PREVALENCE, SEVERITY AND CLINICAL CORRELATES OF PAIN IN PATIENTS WITH SYSTEMIC SCLEROSIS

Orit Schieir, BA

Department of Epidemiology, Biostatistics, and Occupational Health

McGill University, Montreal, Quebec

May 2009

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science

DEDICATION

This document is dedicated to my loving parents, Amnon and Linda Schieir, for their unwavering love and support.

ACKNOWLEDGMENTS

I would like to thank the members of my thesis advisory committee, Dr. Brett D. Thombs, Dr. James Hanley, Dr. Jean-François Boivin and Dr. Marie Hudson for mentoring and providing me with invaluable feedback throughout the present study. I would like to thank Dr. Murray Baron and the Canadian Scleroderma Research Group for providing me with an outstanding scleroderma training program. In addition, I would like to thank the National Study Coordinator, Dr. Suzanne Taillefer and Training Coordinator, Ms. Jessica Bernstein of the Canadian Scleroderma Research Group for providing me with the technical support needed to manage the Registry data used in the present study. Research findings from the present traditional thesis were summarized and submitted as a separate full-length manuscript to Arthritis Care and Research in April 2009. Status of the manuscript is pending review. I would, therefore, also like to thank the manuscript co-authors including Dr. Brett D. Thombs, Dr. Marie Hudson, Dr. Jean-François Boivin, Dr. Russell Steele, Dr. Sasha Bernatsky, Dr. James Hanley, Dr. Murray Baron, and the Members of the Canadian Scleroderma Research Group, for their insightful comments during the preparation of the manuscript. Lastly, I would like to acknowledge personal financial support received from a Fonds de la Recherche en Santé de Québec (FRSQ) Bourse de Formation – Formation Maîtrise (2008 – 2010), a Canadian Scleroderma Research Group Studentship (Canadian Institutes of Health Research [CIHR] Strategic Training Initiative in Health Research Grant [2007-2009]) and a CIHR Frederick Banting and Charles Best Canada Graduate Scholarships – Master's Award (2007-2008).

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

ABSTRACT

Systemic Sclerosis (SSc) is a highly heterogeneous multi-system disease characterized by vasculopathy, immune system activation and fibrosis. Patients are classified into limited or diffuse SSc disease subsets according to the extent of skin involvement. This was the first study to use a large multi-center convenience sample of SSc patients (N=585) to estimate prevalence, severity and associations between clinical variables and pain in SSc and, separately in limited and diffuse subsets. Results from the present study draw attention to the high prevalence of pain in SSc and associations between specific clinical variables and pain, including more frequent episodes of Raynaud's phenomenon, active ulcers, worse synovitis and gastrointestinal symptoms, which may represent potential clinical intervention targets. Subsetting by the extent of skin involvement was only minimally related to pain severity and did not affect associations with clinical variables. More attention to pain and how to best manage it is needed in SSc.

ABRÉGÉ

La sclérose systémique (SSc) se caractérise par une vasculopathie, une dysfonction auto-immune, et une fibrose diffuse. Les personnes atteintes de SSc sont classifiées comme ayant la SSc limitée ou diffuse selon l'étendue de l'atteinte cutanée. Notre étude est la première grande recherche multicentrique d'un échantillon de convenance (N=585) à estimer la prévalence, la sévérité et les associations entre les manifestations cliniques de la SSc et la douleur. Les résultats démontrent que la prévalence de la douleur est élevée, et que certaines variables cliniques sont associées à celle-ci (syndrome de Raynaud, ulcérations actives, synovites et symptômes gastro-intestinaux) et pourraient donc représenter des cibles d'intervention. L'étendue de l'atteinte cutanée affecte très peu ou pas du tout la sévérité de la douleur et les associations observées avec les variables cliniques. Plus d'attention à la douleur et à des stratégies thérapeutiques qui pourraient diminuer son intensité est nécessaire pour les personnes atteintes de SSc.

CHAPTER 1

Systemic Sclerosis: An Uncommon Autoimmune Disease

1.1 Scleroderma Spectrum Diseases

The word scleroderma comes from the Greek "scleros" meaning hard and "derma" meaning skin (1). Scleroderma can be localized, involving the skin only, or systemic, involving the body's internal organs. Localized scleroderma often occurs in children, and manifests itself as either one or more patches of thick skin throughout the body (called morphea) or skin thickening following a straight line along the head, arms or legs (called linear scleroderma). Localized scleroderma can resolve within a few years either on its own or with treatment by a physician. On the other hand, systemic scleroderma or systemic sclerosis (SSc) is much more severe, often occurring in adults and involving the body's internal organ systems (heart, kidney, lung, gastrointestinal tract) (2, 3). There is currently no known cause or cure for SSc but there are treatments available targeting different aspects of the disease (4). The following will review clinical and epidemiologic aspects of SSc.

1.2 Systemic Sclerosis Pathophysiology: Too little blood flow, too much collagen

SSc is a connective tissue disease characterized by: 1) *vasculopathy* - narrowing/ occlusion of the small blood vessels resulting in reduced blood flow particularly to the extremities (5); 2) *immune system activation* - presence of disease-related auto-antibodies, most notably anti-nuclear antibody (ANA), anti-centromere autoantibody (ACA) and anti-topoisomerase I (anti-SCL 70) (6); and 3) *fibrosis* – an abnormal scarring process associated with an overproduction of collagen by collagen-producing cells (myofibroblasts) found in connective tissues like the skin and tissues surrounding the internal organs (7). Reduced blood flow to the hands often results in Raynaud's phenomenon, which is the most common symptom of SSc and affects 95% of patients. Raynaud's phenomenon, which manifests as a marked white/ blue discoloration of the fingers in response to exposure to cold, is frequently the first SSc symptom experienced by patients (8). Many advances have been made in understanding the interplay between vascular, autoimmune and fibrotic changes that are involved in dangerous internal organ-system complications (heart, lung, kidney, gastrointestinal tract) common in SSc. The trigger of these events, however, remains unknown (9, 10).

1.3 Diagnosis and Classification of Patients with Systemic Sclerosis

Classification criteria for definite scleroderma were developed in 1980 by the American College of Rheumatology (ACR) Subcommittee for Scleroderma (Appendix 1). These criteria are divided into major and minor criteria. The authors of the original criteria reported that 97% of "definite cases" of SSc, but

only 2% of comparison cases with systemic lupus erythematosus, polymyositis/dermatomyositis, or Raynaud's phenomenon were positive for at least one major criterion or two or more minor criteria. However, data from these same patients were used to generate the criteria and "probable" and "overlap" patients were excluded from this analysis (11). When used for the purposes of clinical diagnosis, experts experienced in SSc estimate that these criteria exclude at least 10% of cases, most often cases with early disease and patients with sine scleroderma, which is a subset of cases without skin involvement but with SSc-related internal organ-system involvement (12, 13). The ACR criteria are typically used as inclusion criteria in research studies for purposes of standardization, but the opinion of a rheumatologist experienced in SSc remains the gold standard for clinical purposes.

