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Systemic Sclerosis and Pain: A Systematic Review

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ABSTRACT

Objective: *Systemic sclerosis (SSc) is one of the most common autoimmune diseases causing disability and chronic pain. Despite the fact that pain remains the major condition impacting quality of life in patients, surprisingly, it is still not well evaluated and often underestimated.*

We did a systematic review to assess the effectiveness of the relationship between pain and SSc, the natural history of pain emerging in the disease and to evaluate patterns of pain incriminated in this condition.

Data Sources: *A key word literature search was conducted using articles listed the last 5 years starting in 2012 until September 2017 in PubMed, Web of Science and The Cochrane Library. Manual searches were made of all retrieved articles to analyze those that met the review inclusion criteria.*

Study Selection: *To be included in the review, articles needed to be written in English between 2012 and 2017. Search terms used: Systemic sclerosis and pain or systemic scleroderma and pain. Quality of life in SSc was also used.*

387 articles and abstracts were retrieved. All articles or titles who did not include those terms were excluded. All Abstracts with the word pain contain were manually analyzed with their full articles. Only 25 trials were analyzed of which, 9 articles met our inclusion criteria. 2 authors were contacted via emails in order to retrieve their full articles without success. At the end, only 7 articles were finally analyzed.

Data Synthesis: *We identified 7 articles including 1956 people with SSc. Pain is a major patients' complaint. It seems to appear with or without digital ulcers usually at the Raynaud phenomenon stage. Multilevel modeling was estimated in one study to show that pain has emotional, psychological and social components beyond its neuropathic and somatic composition. It is suggested that better comprehensive pain models conducted to a better pain management when several aspects of the SSc still resist to a lonely therapeutic management.*

Conclusion: *Many people suffer from chronic pain and there is a little agreement on what medications are helpful. One reason for this is that clinical trials remain poor in assessing pain and measuring meaningful improvement. Despite the paucity of literature evaluating pain in SSc, this review tried to awareness clinicians to the importance of evaluating pain at the beginning of the disease and to consider other aspects and patterns of pain for a better care.*

Keywords

Systemic sclerosis, Systemic scleroderma, Pain, Quality of life.

Introduction

Systemic sclerosis is a rheumatic disease characterized by a vascular damage, fibrosis and thickening of skin and internal organs damage. The Raynaud phenomenon and ischemic digital ulcers are the hallmarks of the SSc [1].

Digital ulcers have been recognized in 44-60% of patients with

SSc [1]. They are considered responsible of severe pain and quality of life impairment. Pain is a well-known issue in SSc. In fact, 83% of patients in a Canadian cohort reported major pain which is correlated with more frequent Raynaud phenomenon, active ulcers, worse synovitis, and gastrointestinal symptoms [2]. The same rate was found in other studies [3,4]. Although its impact on the patient's quality of life, pain is still not included in assessment of SSc severity.

Early disease is characterized by non-specific muscle pain and stiffness [5]. Gastrointestinal symptoms and gut discomfort occur as the disease progresses [6]. In the ECLIPSE study, the authors found that within 190 patients with SSC included, 105 patients (52.2%) had digital ulcers as the first manifestation without Raynaud phenomenon and the mean time between the first episode of digital ulcers occurrence and the Raynaud phenomenon was 6.6 ± 9 .1 years [1]. This is said that pain complain may occur without Raynaud phenomenon and patients could suffer at the beginning of the first episode of digital ulcers and at the beginning of the disease.

It has been reported that digital ulcers emergence and their activity reduce wrist mobility and then increase hand disability and alter quality of life [1,7]. In the biomedical model of the SSc, pain appears holding a strong neuropathic component in comparison to the nociceptive mechanism. It is found in one study at 46.3% in patients with SSc [8]. Several studies demonstrated that pain is not related to disease severity in SSc. Indeed, patients with localized sclerosis typically reported less pain that the diffuse form but the difference is generally small and statistically not significant [2,3,9].

Alternatively, authors start to build another pain model which englobes other components than somatic mechanisms. Chronic pain is like a prism with multiple dimensions: psychological, cognitive and social ones. This biopsychologic model seems to play a better role in the prevalence and severity of SSc pain [10,2,11,12].

