Pain Intensity and Interference Levels and Associated Factors in Systemic Sclerosis: A Cross-sectional Study of 2157 Participants from the Scleroderma Patient-centered Intervention Network (SPIN) Cohort

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ABSTRACT

Background: Pain is important for people with systemic sclerosis (SSc; scleroderma) but often overlooked in research and clinical care. Objectives were to (1) assess levels of pain intensity and interference and (2) evaluate disease factors associated with pain intensity and interference.

Methods: Participants in the Scleroderma Patient-centered Intervention Network Cohort who completed pain intensity and interference measures (Patient Reported Outcomes Information System-29 profile version 2·0) as part of baseline assessments were included. Associations of pain intensity and pain interference with SSc-related variables and overlap syndromes, controlling for sociodemographic variables, were assessed with multiple linear regression. Continuous independent variables were standardized.

Findings: Among 2157 participants, 1870 (87%) reported at least mild pain (≥ 1 on 0 to 10 scale), and 815 (38%) reported moderate-to-severe pain (≥ 5); 757 (35%) reported moderate-to-severe pain interference. Greater pain intensity was independently associated with female sex (0·58 points, 95% confidence interval [CI] 0·26 to 0·90), non-White race/ethnicity (0·50 points, 95% CI 0·21 to 0·79), less education (0·30 points per standard deviation [SD], 95% CI 0·19 to 0·41), country (reference=United States; Canada, 0·29 points, 95% CI 0·01 to 0·57; United Kingdom, 0·58 points, 95% CI 0·21 to 0·95), greater BMI (0·35 points per SD, 95% CI 0·24 to 0·45); joint contractures (0·67 points, 95% CI 0·39 to 0·94), digital ulcers (0·33 points, 95% CI 0·10 to 0·55), gastrointestinal involvement (0·66 points, 95% CI 0·33 to 0·98), skin involvement (0·22 points per SD, 95% CI 0·10to 0·35), rheumatoid arthritis (0·96 points, 95% CI 0·50 to 1·43) and Sjögren's syndrome (0·42 points, 95% CI 0·01 to 0·83). Pain interference results were similar.

Interpretation: Pain is common among people with SSc. Controlling for sociodemographic variables, greater pain was associated with multiple SSc-related manifestations, including joint contractures, digital ulcers, gastrointestinal involvement, skin involvement, and the presence of overlap syndromes.

RESEARCH IN CONTEXT

Evidence before this study: We searched PubMed using the term "pain" with "systemic sclerosis" or "scleroderma" on June 7, 2021 to attempt to identify previous studies with 200 or more people with systemic sclerosis (SSc) that examined pain levels and included an evaluation of associated sociodemographic and disease factors in multivariable analyses. A 2010 study that analysed data from 585 Canadian participants found that 83% reported at least mild pain and 37% reported moderate to severe pain (≥ 5 on 0 to 10 scale; mean [standard deviation] = 3.6 [2.8]). Pain intensity was independently associated with Raynaud's phenomenon, active ulcers, worse synovitis, and gastrointestinal symptoms. The 2018 European Scleroderma Observational Study studied 326 participants from 19 countries but did not evaluate multivariable associations of pain with sociodemographic and disease variables. Mean (standard deviation) pain was 32.9 (26.9) on a 0 to 100 scale. No studies have assessed levels of pain interference with daily activities or factors associated with pain interference.

Added value of this study: We evaluated pain intensity, pain interference, and factors associated with both among 2157 people with SSc, which is almost 4 times as many participants as the only previous study that evaluated multivariable factors associated with pain in SSc. Results underline the centrality of pain in the experiences of people living with SSc. Almost 9 of 10 participants reported at least mild pain intensity, and almost 4 of 10 reported moderate to severe pain. More than 3 of 10 participants reported moderate to severe pain interference in their ability to carry out daily activities. SSc disease manifestation is highly diverse, and results showed that many SSc-related factors may contribute to pain among people with SSc, including joint contractures, digital ulcers, degree of skin thickening and hardening, gastrointestinal involvement, and the presence of overlap syndromes (rheumatoid arthritis, Sjögren's syndrome).