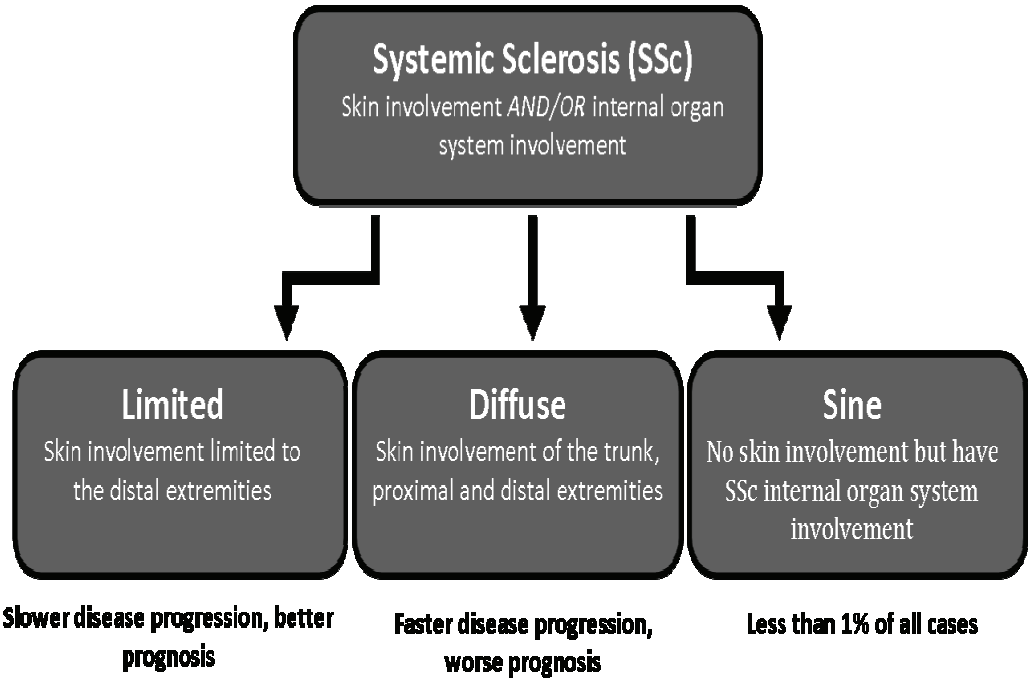
The clinical profile of SSc is highly heterogeneous and often requires a tailored course of action for each individual patient (14). Classification of patients into SSc disease subsets, identification of serological markers and estimated disease duration provide important prognostic information about the course of the disease (15). Patients are most commonly classified as having either limited or diffuse SSc based on the extent of skin thickening throughout the body. According to the most widely used criteria described by LeRoy et al. (16), limited cases typically have had episodes of Raynaud's phenomenon for many years prior to developing skin changes and only have skin involvement distal to the knees and elbows (i.e. limited to the face, neck, forearms, hands, lower legs and feet). Patients with limited SSc may have a constellation of symptoms referred to as CREST syndrome - an acronym referring to the presence of calcinosis (**C**),

Raynaud's phenomenon (**R**), esophageal involvement (**E**), sclerodactyly (skin thickening of the hands) (**S**) and telangiectasias (visible dilated blood vessels on the skin) (**T**), and are at risk for developing late-onset pulmonary hypertension. Patients with limited disease are more often positive for anti-centromere (ACA) autoantibody.

Patients with diffuse SSc, on the other hand, typically have episodes of Raynaud's phenomenon for a short duration or start experiencing episodes of Raynaud's phenomenon simultaneously with other disease features and have rapidly progressive skin involvement extending to the trunk and proximal extremities within the first few years of disease. Patients with diffuse SSc commonly have tendon friction rubs, skin inflammation, esophageal involvement and are at risk for developing severe internal organ-system complications much earlier than patients with the limited form of SSc (17). They are also more likely to be positive for anti-topoisomerase I (anti-SCL 70) autoantibody.

There is a third subset of patients with SSc who have sine scleroderma ("sine" meaning without, "scleroderma" meaning hard skin), which is far less common, accounting for less than 1% of all SSc cases. Patients with sine SSc do not present with the hallmark skin thickening seen in patients with limited and diffuse SSc, but have SSc-related internal organ system involvement (18). The remainder of this review will focus on the limited and diffuse forms of SSc only. Classification of SSc-disease subsets is summarized below in Figure 1.1.

Figure 1.1 Summary of Systemic Sclerosis Classification



1.4 Epidemiology of Systemic Sclerosis

INCIDENCE AND PREVALENCE OF SSC

There are several challenges in obtaining reliable and valid estimates of incidence and prevalence from examining individual epidemiologic studies. These include: a) heterogeneity in case definition/diagnosis; b) different methods of case ascertainment; c) variability in study time periods and duration across studies; d) small sample sizes; and e) the lower likelihood of sampling cases that have yet to be diagnosed and / or severe cases that die early in the course of their disease (19, 20). A recent systematic review of 32 reports from 6 continents from 1947-2002 (21) reported a world-wide prevalence of SSc of 50-300 cases per million, excluding specific cluster studies (22-24) and specific population studies (25). One of the largest studies included in this review (26) estimated incidence and prevalence of SSc in the US from a sample of 2.9 million people living in the Detroit area between 1989-1991 and reported a prevalence of 242 cases per million and an incidence of 19.3 cases per million per year. These estimates increased to 276 and 21 cases per million per year, respectively, after using a capture-recapture method. These findings were consistent with another large US study (27) from Virginia from 1978-1982 that reported an incidence of 18 (95% CI:15 to 21) SSc cases per million per year. Recent estimates are higher than in studies of SSc prior to 1980, which generated incidence estimates between 0.6-12 cases per million per year (28). These differences may be due to a true increase in incidence over time. On the other hand, they may be due to improved

understanding and tracking of patients with SSc in more recent years, publication of classification criteria for SSc and subsets of SSc, longer survival of patients with SSc, availability of electronic hospital records, or the establishment of SSc disease registries and patient advocacy groups (20).