The natural history of pain across the SSc evolution is poorly explored and little is known regarding whether pain improves, remains stable or worsens. Only one study found not differences in pain when the sample was stratified by perceived in health status [13].

It is critical to understand pain in the early SSc stages due to the high level of disease activity, (tissue damage) at that time, and because it is an important period of psychosocial adjustment. Knowledge about the course of early-disease pain may identify and then tailor better interventions care to improve quality of life in the long term. This is crucial, because disease-associated damage is often difficult to reverse and curative therapies are not yet available.

Therefore, the aims of our review were to describe patterns of pain in the early SSc disease, time when pain emerges (with digital ulcers, Raynaud phenomenon or GI symptoms), and their trends over time across the SSc. We also tried to explore pain and its links and interconnections with emotional, cognitive, social, and perceived health status.

Methods

Search Strategy

Three databases (PubMed, Cochrane library, Web of science) were searched in September 2017 using 2 diagnoses ("systemic sclerosis," "systemic scleroderma") with "pain" and with 1 additional key word ("quality of life"). Thus, 167, 2, and 218 searches were performed per database respectively, 387 searches in all. The abstracts were read of those articles whose titles indicated they might have examined the associations between at least 1 diagnosis and pain. The entire article was read if the abstract indicated the article potentially met the inclusion criteria. References and bibliographic lists of all of these articles were also examined.

Article Inclusion and Exclusion Criteria

In order to be included in this review, the article must have (1) been written in English, (2) included as participants human adults with one of the two diagnoses who also had or reported having pain, (3) or included the quality of life measure. Article exclusion criteria were reports or studies that (1) were not published in peer-reviewed journals (eg, dissertations), (2) reported results using pain management essentially in patients with SSc.

Data Extraction

Data extraction was completed by the principal author (H.N) using a form developed specifically for this purpose. The data extracted included (1) study author names, (2) publication dates, (3) study designs (eg, cross-sectional, prospective, and longitudinal), (4) sample sizes, (5) diagnostic groups studied, (6) psychosocial domains assessed and measures used to assess those domains, (7) domains assessed (eg, pain severity, physical functioning, psychological functioning), (8) specific criterion domains assessed (eg, "depression," "functional independence") and measures used to assess those domains.

Results

Study Descriptions

The review process is summarized in figure 1 according to QUOROM guidelines. Nine studies met the review inclusion criteria. Two of them could not be retrieved even after trying to reach the authors by email. Two of the seven studies used samples of adults with a psychobiomedical model building. 6 studies examining the associations between psychosocial predictors and psychological, physical functioning in SSc were identified. The majority of the studies included cross-sectional correlational analyses. One of these studies also included prospective analyses to determine whether psychosocial factors assessed predicted subsequent change in 1 or more criterion variables. An additional study only used prospective predictive analyses, assessed pain in digital ulcers and its impact on functioning and disability type of analysis.

The psychosocial domains examined most often in these studies were catastrophizing. Also, pain-related beliefs were assessed in

these studies, and social factors were also identified. The criterion domain evaluated most often was psychological functioning, but physical functioning and pain severity were also frequently measured. Two of the studies reported only univariate associations. Three of the studies performed multivariate analyses.

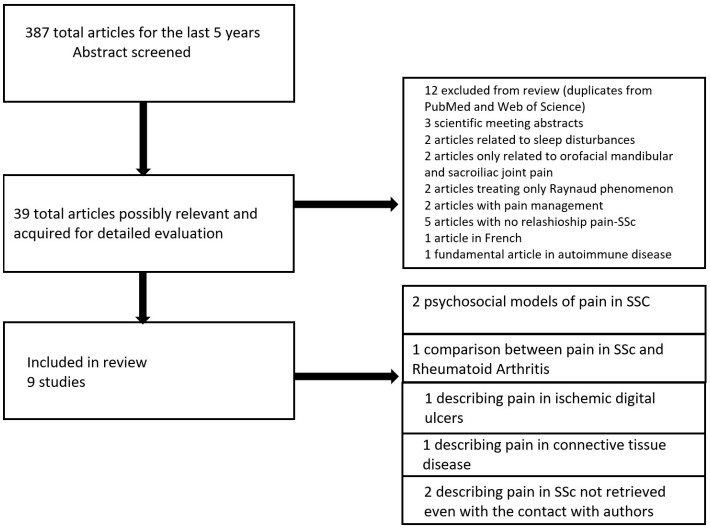

Figure 1: Flow chart.