Implications of all the available evidence: Pain levels in SSc appear to be similar to levels reported in rheumatoid arthritis, in which pain is a central focus for clinical intervention. Pain interferes significantly with the ability to carry out normal daily activities for many people with SSc. Aspects of SSc associated with pain are manifold and likely differ between individuals. Health care providers should be aware that patients with joint contractures, digital ulcers, gastrointestinal involvement, skin involvement, and the presence of overlap syndromes may be experiencing pain that should be addressed. Research is needed to better understand the course of pain in SSc, to isolate disease manifestations most closely associated with high pain levels, and to develop interventions that effectively target pain sources and that support effective coping to reduce pain interference. Health care providers should collaborate with patients to identify disease aspects causing pain and attempt to address them. They should also support behavioural strategies to reduce the impact of pain on function and quality of life.

INTRODUCTION

Systemic sclerosis (SSc, or scleroderma) is a chronic autoimmune disease characterized by fibrosis of the skin and internal organs, including the lungs, gastrointestinal tract, and heart.[1] People with SSc emphasize the role of pain in quality of life, but pain is often overlooked in research and clinical care. Studies in Canada (N = 464)[2] and Europe (N = 537)[3] have found that painful disease manifestations (e.g., Raynaud's phenomenon, joint pain, muscle pain, cutaneous ulcers) are among SSc symptoms with the greatest negative functional impact. A 2010 Canadian study (N = 585) found that 83% of participants experienced at least mild pain ($\geq$ 1 on 0 to 10 scale) and 27% experienced moderate to severe pain ($\geq$ 5 on 0 to 10 scale).[4] Pain is by far the most common reason that people with SSc seek physical or occupational therapy services,[5] and pain management was identified in a recent survey of people with SSc as a priority for intervention research (N = 100).[6] No health care providers who responded to the same survey, however, identified pain as a priority (N = 24). Pain has not been the primary outcome in any SSc clinical trials; and few SSc trials have included pain as an outcome at all.

Only two studies with 200 or more participants have described SSc disease manifestations associated with pain. The European Scleroderma Observational Study (N = 326; data collected 2010 to 2014) found that Raynaud's phenomenon, gastrointestinal problems, breathing problems, and digital ulcers were significantly associated with pain intensity, but only bivariate analyses were conducted.[7] The Canadian Scleroderma Research Group (N = 585; data collected 2004 to 2008) found that more frequent episodes of Raynaud's phenomenon, active ulcers, worse synovitis, and gastrointestinal symptoms were associated with pain intensity in multivariable analysis.[4] Neither study examined pain interference in daily activities, and it is not known whether pain management and control has improved since those studies were conducted.

A better understanding of pain intensity and interference and SSc disease manifestations that may be associated with them would support research to improve pain management in SSc. The objectives of this study were to (1) describe levels of pain intensity and interference and (2) identify associated SSc disease-related factors, controlling for sociodemographic variables, in a large multinational SSc cohort.

METHODS

This was a cross-sectional study that evaluated baseline data from the Scleroderma Patient-centered Intervention Network (SPIN) Cohort.[8,9]

Participants and Procedures

The SPIN Cohort is a convenience sample. Eligible patients at SPIN recruiting sites are invited by the attending physician or a nurse coordinator to participate. Eligible participants must be classified as having SSc according to 2013 ACR/EULAR classification criteria;[10] ≥ 18 years of age; and fluent in English, French or Spanish. After written informed consent is obtained, the recruiting site physician or nurse coordinator completes and submits an online medical data form. An automated email is then sent to participants with instructions on activating their SPIN online account and completing measures. SPIN Cohort participants complete outcome measures via an online portal upon enrolment and subsequently every three months. The SPIN Cohort study was approved by the Research Ethics Committee of the Centre intégré universitaire de santé et de services sociaux du Centre-Ouest-de-l'Île-de-Montréal (#MP-05-2013-150) and by the ethics committees of all recruiting sites. The present study used baseline assessment data from participants enrolled between April 2014 and January 2020 from 46 centres in Canada, the United States, the United Kingdom, France, Spain, Mexico, and Australia. Characteristics of participants in the SPIN Cohort are comparable to those of participants in other large SSc cohorts.[9]

Measures

Sociodemographic and medical variables

Participants reported sociodemographic information. SPIN physicians provided medical information, including height, weight, date of initial onset of non-Raynaud's phenomenon symptoms; SSc subtype (limited, diffuse, sine); presence of joint contractures (none to mild [≤ 25% range of motion limitation]; moderate to severe [> 25%]); digital ulcers anywhere on the fingers (present; absent); presence of gastrointestinal involvement (oesophageal, stomach, or intestinal involvement; none); current tendon rubs (present; absent); modified Rodnan Skin Score (mRSS);[11] presence of overlap syndromes (systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome) along with SSc; and SSc-related antibodies, including antinuclear antibody, anti-centromere, anti-topoisomerase I, anti-RNA polymerase III (positive or negative according to each site's local laboratory standards).