GENDER AND RACIAL DIFFERENCES IN SSC

Incidence and prevalence rates of SSc have been shown to vary quite substantially by gender and race. Although ratios differ across studies, SSc is consistently reported to occur more often in women than in men (3:1 to 14:1 female to male ratio) (21) and disease onset is particularly prominent in women during the childbearing years (27). Three large US studies from Detroit, Virginia and Michigan respectively (26, 27, 29), all showed that Blacks had an earlier age of SSc disease onset, higher incidence of diffuse disease and worse age adjusted mortality than Whites. One study (26) reported that male sex was associated with younger SSc disease onset, higher incidence of diffuse disease and higher mortality. No differences were reported between white and black males. The largest cluster of SSc cases reported to date was in a particular Aboriginal population, the Choctaw Indians of South Eastern Oklahoma (25). The 4-year period prevalence of SSc was 8 cases out of a sample of 1,704 Choctaw Indians (1990-1994), equivalent to approximately 4,690 cases per million which is more than 15 times the prevalence of SSc reported by Mayes et al. (26) in the Detroit area from 1989-1991 after using a capture re-capture method. Cases had a homogeneous clinical profile of diffuse disease and anti-topoisomerase I autoantibody status. Prevalence was significantly higher in pure-blood Choctaw

Indians than in other Native populations residing in Oklahoma and higher than in half- blood Choctaw Indians. Study investigators reported a strong risk of SSc associated with a specific genetic haplotype found in pure-blood Choctaw Indians. These sex and racial disparities in SSc suggest strong hormonal and / or genetic risk factors for developing SSc and specific clinical phenotypes of SSc.

SSC MORBIDITY AND MORTALITY

SSc is associated with increased morbidity and mortality (30). Ten to fifteen percent of patients with SSc develop pulmonary arterial hypertension (31); 25-90% develop interstitial lung disease (also called pulmonary fibrosis) (32); approximately 10% develop scleroderma renal crisis (33); 20-25% experience heart complications (34) and over 90% have gastrointestinal problems (35). Other common features of SSc are orofacial changes including narrowing of the oral aperture; dry eyes and mouth suggestive of secondary Sjogren's syndrome (36); and musculoskeletal involvement of joints, muscles and/or tendons (37).

The rate of mortality from SSc has dropped in recent decades but is still significantly higher than in the general population. Ten-year survival of patients with SSc (mean age of SSc disease onset 40-43 years of age) increased from 53% in the 1970s to 67% in the 1990s (38). A meta-analysis of individual patient data from 6 international SSc cohorts showed that standardized mortality ratios based on incident cases of SSc ranged from 1.5 to 7.2 (39), consistently showing worse mortality in SSc compared to age and sex matched populations without SSc. Internal organ-system involvement of the heart, kidney and/or lungs, male sex, older age of onset, more skin involvement (diffuse disease), presence of anti-

topoisomerase I autoantibody, anti-centromere autoantibody negativity, increased erythrocyte sedimentation rate (ESR) (a general marker of inflammation), and proteinuria have been associated with increased mortality (30, 39-41). SSc lung disease is the most frequent cause of death (38, 42).

1.5 Living with Systemic Sclerosis: Understanding Patient Disease Burden

Along with higher morbidity and mortality, patients with SSc face significant financial, physical, emotional and social burdens that affect their health-related quality of life.

SSc is associated with considerable economic costs. A recent study of Canadian patients with SSc part of the Canadian Scleroderma Research Group (CSRG) Registry (N =457) (43) reported annual costs (direct medical costs and indirect costs due to productivity losses in paid and unpaid labour) of more than $18,000 2007 Canadian Dollars per patient per year, with patients with diffuse disease experiencing higher annual costs (approximately $22 000 2007 Canadian dollars) than patients with limited disease (approximately $16 000 2007 Canadian dollars). These figures suggest total annual costs due to SSc as high as 1.9 billion US dollars per year across North America and 3.1 billion Euros per year across Europe. Moreover, costs for patients with limited disease were comparable to annual costs estimated in patients with rheumatoid arthritis (N =253) (44) equivalent to approximately 16,000 2007 Canadian dollars per patient per year (43) and even higher than in rheumatoid arthritis for patients with diffuse disease. Younger age, greater disease severity and poorer health status were strongly

associated with higher annual costs (43). Consistent with the Canadian study, high direct and indirect costs of SSc have also been reported in studies in the US (45) and Italy (46).

Several studies (47-50) have highlighted the physical and psychosocial burdens of SSc including: a) symptoms such as pain, fatigue, troubled sleep, gastrointestinal problems, skin disturbances, ulcers and calcinosis in the distal extremities and shortness of breath; b) emotional disturbances such as fear, depression, helplessness, low-self esteem, concerns about physical appearance and uncertainty about the future; and c) social/lifestyle disruptions such as interference in daily activities from disease symptoms, family and marital conflicts, work disability, social withdrawal and discomfort with the perception of their illness by others. A systematic review by Thombs et al. (51) of 8 studies that used self-report depression symptom questionnaires showed consistently high prevalence of above threshold depressive symptoms across studies in SSc, ranging from 36-65%. These prevalence rates were high even when compared to other disease groups using the same instruments and cut-offs. Moreover, Hyphantis et al. (52) examined the independent effect of having a diagnosis of SSc on psychiatric symptoms (including general distress, anxiety and depressive symptoms) and showed that after controlling for demographic (age, sex, education) and personality variables (defence style, hostility, sense of coherence), presence of SSc was associated with 4.5 times higher odds (95% CI: 1.3 to 15.3) of screening positive for elevated psychiatric symptoms.

The high SSc-related financial, physical and emotional burdens suggest that patients with SSc experience significant declines in quality of life due to their

illness. This has been confirmed in studies that have examined data on global measures of health-related quality of life. Georges et al. (53) administered the Medical Outcome Studies Short Form 36 (SF-36) to 89 patients with SSc and found that scores in all domains (physical functioning, physical role limitation, emotional role limitation, bodily pain, general health, mental health, vitality and social functioning) were significantly worse in SSc compared with US and French general population samples. Johnson et al. (54) examined quality of life measured by the physical component score of the SF-36 in patients with SSc (N = 82), rheumatoid arthritis (N = 42), psoriatic arthritis (N =82), lupus (N = 75), and healthy controls (N = 60). All 4 patient groups had significantly reduced quality of life compared to healthy controls, and quality of life was similar across all 4 patient samples. Additionally, a large study of Canadian SSc patients part of the CSRG Registry (N =402) (55) found that levels of quality of life based on the World Health Organization Disability Assessment Schedule II were significantly below that of Canadian healthy population norms and were similar to other SSc samples as well as samples of patients with ankylosing spondylitis, chronic low back pain and other musculoskeletal conditions. Thus, evidence across studies consistently shows that patients with SSc experience significant reductions in quality of life that are similar to those reported in other rheumatic diseases.