Psychosocial predictor variables as a multilevel model predicting pain, physical function, and psychological functioning

As mentioned, 3 studies presented findings from multivariate analyses. In the 7 studies analyzed, at least 1, and often more than 1, of the psychosocial predictor variables examined were found to be statistically significantly associated with at least 1 criterion (pain or functioning) variable, even when controlling for other possible confounding variables.

One study (Perrot, et al.) reported that pain intensity did not correlate with disease activity (r=0.55). Functional impairment was severe in patients with rheumatoid arthritis than SSc patients. Pain intensity was lower in limited cutaneous sclerosis than the SSc form. More interestingly, catastrophizing, helplessness and magnification did not differ in the two groups (P= 0.051).

In another study, Merz et al. [14] demonstrated the importance of a psychosocial model in understanding pain in SSc. They compared 3 subgroups where the distressed and the resilient groups reported more greater pain than the managing group ($P < 0.001$). Moreover, managing group class was significantly less likely to be taking pain killers.

Author, Year, Study Design	Psychosocial	Criterion	Primary Findings
Total Sample Size	**Domains Measured**	**Variables**	
Perrot et al, 2013 [8]	Catastrophizing	Pain	Univariate analyses
Cross-sectional design	Coping	Physical functioning	pain level does not reflect disease activity
N=153	depression, anxiety	psychological functioning	Neuropathic pain component with higher DN4 score
			Pain catastrophizing is high
Mouthon et al, 2014 [1]	Emotional role	Pain	Multivariate analyses
Prospective predictive	Social	Physical functioning	Presence of active digital ulcers at inclusion accounted for significantly
N=190	Mental health		unique variance in 24-mo change in hand functioning
Merz et al, 2014 [14]	Health worry	Pain	Univariate analyses
Cross-sectional design	Mental health	Physical functioning	Change in control beliefs, catastrophizing, social support, well perceived
N=333	Social	Psychological functioning	physical health accounted for unique variance in SSc manifestations
Di Franco et al, 2015 [21]	Quality of life	Pain	Poorer quality of life in patients with SSc
Descriptive design			
Almeida et al, 2015	Work productivity	Pain	Depressive mood, perceived health, sleep disturbances are independent
Review [22]	Depression	Physical functioning	predictors of the severity of SSc
N=117 (articles)	Sleep	Psychological functioning	
	Sexual activity		
Racine et al, 2016 [23]	Social	Pain	Multivariate analyses
Cross-sectional design	Depression	Physical functioning	pain and itching accounted for changes in physical and psychological
N=964	Itching	Psychological functioning	functioning
Merz et al, 2017 [15]	Social	Pain	Multivariate analyses
Prospective design	Emotional health		Better emotional health and perceived physical health are associated
N=316	Health worry		with low initial pain
	Perceived physical health		
Willems et al, 2014	Article not retrieved		
Cross-sectional design			
N=537			
Stisi et al, 2014	Article not retrieved		
Descriptive design			

Table 1: Summary of Findings From Studies Examining the Association Between Pain and SSc for the last 5 years.

The only prospective study which dealt with specifically digital ulcers and pain in SSc was Mouthon et al. It evaluated in 190 patients with 2 years of follow up (already on Bosentan therapy) the impact of recurrent digital ulcers on hand functioning and disability. Two major findings were identified. First of them was that digital ulcers are the major sign of the SSc without the occurrence of Raynaud phenomenon. In fact, the mean time between the occurrence of the Raynaud and the first digital ulcer was 6.6 ± 9.1 years. Secondly, the presence of ulcers was associated with pain and hand disability.

Quality of life as a global assessment is altered. In a review of 337 articles analyzed (Almeida et al), all of studies reported at least one item related to the quality of life impairment. The strength of a multidisciplinary model was considered to explain pain in SSc patients. All the following items were altered: work productivity, sleeping, sexual function, psychological item, Raynaud phenomenon, skin and gastrointestinal disturbances were reported.