Pain

Pain intensity and interference in the last 7 days were evaluated with the Patient Reported Outcomes Information System (PROMIS)-29 profile version 2·0.[12] Pain intensity is assessed with a 11-point numeric rating item (0 = no pain to 10 = worst imaginable pain), "In the past 7 days, how would you rate your pain on average". Pain interference on daily functioning is assessed with 4 items (day to day activities; work around the home; participation in social activities; household chores), which are scored on a five-point response scale (1 = not at all to 5 = very much). Pain interference item scores are summed to yield a domain score, which is converted into a T-score calibrated to the United States general population (mean = 50, standard deviation [SD] = 10). The PROMIS-29 v2.0 has been validated in the SPIN Cohort.[13]

Participants were categorized as having no, mild, moderate, or severe pain intensity and interference. For pain intensity, we used thresholds previously used in SSc[4] and other chronic pain populations[14,15] (none = 0, mild = 1 to 4, moderate = 5 to 7, severe = 8 to 10). Pain interference scores were classified as none (T-score < 50), mild (T-score 50-60), moderate (T-score 60-65), and severe (T-score > 65).[16]

Statistical Analysis

Descriptive statistics were computed for the total sample and those with diffuse and limited (including sine) SSc separately. To assess the association of SSc disease-related variables with pain intensity and interference, separately, controlling for sociodemographic variables, we used hierarchical linear regression. Variables included in models were identified *a priori* based on a review of variables included in previous studies on factors associated with pain in SSc[4,7] with confirmation of clinical relevance by team members who have SSc or are involved in SSc patient care. We did not include psychosocial or functional variables (e.g., depressive symptoms, anxiety symptoms, physical function, fatigue, self-efficacy) in the model as predictors because, similar to pain, they are often outcomes of SSc, and they would be expected to have bidirectional causal associations with pain. When there is reverse causation in models, meaning that outcome variables may be causally linked to predictor variables, (1) all model coefficients may be biased, which could mask potentially important associations between disease variables and pain; (2) goodness-of-fit estimates (R^2) are likely to be spuriously inflated; and (3) there is no way to determine the relative causal influence between the variables for which reverse causation is likely.[17]

Variables were added hierarchically in steps to assess change in adjusted R^2 separately for sociodemographic variables and body mass index, SSc-related variables, and overlap syndromes.

Sociodemographic variables (age, sex, race/ethnicity, education, country) and body mass index (BMI) were included in step 1. SSc variables (joint contractures, current tendon rubs, digital ulcers, gastrointestinal involvement, mRSS score) were added in step 2. Overlap syndromes (rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome) were added in step 3. Missing data were dealt with using multiple imputation via chained equations with 20 imputations, including all variables in the main regression models, plus depressive symptoms and limited versus diffuse disease subtype.

In sensitivity analyses, first, we conducted complete case analyses of our main models for pain intensity and interference including only participants without missing data. Second, we explored associations of SSc-related antibodies with pain intensity and interference by adding SSc-related antibody tests that were significantly associated with pain intensity or interference in bivariate analyses ($p < 0.05$) to the main models as step 4. We evaluated antibodies because of evidence that crude classification of SSc disease subtype and manifestations is limited in capturing the heterogeneity of the disease and that antibodies may help in classification and evaluation of prognosis.[18,19] Approximately 50% (N = 1018) of participants did not have information about anti-RNA polymerase III. Therefore, models evaluating anti-RNA polymerase III included only participants with complete data on all included variables. Third, to facilitate comparison with results from the 2010 Canadian Scleroderma Research Group study,[4] we performed a sensitivity analysis including only participants from Canada.

For all models, continuous predictor variables were standardized by subtracting raw scores from the mean and dividing by the SD. Unstandardized regression coefficients with 95% confidence intervals (CIs) were reported, along with total explained variance for each model (adjusted R^2) and change in adjusted R^2 from the previous model step. All regression analyses

were conducted using Stata Version 13. For each outcome, hierarchical linear regressions using multiply imputed data were fit using the mibeta command. Adjusted R^2 estimates were based on Fisher's Z transformation, using the option fisherz.

Role of the Funding Source

No funder had any role in any aspect of study design; data collection, analysis, and interpretation; manuscript drafting; or the decision to submit for publication. The corresponding author had access to all data and final responsibility for the decision to submit for publication.