1.6 Summary and Key Messages

SSc is a disease characterized by vascular, immune system and fibrotic changes that frequently affect the skin and internal organ systems. Patients are

most commonly classified into either limited or diffuse SSc disease subsets. Diffuse cases typically have more rapid disease progression, widespread skin thickening, earlier internal organ system involvement and a worse prognosis, than limited cases. SSc largely affects young women, with disease onset common in the childbearing years, and along with high rates of morbidity and mortality, SSc has a significant impact on multiple aspects of quality of life.

KEY MESSAGES

- The clinical profile of SSc is heterogeneous and subsets of patients with limited and diffuse SSc often require different treatment considerations.
- There is currently no known cure for SSc. Therefore, research aimed at preventing disability and improving patient's quality of life is urgently needed.

CHAPTER 2

Patient-Centered Targets for Disease Management: The Role of Pain

2.1 Pain in Rheumatic Disease

Pain is prominent in rheumatic diseases and is highly predictive of physician consultation, disability and health-related quality of life (56-58). Pain severity is a core outcome measure of disease activity in most rheumatic diseases, including rheumatoid arthritis, osteoarthritis, fibromyalgia, ankylosing spondylitis and psoriatic arthritis (59-63). Moreover, pain is an important priority to patients with rheumatic disease. One study (64) surveyed 1,024 (68.6%) patients from the Oslo Rheumatoid Arthritis Registry and found that patients prioritized improvements in pain management above any other treatment area, even after controlling for age, sex, employment status and disability. In that study, 50% of patients in the lowest intensity pain group identified pain as their first priority for improvement, suggesting that pain need not reach high levels to greatly affect patient care needs. The following will review the current evidence regarding associations between pain and heath outcomes in SSc.

2.2 Pain and Patient-Reported Health Outcomes in Systemic Sclerosis

Results across studies of patients with SSc are consistent and suggest that pain is strongly associated with SSc clinical and emotional health status. One study (65) re-analyzed data from 74 patients with early diffuse disease enrolled in the Scleroderma Methotrexate Trial and found that patients with pain scores below the median on a common measure of pain severity, the pain visual analogue scale of the Stanford Health Assessment Questionnaire (HAQ-PVAS), at baseline, had 5 times the odds of having a 20% improvement in patient-rated disease severity at 1-year follow-up (OR: 5.0, CI: 1.55-16.09) compared to patients with pain scores at or above the median. Patients with pain scores below the median at baseline also had on average twice the odds of having a 20% improvement in physician-rated disease severity at 1-year follow-up; however this association was not statistically significant (OR: 2.13, CI: 0.76-5.93). A study of 49 patients with SSc showed that pain (HAQ-PVAS) was highly correlated with disability ($r = 0.62$, $p < 0.01$) (49). Another study of 114 patients with SSc (66) using path analysis methods reported a significant direct path from pain to disability (standardized regression coefficient 0.52, $p < 0.001$) and a significant direct path from pain to psychosocial adjustment (standardized regression coefficient 0.34, $p<0.0005$). Another study (N =142) showed that McGill Pain Questionnaire scores were independently associated with depressive symptoms and social adjustment, and were the most robust predictor of disability after adjusting for SSc disease subset status, employment status, depressive symptoms and social networking (67).

Pain scores are also robustly associated with common measures of health-related quality of life. A study by Georges et al. (53) (N = 89) showed that pain (HAQ-PVAS) was significantly associated with both the physical component summary score (r = 0.69) and the mental component summary score (r = 0.34) of the SF-36. The physical component score of the SF-36, however, consists of physical domains including bodily pain which could have artificially increased the estimated association. Nonetheless, a large study of 337 patients with SSc (68) enrolled in the CSRG Registry that used separate scales to assess pain and quality of life showed that pain was highly correlated with decreased quality of life (tau b=0.41) in unadjusted analysis, and was a strong independent predictor of lower quality of life in multivariable analysis (standardized regression coefficient = 0.135, p = 0.003) after adjusting for demographic (age, sex, education), clinical (duration, skin score, shortness of breath, finger contractures, finger ulcers, fibromyalgia tender points, swollen and tender joints) and other psychosocial variables (fatigue, depressive symptoms).

2.3 Summary and Key Messages

Pain is highly predictive of adverse health outcomes in most rheumatic diseases, and better pain management is an important priority for these patients. Relatively few studies have assessed pain and health outcomes in SSc, but these studies report consistent strong associations between pain and worse SSc health status, including greater disability and decreased quality of life. Pain may be an

important target to reduce disability and improve quality of life in patients with SSc.

KEY MESSAGES

- Pain is associated with poorer SSc heath status, most notably higher disability and decreased quality of life.
- Research aimed at improving the understanding of pain in SSc may ultimately lead to better functioning and quality of life for these patients.

CHAPTER 3

A Review of What is Known and Unknown about Pain in Systemic Sclerosis

3.1 The Challenge of Understanding Pain in Systemic Sclerosis

Pain is a widely acknowledged problem in most rheumatic diseases, however, pain continues to receive relatively little attention in the context of SSc. Subsequently, estimates of prevalence and severity of pain in SSc are based on few studies with relatively small samples. Further, contrary to other rheumatic diseases where sources of pain are well defined, SSc is a complex multi-system disease where pain may arise from multiple sources. The lack of studies that assess specific sources of pain in SSc makes it difficult for health care providers to evaluate possible sources of pain in SSc (69). The following will review evidence regarding prevalence, severity and potential sources of pain in SSc. Study objectives are also presented.

3.2 Prevalence and Severity of Pain in Systemic Sclerosis

Small studies based on 19, 49 and 142 patients with SSc (49, 50, 67) have shown that pain is common, and that at least some pain is present in 60-75% of patients with SSc. Mean pain in SSc samples has been suggested to be in the mild range (47, 70). Nonetheless, no significant or clinically meaningful differences have been observed between patients with SSc and other chronic pain and rheumatic disease groups in studies that used the same pain assessment tools for comparison (54, 67, 71). This suggests that pain is a common problem and likely as severe in SSc as in other rheumatic diseases where pain is a widely recognized concern.

Patients with diffuse SSc typically experience a more rapid and more severe disease process than patients with limited SSc, and it is therefore reasonable to hypothesize that diffuse cases may experience more severe pain than limited cases. Several studies, summarized below in Table 3.1., have assessed pain in subsets of patients with limited and diffuse SSc, and all have reported higher pain scores in diffuse cases than in limited cases. Although all of these studies report small and statistically non-significant effect sizes with the exception of the Malcarne study that reports a moderate to large and statistically significant effect size.

