusion, researchers and clinicians should be encouraged to assess perceived physical health, health worries, mental health, and social support, in addition to routinely evaluating skin disease severity and lungs in SSc patients.

■ REFERENCES

1. Medsger TA. Natural history of systemic sclerosis and the assessment of disease activity, severity, functional status, and psychologic well-being. *Rheum Dis Clin North Am.* 2003; 29: 255-73.
2. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol.* 1988; 15: 202-5.
3. Schieir O, Thombs BD, Hudson M, Boivin JF, Steele R, Bernatsky S, et al. Prevalence, severity, and clinical correlates of pain in patients with systemic sclerosis. *Arthritis Care Res.* 2010; 62: 409-17.
4. Benrud-Larson LM, Haythornwaite JA, Heineberg LJ, Boling C, Reed J, White B, et al. The impact of pain and symptoms of depression in scleroderma. *Pain.* 2002; 95: 267-75.
5. Richards HL, Herrick AL, Griffin K, Gwilliam PD, Fortune DG. Psychological adjustment to

- systemic sclerosis – exploring the association of disease factors, functional ability, body related attitudes and fear of negative evaluation. *Psychol Health Med.* 2004; 9: 29-39.
6. Edwards RR, Goble L, Kwan A, Kudel I, McGuire L, Heinberg L, et al. Catastrophizing, pain, and social adjustment in scleroderma: relationships with educational level. *Clin J Pain.* 2006; 22: 639-46.
 7. Franck-Larsson K, Graf W, Rönnblom A. Lower gastrointestinal symptoms and quality of life in patients with systemic sclerosis: a population-based study. *Eur J Gastroenterol Hepatol.* 2009; 21: 176-82.
 8. Carreira PE. "Quality of pain" in systemic sclerosis. *Rheumatology.* 2006; 45: 1185-6.
 9. Edwards RR, Cahalan C, Mensing G, Smith M, Haythornthwaite JA. Pain, catastrophizing, and depression in the rheumatic diseases. *Nat Rev Rheumatol.* 2011; 7: 216-24
 10. Georges C, Chassany O, Toledano C, Mouthon L, Tiev K, Meyer O, et al. Impact of pain on health related quality of life of patients with systemic sclerosis. *Rheumatology.* 2006; 45: 1298-302.
 11. Malcarne VL, Hansdotir I, McKinney A, Upchurch R, Greenbergs HL, Henstorf GH, et al. Medical signs and symptoms associated with disability, pain, and psychosocial adjustment in systemic sclerosis. *J Rheumatol.* 2007; 34: 359-67.
 12. Richards HL, Herrick AL, Griffin K, Gwilliam PD, Loukes J, Fortune DG. Systemic sclerosis: patients' perceptions of their condition. *Arthritis Rheum.* 2003; 49: 689-96.
 13. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: Scientific advances and future directions. *Psychol Bull.* 2007; 133: 581-624.
 14. Thombs BD, Taillefer SS, Hudson M, Baron M. Depression in patients with systemic sclerosis: A systematic review of the evidence. *Arthritis Rheum.* 2007; 57: 1089-97.
 15. Legendre C, Allanore Y, Ferrand I, Kahan A. Evaluation of depression and anxiety in patients with systemic sclerosis. *Joint Bone Spine.* 2005; 72: 408-11.
 16. Kwakkenbos L, van Lankveld WG, Vonk MC, Becker ES, van den Hoogen FH, van den Ende CH. Disease-related and psychosocial factors associated with depressive symptoms in patients with systemic sclerosis, including fear of progression and appearance self-esteem. *J Psychosom Res.* 2012; 72: 199-204.
 17. Hyphantis TN, Tsifetaki N, Pappa C, Voulgari PV, Sifakaki V, Bai M, et al. Clinical features and personality traits associated with psychological distress in systemic sclerosis patients. *J Psychosom Res.* 2007; 62: 47-56.
 18. Edwards RR, Bingham CO, Bathon J, Haythornthwaite JA. Catastrophizing and pain in arthritis, fibromyalgia, and other rheumatic diseases. *Arthritis Rheum.* 2006; 55: 325-32.
 19. van Lankveld WG, Teunissen H, Näring G, Vonk MC, van den Hoogen FH. Social support, disease-related cognitions and coping as predictors of depressed mood in systemic sclerosis. *Cognit Ther Res.* 2008; 32: 434-47.
 20. Savelkoul M, Post MW, de Witte LP, van den Borne HB. Social support, coping, and subjective well-being in patients with rheumatic diseases. *Patient Educ Couns.* 2000; 39: 205-18.
 21. Reveille JD, Fischbach M, McNearney T, Friedman AW, Aguilar MB, Lisse J, et al. Systemic sclerosis in 3 US ethnic groups: A comparison of clinical, sociodemographic, serologic, and immunogenetic determinants. *Semin Arthritis Rheum.* 2001; 30: 332-46.
 22. Kahaleh MB, Sultany GL, Smith EA, Huffs-tutter JE, Loadholt CB, LeRoy EC. A modified scleroderma skin scoring method. *Clin Exp Rheumatol.* 1986; 4: 367-9.
 23. Furst D, Khanna D, Matucci-Cerinic M, Clements P, Steen V, Pope J, et al. Systemic sclerosis – continuing progress in developing clinical measures of response. *J Rheumatol.* 2007; 34: 1194-200.
 24. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care.* 1992; 30: 473-83.
 25. Pilowsky I, Spence ND. Patterns of illness behaviour in patients with intractable pain. *J Psychosom Res.* 1975; 19: 279-87.
 26. Merz EL, Malcarne VL, Roesch SC, Sharif R, Harper BE, Draeger HT, et al. Measuring illness behavior in patients with systemic sclerosis. *Arthritis Care Res.* 2013; 65: 585-93.
 27. Cohen S, Mermelstein R, Kamarck T, Hoberman H. Measuring the functional components of social support. In: Sarason I, Sarason B, eds. *Social support: theory, research, and applications.* Boston, MA: Martinus Nijhoff. 1985; 73-94.
 28. Lanza ST, Flaherty BP, Collins LM. Latent class and latent transition analysis. In: Schinka JA, Velicer WA, eds. *Handbook of psychology: research methods in psychology.* New York, NY: Wiley. 2003; 663-85.
 29. Stisi S, Bellissimo S, Venditti C, Sarzi-Puttini P, Batticciotto A, Biasi G, et al. Prevalence of chronic widespread pain in SSc patients. *Ann Rheum Dis.* 2013; 72: 654.