RESULTS

Of 2283 participants who completed baseline SPIN Cohort self-report measures, 126 (5·5%) were missing pain intensity or interference scores and were excluded. As shown in Table 1, the remaining 2157 participants were predominantly female (87%; N = 1889) and White (83%; N = 1791). Mean (SD) age was 54·8 (12·7) years, mean (SD) education was 15·0 (3·7) years, and mean (SD) BMI was 25·5 (5·8). Participants were from the United States (36%; N = 780), France, (24%; N = 528), Canada (24%; N = 522), the United Kingdom (11%; N = 238) and Mexico, Spain, or Australia (4%; N = 89). Supplementary Table 1 lists participants by countries and recruitment sites. Mean (SD) time since onset of first non-Raynaud's symptoms was 11·1 (8·7) years, and 61% (N = 1295) of participants had limited SSc.

As shown in Table 2, mean (SD) pain intensity was 3·6 (2·6), 87% (N = 1870) of participants reported at least mild pain intensity, and 38% (N = 815) reported moderate-to-severe intensity. By country, pain intensity was highest for participants from the United Kingdom (mean = 4·2, SD = 2·8; Supplementary Figure 1). Participants with diffuse disease (mean = 3·9, SD = 2·7; Supplementary Figure 2) reported higher pain intensity scores than those with limited disease.

Pain interference was at least mild (T-score ≥ 50) for 72% (N = 1554) of participants and moderate-to-severe (T-score ≥ 60) for 35% (N = 757). Pain interference (total sample mean = 55·5, SD = 9·6) was substantially greater for participants from the United Kingdom (mean = 58·1, SD = 9·3) than for all other countries (Supplementary Figure 3) and for participants with diffuse disease compared to those with limited disease (Supplementary Figure 4).

Results of bivariate and multivariable hierarchical linear regression analyses are shown in Table 3 for pain intensity and Table 4 for pain interference. For pain intensity, among SSc-related and overlap syndrome variables, greater pain intensity (0 to 10 scale) was independently associated with presence of moderate-to-severe joint contractures (0·67 points, 95% CI 0·39 to 0·94), digital ulcers (0·33 points, 95% CI 0·10 to 0·55), gastrointestinal involvement (0·66 points, 95% CI 0·33 to 0·98), greater mRSS scores (0·22 points per SD, 95% CI 0·10 to 0·35), and the presence of rheumatoid arthritis (0·96 points, 95% CI 0·50 to 1·43) and Sjögren's syndrome (0·42 points, 95% CI 0·01 to 0·83). Current tendon rubs were also positively associated, although this was not statistically significant (0·35 points, 95% CI -0·02 to 0·71). Results were similar for pain interference.

Adjusted R^2 for the final model was 0·11 for pain intensity and 0·10 for pain interference. All tolerance values were between 1·02 and 1·23 for both models, indicating multicollinearity was not problematic.

Results from complete case analyses, which included 1542 participants with no missing data, were similar to those from the main models for pain intensity and interference (Supplemental Tables 2 and 3).

Of the four SSc-related antibodies, only anti-RNA polymerase III was associated with pain intensity and interference in bivariate analyses. It was not, however, significant in the multivariable analyses.

When considering only participants recruited from sites in Canada (N = 522), pain intensity (89% at least mild pain, N = 463; mean = 3·7, SD = 2·6) and pain interference (mean = 55·6, SD = 9·5) levels were comparable with the full sample. Only education, BMI, presence of gastrointestinal symptoms, and presence of rheumatoid arthritis were significantly associated with pain intensity (Table 2) and interference (Table 3), although association magnitudes and direction were generally consistent with the full sample models across variables.

DISCUSSION

Among 2157 participants with SSc from seven countries, 87% reported at least mild pain intensity during the past seven days, including 38% with moderate-to-severe pain intensity. At least mild pain interference in daily functioning was reported by 72% of participants and moderate-to-severe interference by 35%. Disease manifestations in SSc are highly diverse and, consistent with this, we identified many factors significantly associated with both pain intensity and interference. Among sociodemographic and general health characteristics, female sex, self-reported race/ethnicity other than White, fewer years of education, and higher BMI were associated with greater pain intensity and interference. SSc disease manifestations associated with greater pain intensity and interference included moderate-to-severe joint contractures, the presence of digital ulcers, gastrointestinal involvement, higher mRSS scores, and the presence of rheumatoid arthritis and Sjögren's syndrome. While some people with SSc may experience none or only one of these SSc-related manifestations, many people experience several.