To date, studies of pain in SSc have been based on relatively small samples and larger sample sizes are required to obtain robust estimates of the prevalence and the severity of pain in SSc as well as to determine whether

patients with limited and diffuse disease experience clinically meaningful differences in pain.

Table 3.1. Studies Examining Pain Severity in Limited and Diffuse Subsets

Study	*Pain Measure*	*Range*	*n limited / n diffuse*	*Limited mean (SD)*	*Diffuse mean (SD)*	*Effect Size[e] (95% CI)*
Del Rosso et al. (72)	BP SF-36[a]	0 -100	15 / 9	47 (26)	42 (15)	0.2 (-0.6, 1.0)
Rannou et al. (73)	BP SF-36[a]	0-100	23 / 27	51 (24)	43 (24)	0.3 (-0.3, 0.8)
Richards et al. (49)	Pain VAS[b]	0 -100	33 / 16	47 (32)	43 (28)	0.1 (-0.5, 0.7)
Johnson et al. (54)	HAQ-PVAS[c]	0 -3	42 / 40	0.94 (0.98)	1.24 (0.90)	0.3 (-0.1, 0.8)
Malcarne at al. (66)	HAQ-PVAS[c]	0 -3	41 / 73	0.87 (0.67)	1.37 (0.86)	0.6 (0.2, 1.0)
Benrud-Larson et al. (67)	MPQ Total Score[d]	0 - 45	91 / 50	9.33 (8.85)	9.64 (7.56)	0.0 (-0.3, 0.4)

[a] BP SF-36 = Bodily Pain Subscale of the Medical Outcomes Study Short Form 36; [b] Pain VAS= Pain Visual Analogue Scale; [c] HAQ-PVAS = Pain Visual Analogue Scale of the Stanford Health Assessment Questionnaire; [d] MPQ Total Score = McGill Pain Questionnaire Total Score; and [e] Hedges' g estimated with pooled standard deviations using degrees of freedom (rather than total n) as the divisor.

3.3 Possible Sources of Pain in Patients with Systemic Sclerosis

Many different clinical signs and symptoms of SSc may represent potential sources of pain. These include: i) skin changes, which are universal in SSc and commonly lead to tightening, inflammation and itching in areas throughout the body (3); ii) vascular problems, such as Raynaud's attacks, which are experienced by 95% of patients, and digital ulcers, which are present in up to 50% of patients (74-76); iii) involvement of the gastrointestinal tract, including problems of the esophagus, stomach and intestines, that are present in up to 90% of patients with SSc (35, 77); iv) musculoskeletal involvement including contractures and joint problems (usually non-inflammatory) that are present in 24-97% of patients (37), involvement of the muscles (usually non-inflammatory muscle pain or weakness) in 70-96% of patients (37), and involvement of the tendons, predominantly in diffuse patients, in up to 35% of cases (37).

3.4 Evidence Regarding Clinical Sources of Pain in Systemic Sclerosis

Few studies, all with small samples, have examined the association between specific clinical variables and pain in patients with SSc. A qualitative study of 19 patients with SSc (50) reported that most participants complained about pain and that they described pain related to widespread joint and musculoskeletal pain ("I pretty much had pain in most of my joints most of the time"), skin pain (aching, pinching, burning, tingling and tightness), pain in the digits associated with Raynaud's phenomenon ("When they turn purple, it hurts and you feel like a tightening and tingling sensation, like when your foot falls

asleep"), gastrointestinal and digestive pain (trouble swallowing and digesting foods, constipation, diarrhea and bloating) and pain in the distal extremities (calcinosis and ulcers). Two quantitative studies have examined bivariable associations between specific SSc clinical variables and pain. One study of 82 patients with SSc (50) examined crude associations between the presence of fibromyalgia tender points (defined as ≥ 11 points out of a possible 18), joint involvement (dichotomized as present / absent) and gastrointestinal disease (dichotomized as present/absent) with pain measured by the HAQ-PVAS and found that all were significantly associated with higher pain (fibromyalgia tender points mean (SD) 1.61 (0.90) vs. 0.67 (0.80), joint involvement mean (SD) 1.36 (0.90) vs. 0.80 (0.92) and gastrointestinal involvement mean (SD) 1.27 (0.95) vs. 0.67 (0.83), $p < 0.05$). The second study (N=281) (75) reported higher mean pain scores in patients with active digital tip ulcers (digital tip ulcers mean 1.50 vs. no digital tip ulcers mean 1.11, $p < 0.001$). Only one published study (N =114) has examined multiple sources of pain with multivariable analysis (66). This study examined the association of 28 clinical variables with pain and found that 15, including 4 continuous physician measures (skin score, tender joint score, total tender points, joint contracture score) and 11 binary patient reported symptoms (hand swelling, hyperpigmentation, morning stiffness, joint pain on motion, joint tenderness, joint contracture, muscle pain, muscle weakness, palpitations, leg swelling and dry eyes) were associated with pain in unadjusted analysis. Results from multivariable analysis, which included only the 15 significant variables from unadjusted analyses as predictors of pain, indicated that skin score, patient-reported leg swelling and patient-reported joint tenderness independently

predicted pain. This study, however, had too many predictor variables given the total number of patients. The authors therefore used significant results from unadjusted analyses to screen-in variables for multivariable analysis and an automated stepwise procedure to select variables for their final model. This approach can cause severe biases in model fit statistics (R squared fit statistic biased upward), losses in valuable information from deleting variables like severity of Raynaud's phenomenon, ulcers and gastrointestinal symptoms found to predict pain in other studies, and a high likelihood of spurious results that will not be replicated (78).

There is a trend for patients with diffuse SSc to report higher pain than patients with limited SSc. Moreover, limited and diffuse subsets of patients with SSc experience different patterns of disease expression and often require different treatment considerations. It is therefore reasonable to hypothesize that sources of pain in SSc may differ in subsets of patients with limited and diffuse disease. No published studies, however, have examined whether and to what extent clinical predictors of pain differ between limited and diffuse cases.

3.5 Summary and gaps in the literature

To date, descriptive studies of pain in SSc have been based on relatively small samples (Ns ranging from 19 to 242 patients). Larger sample sizes however, are required to obtain robust estimates of the prevalence and the severity of pain in SSc and to determine whether patients with limited and diffuse disease experience clinically meaningful differences in pain. Furthermore, SSc is a

complex multi-system disease where pain may have multiple sources. No studies have rigorously examined associations between multiple SSc clinical manifestations and pain, which would help identify potential clinical intervention targets. Moreover, no studies have examined whether and to what extent clinical correlates of pain differ in limited and diffuse sub-sets with differing disease manifestations.