Merz, et al. in in recent study Merz et al [15], stressed again the role of the multilevel model in understanding pain. The authors found that the trend of pain does not change across the disease course over a 3 year of follow up. And that the proportion of reduction in unexplained variance between the psychosocial model (emotional health, perceived physical health, health worry and social support) and the medical model suggested that the addition variance of psychosocial characteristics explained additional variance in pain.

In addition to consistent findings regarding the prediction of pain intensity or severity, psychological functioning, and physical functioning, the analyses the majority of these studies also identified that psychosocial factors were significantly associated with the quality of life, social integration, and global evaluation of general health, even when controlling for demographic and clinical variables.

In sum, the findings from the multivariate analyses examining the faculty of psychosocial factors as a multilevel model to predict pain and functioning provide strong and consistent support for the associations between psychosocial factors and measures of important patient functioning domains, even when controlling for patient demographic and clinical variables.

Discussion

SSc is a serious condition in which pain has been much less studied. It is still not considered a scoring item in the severity of the disease. To the best of our knowledge, this is the first systematic review specifically dedicated to evaluate the importance of pain in psychosocial and physical functioning in SSc patients.

Digital ulcers remain a frequent complication of the SSc, more often in the absence of the Raynaud phenomenon which is considered the first sign. Clinicians who are prompt to identify patients at the early disease stages, will found very hard to better manage patients at the Raynaud phenomenon stage for example in a dedicated advanced consult because the fact that patients could come to see specialists already at the digital ulcers stage. It shed light to be aware to detect those patients whom the activity of the disease is worrying.

Pain in general has been conceptualized according to a strict biomedical model suggesting that pain is a symptom like others related to disease activity or intensity. Other models, still in infancy start to build other predicting outcomes notably loss of function and disability. In SSc, effective pain management is a primary goal of patient care, although not all patients respond to pharmacological therapy per se. An alternative is postulated to be able to explain pain with other aspects such as emotional, psychological, cognitive, and social components. It is widely recognized nowadays in general across disciplines and diseases. Thus, postulating this, pain management should target multilevel aspect in order to a better care of patients.

The aim of our review was to describe the natural history of pain emergence at the early stages of the SSc disease because it is a critical period of psychological adjustment. This aspect is very important in the management of SSc because it is still an incurable condition with disfiguring tissue damage, generally with digital ulcers sequelea.

One potential explanation of the fact that pain per se changed very little over time, is that patients change their adjustment and recalibrate their priorities regarding their disease exactly they do with cancers [16].

More severe disease was associated with worse initial pain, but the association was reduced to nonsignificance after adjustment for the psychological variables. Better emotional health, and perceived physical health were associated with lower initial pain. Social support has been also recognized one of the major supporting factors in caring patients [17]. It is considered in the understanding of the SSc patients specifically related to social avoidance due to the appearance concerns.

It is well known that pain and emotional health are interrelated with up to half with depression and anxiety [17]. It is also true in rheumatic diseases [9,18]. Different approaches such as cognitive-behavioral therapy (which include relaxation, coping, social support, and changing maladaptive beliefs) are experienced in general pain populations [9,17,19,20]. Implementing such as methods means that pain could be ameliorated from a strict medical point of view which is not totally effective. Patients in contrary reported already a different experience of their disease with this model. Clinicians are prompted and encouraged to identify those patients and assess psychosocial aspects in a clinical setting when they are not trained to do it.

Furthermore, even the growing appreciation of this model of pain in SSc, we do not know how exactly, these factors interact between them in the same cluster because it happens that a lot of hetegeneity

exists between them. We still do not know which typology and the exact pattern of pain has a real impact on the disease course.

Our review has a limitation. We lacked two studies from the nine included and could not be retrieved even several trials. We could not find whether it included late- stages SSc where typically patients experienced more pain. Almost of the data were cross-sectional, thus we could not analyze whether poorer patients were functioning poorly prior to the diagnosis.

Conclusion

This review shed light for the first time of the detrimental role of the psychosocial functioning in evaluating pain in SSc. Clinicians will have an essential role in detecting patients who need a global approach and then tailor a better care plan for them.

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