The adjusted R^2 values for pain intensity and pain interference models were low. High R^2 values are important in predictive modelling, but much less so when models are used for testing hypotheses about the possible effects of variables of interest. In this case, including in the present study, having a sufficiently large sample size to generate reasonably precise parameter estimates is a more important consideration.[17]

The 87% of participants in our study who experienced at least mild pain in the past 7 days and 38% with moderate-to-severe pain is consistent with the 83% and 37% reported in the 2010 Canadian Scleroderma Research Group registry study. The mean pain intensity (3·5 out of 10) was also similar to levels in that study (3·6 out of 10)[4] and from the European Scleroderma Observational Study (32·9 out of 100).[7] Pain intensity in the present study was also similar to levels reported in recent studies of people with rheumatoid arthritis, a condition that is largely defined by pain and is commonly considered more painful than SSc. A study of 2029 Dutch and Flemish rheumatoid arthritis patients reported mean pain intensity of 3·6 out of 10,[20] and a study of 177 patients at a US academic centre reported 31 out of 100.[21] In contrast, a study that compared pain among 82 people with SSc and 71 with rheumatoid arthritis from rheumatology and internal medicine departments in two university hospitals in Paris, France found that both pain intensity and interference were significantly greater in rheumatoid arthritis. Pain intensity was 4·2 out of 10 in SSc versus 5·4 in rheumatoid arthritis.[22]

We found that sociodemographic variables (sex, race/ethnicity, education) and BMI were associated with both pain intensity and interference, consistent with previous findings in rheumatoid arthritis and other chronic pain populations.[23,24] Among SSc symptoms and disease overlap, we found that the presence of moderate-to-severe joint contractures, the presence of digital ulcers, any gastrointestinal involvement, mRSS, and overlap syndromes (rheumatoid

arthritis, Sjögren's syndrome) were independently associated with pain intensity and interference. Current tendon rubs were associated in bivariate analysis but not multivariable regression. Magnitudes of associations were between 0·4 and 1·2 points on a 0-10 pain scale in bivariate analyses and between 0·4 and 1·0 points in multivariable analysis. In the previous study by the Canadian Scleroderma Research Group,[4] the number of patient-reported episodes of Raynaud's phenomenon in the last week, active non-digital tip ulcers, swollen joint count, and the total number of gastrointestinal symptoms (out of 6) were significantly associated with pain intensity; mRSS, active fingertip ulcers, finger and joint contractures, and tendon friction rubs were not. Magnitudes of associations also differed somewhat. Differences between the studies may be explained by the relatively smaller sample and lower precision of estimates in the previous study, as well as differences in the way disease manifestations were assessed. The previous study, for example, specifically assessed active digital tip ulcers and other ulcers, evaluated six different gastrointestinal symptoms, included patient-reported number of Raynaud's episodes, assessed joint and finger contractures separately, and included a swollen joint count. In contrast, in the present study, apart from mRSS, disease manifestations were assessed dichotomously as present or absent, and overlap syndromes were included in the main analysis. We did not include dichotomous Raynaud's phenomenon in models, since it was present in virtually all participants in the SPIN Cohort, and we did not have a frequency-based assessment.

Only one of four SSc-related antibodies evaluated was significantly associated with pain intensity or interference in bivariate analyses, and this relationship did not persist after adjusting for sociodemographic and clinical variables. This finding differs from reports demonstrating associations between SSc-related antibodies and specific clinical phenotypes.[18] Previous studies

have largely, however, focused on relatively well-defined phenotypes, such as cancer, inflammatory myositis, or vascular disease.[19] Pain is fundamentally different from these outcomes, as it is multifactorial in origin and highly subjective in nature.

Taken together, the findings of the present study, which assessed pain intensity and interference, and the previous study by the Canadian Scleroderma Research Group on pain intensity emphasize that pain levels are higher in SSc than might be assumed and may be similar to levels in rheumatoid arthritis.[20-22] The present study shows that pain plays a critically important role in the functional ability of people with SSc. The two studies underline the multifactorial nature of pain in SSc. People with SSc may experience pain from many sources, including skin hardening and thickening, joint contractures, ulcers, and manifestations of overlap syndromes, including rheumatoid arthritis and Sjögren's syndrome.