Given the limitations of the current pain literature in SSc, SSc treating physicians do not have strong research evidence on which to base their understanding of prevalence, severity, and potential sources of pain in these patients. Important questions remain unanswered, including a) how common and how severe is pain in SSc?; b) is pain more severe in diffuse cases than in limited cases of SSc?; c) what clinical variables are associated with pain in patients with SSc?; and d) do associations between clinical variables and pain differ in limited and diffuse subsets?.

3.6 Study Objectives

The objectives of the present study were to use data from a large convenience sample of nearly 600 patients enrolled in a multi-center Canadian SSc registry to:

I. Estimate prevalence and severity of pain in patients with SSc;

II. Estimate the difference in pain severity between limited and diffuse SSc subsets;

III. Estimate associations between clinical variables and pain in all patients with SSc; and

IV. Estimate whether associations between clinical variables and pain differ between limited and diffuse SSc subsets.

CHAPTER 4

Materials and Methods

4.1 Study Design

The present study was a cross-sectional analysis of a convenience sample of patients with SSc enrolled in the CSRG Registry.

4.2 Patients and Procedures

Important challenges when conducting research in SSc are: I) SSc is uncommon and highly heterogeneous, making it difficult to recruit the large numbers of patients required to obtain results that are precise; and II) different studies use different measures of varying quality, making it difficult to compare and interpret results across studies in SSc. In order to maintain a high level of scientific rigor and maximize efficiency and feasibility, the present study analyzed existing data obtained using standardized data collection procedures from a large sample of patients with SSc enrolled in the CSRG Registry.

THE CANADIAN SCLERODERMA RESEARCH GROUP (CSRG)

The CSRG Registry is an ongoing clinical cohort study of patients with SSc from 15 rheumatology centers across Canada (Appendix 2). The CSRG was founded in September 2004 to facilitate multi-disciplinary research on clinical, epidemiologic and psychosocial aspects of adult scleroderma.

PATIENT ELIGIBILITY CRITERIA

To enrol in the CSRG Registry, participants must have a confirmed diagnosis of SSc by a CSRG participating rheumatologist, be 18 years or older, be fluent in English or French, be deemed likely to be compliant with study procedures, and agree to provide written informed consent. Patients with overlap disease (patients who also meet criteria for another rheumatic disease) are eligible to enrol in the Registry as long as the recruiting rheumatologist determines that the patient has SSc, as well. Patients are excluded if they have any condition that compromises their ability to give informed consent. Only data from patients with a diagnosis of either limited or diffuse SSc enrolled in the CSRG Registry prior to November 2008 were analyzed in the present study.

PATIENT RECRUITMENT

Most CSRG Registry participants are patients of clinically active CSRG investigators recruited to participate in the Registry by their rheumatologists, although some are referred to the CSRG through other sources, typically other rheumatologists or patient advocacy groups. Patients with SSc can be recruited at

any stage of their disease. The CSRG has a very close partnership with the Scleroderma Society of Canada (SSC) (Appendix 3), the largest SSc patient group in Canada. The SSC actively promotes participation in the CSRG Registry on their website, mailings and group events. In addition, the CSRG holds its annual investigator research meeting at the same time and location as the SSC annual general meeting with the goals of disseminating CSRG research findings in the past year directly to family members and patients with SSc as well as sustaining a strong supportive relationship between the CSRG and the community.

Clinically active CSRG investigators do not typically attempt to recruit all of their patients to participate in the Registry due to various reasons (e.g., time constraints, end-stage disease). Therefore, the decision of who to approach is left to the discretion of the rheumatologist at each site. Patients who are approached and agree to participate see the research nurse or study coordinator on site; the study consent form is explained and written informed consent is obtained. Site coordinators are asked to keep track of any refusals to participate as well as the reason for refusal. Based on this information, the CSRG has estimated that more than 90% of patients who are recruited agree to participate.

GENERATING THE CSRG STANDARDIZED PATIENT ASSESSMENT

The European Scleroderma Study Group (EScSG), along with the Scleroderma Clinical Trials Consortium, held a symposium regarding the assessment of patients with SSc in 2003 (79). The goal of this symposium was to define a core set of clinical and laboratory variables, including measures of organ-

system involvement (80-85), non-organ based laboratory markers (86), disease activity (87) and disease severity (88) that should be used when evaluating SSc patients. This collaborative venture produced a manual of signs, symptoms, methods and procedures for assessing patients with SSc (89). This was a breakthrough achievement in terms of creating a consensus among SSc researchers concerning the type of data to collect on individual patients so that research from different centers could become more standardized. Despite this effort, validated outcome measurements for use in studies of patients with SSc were still lacking. The Outcome Measures in Rheumatology Initiative (OMERACT) (90) has defined core sets of domains and reporting requirements for use in longitudinal studies in rheumatology (91). In the last few years, OMERACT has validated measures for use in studies of patients with SSc and has published recommendations for the assessment of organ specific involvement, laboratory markers, function, pain and health-related quality of life (92). Measurements obtained by the CSRG are consistent with the above mentioned manual and recommendations.

DATA COLLECTION PROCEDURES

All patients that have consented to participate in the Registry complete the standardized assessment at the offices of clinically active CSRG rheumatologists. At baseline, the rheumatologist collects a detailed medical history, performs the patient physical exam and sends each patient for a chest x-ray, pulmonary functions tests, electrocardiogram (ECG) and echocardiogram or records results for the same tests if taken within 6 months. A registry nurse records the patient's

vital signs, hand measurements (finger-tip to palm distance, hand span and hand length) and collects blood and urine specimens for laboratory investigations. Patients also complete a series of questionnaires assessing demographic information, physical and psychosocial health status. The research nurse completes the first section of the patient case report form regarding personal information together with the patient, answers any questions that the patient may have and instructs the patient to complete the remainder of the case report form on their own. In most cases (90-95%), patients either complete the case report form the same day at the office of the CSRG specialist or complete the forms at home. In the latter case, the patient is provided with an addressed envelope including postage and is instructed to return the questionnaires by mail to the investigator within two weeks. Fewer cases (5-10%) ask to have the case report forms mailed to them 1-2 weeks prior to their scheduled registry visit so that they may bring in their completed questionnaire on the day of their registry clinical assessment. In all cases completion of the case report form is done as close as possible to the clinical assessment date, usually within a two week period. The research nurse or data entry personnel follow up with the patient by phone until the questionnaire is received and verifies all forms for completeness. A due date is then generated at 1 year intervals from the date of the baseline assessment (i.e. 0, 12 months, 24, months, 36 months, etc.) and patients are asked to return to the specialist office to complete a follow-up assessment within 1 month of the due date generated. Follow-up continues annually unless the patient withdraws (no longer wishes to participate, moves away or dies). At every scheduled Registry visit, research personnel complete a form indicating whether the patient was seen for their

Registry visit, temporarily dropped-out or permanently dropped-out as well as the reasons for a missed visit (e.g., health problems, refused, moved, other).

Patient data were entered from each center locally via a secured site on the internet into a central database maintained by DataZoom Solutions in Toronto. Nominative personal data such as name, address, phone number, etc., are not entered into the database. Rather, a unique subject identifier made up of numbers (physician ID, patient ID and visit number) and letters (4-letter patient monogram) is linked to the data provided by each patient in order to maintain confidentiality. Patient identifying information is kept under lock in the office of the examining rheumatologist and is not available to anyone else. When registering a new patient record in the database, data entry personnel must enter the patient's unique ID, date of birth and complete the section indicating that all inclusion criteria are met. There are then 3 forms (patient, physician, investigations) to be entered. Each patient form has 15 sections, the physician form has 10 sections and the investigation form has 3 sections. For each section, data entry personnel indicate that the section is **complete** (section done), **open** (no data entered yet), **in process** (data entered but not complete yet) or **skip** (entire section or form not done). Subsequently, the data personnel also indicate whether the entire patient, physician and investigation forms are complete, open, in process or skipped. Hundreds of electronic controls in the database provide prompts to data entry personnel when sections are incomplete or when unlikely values are entered in order to reduce data entry errors.

4.3 Ethical Considerations

Ethics committee approval for CSRG registry procedures was obtained at each site and each patient provided written informed consent. Ethics committee approval specifically for the present study was obtained from the Internal Review Board of McGill University (Appendix 4).

4.4 Measures

A subset of CSRG measures was used in the present study and is described in detail below.

CLINICAL VARIABLES

Disease Subsets - Patients were classified into disease subsets by the examining rheumatologist according to the extent of skin involvement based on the most widely used classification scheme for limited and diffuse SSc described by LeRoy et al. (16). Patients with skin involvement distal to the knees ad elbows only are considered to have limited SSc and patients with skin involvement both distal and proximal to the knees and elbows or involving the chest or trunk are considered to have diffuse SSc.

Severity of Skin Involvement - Severity of skin involvement was measured using the modified Rodnan Skin Score (MRSS) (93). The MRSS is a widely used clinical assessment where the examining rheumatologist records the degree of skin thickening ranging from 0 (no involvement) to 3 (severe thickening) in 17 areas of the body, generating a total body skin score ranging from 0 to 51. The MRSS is currently the best available and only skin scoring

method that is recommended for use in clinical trials (95). The MRSS has been shown to have acceptable face, construct, content, criterion and discriminant validity as well as feasibility (92, 94, 95). Moreover, the MRSS has been shown to predict SSc morbidity (SSc internal-organ system involvement) and mortality (96-99). Better reliability of the MRSS has been reported in rheumatologists that are specialists in SSc, as well as in young rheumatologists that have received specialized training in the MRSS assessment (100-102). In one European multi-center study (102) inter-observer reliability of the MRSS in young inexperienced rheumatologists with the skin score was rather poor with mean (SD) inter-observer variability of 16 (9) points and an ICC of 0.5, however, reliability improved to a mean (SD) inter-observer variability of 12 (4) and ICC of 0.7 after a standardized training session. In contrast, inter-observer reliability of the MRSS for scleroderma specialists was excellent with a mean (SD) inter-observer variability of 8(4) points and an ICC of 0.9. While inter and intra-observer reliability of CSRG rheumatologist ratings were not formally assessed; CSRG rheumatologists are considered to be the top SSc specialists in Canada and all underwent a standardized training session on the skin score for purposes of standardizing CSRG procedures prior to enrolling patients in to the Registry. The MRSS was used as a continuous score in the present analysis, with higher scores representing worse skin involvement.

Raynaud's Phenomenon Symptom Activity - Raynaud's phenomenon has been assessed using the following patient-reported measures: a) the Raynaud's Condition score - an ordinal scale assessing daily or weekly difficulty due to Raynaud's phenomenon; b) a patient visual analogue scale assessing daily or

weekly activity of Raynaud's phenomenon; c) the modified Scleroderma Health Assessment Questionnaire (SHAQ) patient visual analogue scale assessing daily or weekly interference from Raynaud's phenomenon; d) the number of episodes; and e) the duration of episodes of Raynaud's phenomenon per day or week. Merkel et al. (75) reviewed and evaluated the measurement properties of these tools and reported that all have adequate validity, sensitivity to change and feasibility, but that the two visual analogue scales had poor reliability. Moreover, the visual analogue scales and the Raynaud's Condition Score loaded on the same factor as pain and disability (i.e. these quantifiable measures were grouped together under the same latent (unmeasurable) construct based on the strength of their correlation coefficients using factor analysis), suggesting that these are measuring similar constructs. Therefore, the present study used the frequency of episodes of Raynaud's phenomenon in the past week as a continuous score to measure Raynaud's phenomenon symptom activity. Frequency of episodes has been used as an outcome measure of symptom activity/severity in several clinical trials evaluating the efficacy of different drug therapies for Raynaud's phenomenon (103-106).

Ulcers -The rheumatologist records the presence of active digital tip ulcers (ulcers present on the volar surface of the digital tips distal to the proximal interphalangeal joints) and other ulcers (ulcers found anywhere on the body excluding those on digital tips) during the clinical exam. Presence of any digital tip ulcers and any other ulcers were analysed as two separate binary variables due to differences in their underlying pathophysiology. The current understanding of the pathophysiology of ulcers in SSc is that ulcers on the digital tips are

associated with ischemic tissue damage while other ulcers, commonly arising on the tops of joint surfaces, are associated with microtrauma (107).

Calcinosis - Calcinosis refers to calcium deposits in soft tissues that have been structurally damaged or have reduced supplies of blood and/or oxygen (108). Presence of any visible or palpable calcinosis was recorded by the rheumatologist during the clinical exam and analysed as a single binary variable.