Compared to other conditions, such as rheumatoid arthritis, where pain is a focus, relatively little is known about pain in SSc. Studies are needed to understand the course of pain and to what degree it varies with the course of other symptom manifestations. We have identified disease manifestations linked to pain in SSc, but studies are needed that focus specifically on pain and can more precisely delineate the relative contributions of the associations that we have identified. Interventions are needed to address pain, including interventions that target sources of pain and interventions that seek to improve coping and reduce pain interference. Pain outcomes should be included in SSc clinical trials. Although pain intensity and interference share similar associations with SSc-related manifestations, they are not one and the same. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials recommends that pain interference be included as a core outcome in clinical trials related to chronic pain,[25] and pain interference should be included as an outcome in SSc clinical trials.

Clinically, it is important that a patient-centered approach be taken to understanding and intervening to reduce the effects of pain in individual patients. Working with patients to identify SSc manifestations associated with pain and attempting to address them may be helpful. Pain itself may be difficult to treat, but there are interventions that can reduce pain interference in daily activities,[26-29] and approaches used successfully in other diseases may be helpful in SSc. Thus, it is important that healthcare providers ask not only about pain intensity, but also about how pain interferes with their patients' daily lives. Ultimately, understanding pain interference will enable healthcare providers to help patients lead their best lives possible, even if it may not be possible to eliminate pain completely. Clinicians should be aware that pain and depression tend to be closely linked; pain can induce depression, and depression may amplify pain perception. Behavioural and pharmacological approaches may be helpful in addressing both pain and depression.[28,29]

Strengths of our study include its international sample with participants from over 45 sites; its large sample size, which is several times the next largest study; the degree to which patients contributed via leadership in SPIN and via input into the study itself; and the evaluation of pain interference, in addition to pain intensity. There are also limitations. First, the SPIN Cohort is a convenience sample, and participation required answering questions via online forms, both of which may reduce generalizability. Second, 24% of participants were from Canada and may have also been included in the Canadian Scleroderma Research Group study;[4] given the number of years between when data were collected, however, this percentage is likely very low. Data were not available to identify the exact overlap between the cohorts. Third, categorizing pain severity into mild, moderate, and severe groups, though based on previously used standards, may not accurately reflect how individuals characterize their pain. Fourth, because this was a cross-

sectional study, determinations cannot be made regarding causality. Fifth, we did not attempt to evaluate the potential contributions to pain of psychosocial or functional variables, such as depressive symptoms, anxiety symptoms, and reduced physical function or activity level, all of which are common in SSc.[30] Pain can lead to depression and anxiety and reduce mobility, but, at the same time, depression, anxiety, and reduced movement can exacerbate pain.[30] When reverse causation between variables is present, it is not possible to attempt to estimate relative contributions with cross-sectional data. Sixth, variables included in the model were limited to those collected in the SPIN Cohort and how they were assessed. It is possible that not all relevant variables were included, and that the dichotomous measurement of some included variables may have reduced the strength of associations. Calcinosis, which is likely an important source of pain for some people with SSc,[4] is not assessed in the cohort. Additionally, we did not have access to information on medication use and could not evaluate the possible association of different medications with pain intensity or interference. Seventh, 29% of participants were missing a value for at least one variable, which could lead to bias. However, results from complete case analyses were similar to imputed model outcomes.

Almost 9 in 10 people with SSc report at least mild pain, and almost 4 in 10 report moderate-to-severe pain, which has not changed in the past 10 years. More than 1 in 3 report moderate-to-severe interference in their ability to carry out daily activities. SSc is highly divergent in its presentation, and we identified many different SSc-related manifestations associated with pain, including degree of skin involvement, joint contractures, gastrointestinal involvement, digital ulcers, and the presence of rheumatoid arthritis and Sjögren's syndrome. Research is needed to better understand the course of pain in SSc over time and with changes in disease state, isolate disease manifestations most important to understanding pain, and develop

interventions that reduce pain and pain interference via targeting pain sources and pain

behaviours. Clinically, health care providers should work with patients to address pain, including

identifying and addressing SSc manifestations associated with their pain and supporting

behavioural approaches to minimize impact on function and quality of life.

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Data Sharing: De-identified individual participant data with a data dictionary and analysis codes that were used to generate the results reported in this article will be made available upon request to the corresponding author and presentation of a methodologically sound proposal that is approved by the Scleroderma Patient-centered Intervention Network Data Access and

Publications Committee. Data will be available beginning 12 months after publication. Data requesters will need to sign a data transfer agreement.

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