Joint Contractures - Joint contractures are a reduction in one's ability to fully flex a joint inward and fully extend the joint outward resulting in limited range of motion (3). In SSc, finger contractures (fingers remain flexed inward) are more prevalent (37), more highly associated with disability (109, 110), and likely more vulnerable to exacerbation (due to common hand use in daily interactions with the environment) than contractures in other typically affected joints of the body. Severity of finger contractures and contractures of other joints were therefore analyzed separately in the present study. There is currently no gold standard for measuring finger contracture severity in patients with SSc. However, an international study group of expert scleroderma clinical investigators proposed an SSc disease severity index that included finger tip to palm (FTP) distance as a measure of finger-contracture severity (88). FTP distance has also been used in other studies as a measure of finger contracture severity (37, 111, 112). In the present study, Registry nurses recorded FTP distance. This was done by asking patients to make the best fist they could and recording the distance (in cm) from the tip of the 3rd finger to the distal palmar crease. The raw FTP distance in cm was analyzed as a continuous variable, with higher distances representing worse finger contracture severity. Rheumatologists record the presence of contractures

of the wrists, elbows, hips, knees and/ or ankles on both sides of the body during the clinical exam. Each site is scored 0 (absent) or 1 (present). The sum of all contractures (range 0-10) was used as continuous measure of other joint contracture severity.

Joint Disease Activity - Joint counts are a common clinical method for assessing joint-related disease activity. It is common practice to perform both swollen and tender joint counts. While swollen joint counts quantify the amount of synovial swelling (synovitis), tender joint counts quantify the degree of pain associated with synovitis. To assess tender joints, rheumatologists apply pressure to specific joints, and the patient provides a response indicating whether the application of pressure is painful (113). CSRG rheumatologists perform the reduced 28 swollen and tender joint counts (114). The 28 joint counts have been shown to be reliable, valid and easier to perform then full 66/68 joint counts (115-117). One would expect that swollen and tender joint counts would be highly correlated with one another; analysing both scores simultaneously would therefore likely introduce issues of multicollinearity (118). Given that the outcome in the present study was pain and that tender joint count is an aspect of pain, swollen joint count only, entered as a continuous variable, was analyzed as an objective measure of synovitis.

Tendon Involvement - A number of patients with SSc, particularly patients with the diffuse form of SSc, develop tendon friction rubs (inflammation of the tendon sheath) that can be painful with motion (119, 120). Rheumatologists record the presence of tendon friction rubs after palpating tendons in the upper

and lower body during the clinical exam. Presence of any tendon friction rubs was coded as a binary variable.

Muscle Involvement - Muscle pain, proximal muscle weakness and to a lesser extent inflammatory muscle disease (myositis) have been reported in patients with SSc (121-123). Detailed and precise measurements of muscle involvement such as electromyogram (EMG), muscle imaging, and muscle biopsy are invasive and/or not readily accessible. Results of muscle enzymes (CK - creatinine kinase also known as creatinine-phosphokinase) are included in the CSRG laboratory investigations and an elevated CK value, defined according to laboratory cut-offs (male: 42-396 U/L, female: 24-240 U/L), was used as an index of muscle involvement.

Gastrointestinal symptoms - Involvement of the oesophagus, upper and lower gastrointestinal tract is common in SSc (35). Gastrointestinal symptoms previously reported to be associated with pain in a focus group study of patients with SSc (50) including problems swallowing, acid reflux, heartburn, diarrhea,constipation and bloating, were assessed by summing the number of positive responses to the following 6 questions included in the patient case report form: "I have (or have had) on most days either now or since the onset of my scleroderma: 1) difficulty in swallowing – food or liquids sometimes get stuck behind my breastbone on the way down; 2) food or acid-tasting liquid that comes back up into my mouth or nose; 3) burning feeling rising from my stomach or lower chest up towards my neck; 4) constipation; 5) diarrhea; 6) visible swelling of my abdomen or bloating." Using patient reports of gastrointestinal symptoms is

non-invasive and has been shown to be a reliable and valid measure of gastrointestinal disease (77).

CONFOUNDING VARIABLES

Confounder selection is commonly based on the fulfillment of 3 criteria; namely that the variable is associated with the exposure, the variable is associated and/or is a risk for the outcome of interest, and the variable is not on the causal pathway between the exposure and the outcome (124).

Demographic variables: Demographic variables, specifically age, sex, race and level of education, *could* meet the above criteria in that along with being common sources of confounding in epidemiologic studies, these variables are associated to some extent with the clinical variables of interest, can affect one's perception of pain and do not lie on the causal pathway. Whether or not demographic variables are associated with pain specifically in patients with SSc is inconclusive. They were therefore included in the present study as a conservative approach. Information regarding patient age, sex, race and postsecondary education was obtained from a patient-reported demographic questionnaire. Age in years was coded as a single continuous variable. Sex (male or female), race (White or non-White) and post-secondary education ($\leq$ high school diploma or $\geq$ 1 year of post-secondary education) were coded as 3 separate binary variables.

Disease duration - The clinical course of SSc varies according to the duration of the disease; disease duration may also potentially be associated with variation in pain, and disease duration does not lie on the causal pathway. Similar to demographic variables, whether or not disease duration is associated with pain

specifically in patients with SSc is inconclusive. Disease duration was therefore included in the present analysis as a conservative approach. Disease duration was recorded by the examining physician and defined as the number of years from the date of first non-Raynaud's manifestation of SSc until the date of first study visit. This is the standard for measuring disease duration in studies of patients with SSc because almost all patients with SSc have a history of Raynaud's phenomenon and continue to experience episodes of Raynaud's phenomenon throughout their SSc disease; however, only a small proportion of patients with a diagnosis of primary Raynaud's phenomenon will actually develop SSc or other connective tissue diseases (125). Rheumatologists therefore consider the first non-Raynaud's symptom of SSc as the start of their SSc disease process. Disease duration was recorded in years and analyzed as a continuous variable.

Depressive Symptoms - The temporal relationship between pain and depression (i.e. whether higher pain causes depression vs. whether depression causes pain) is not well understood, particularly in SSc. In the context of the present study, if depressive symptoms were on the causal pathway between SSc clinical variables and pain **OR** if depressive symptoms were a consequence of pain in SSc, then adjustment for depressive symptoms would be inappropriate and likely to introduce bias. If, however, depressive symptoms were associated with worsening in SSc clinical variables, were also a risk factor for worse pain symptoms and were not in the causal pathway between the two, then adjusting for depressive symptoms would be warranted to avoid bias due to confounding. Accordingly, in sensitivity analysis, the present study examined models that included and models that excluded depressive symptoms (described further in

statistical analysis). Depressive symptoms were measured using the Center for Epidemiologic Studies Depression Scale (CES-D) (126), a 20-item self-report scale that asks patients to rate the frequency of depressive symptoms in the past week from 0 (rarely or none of the time) to 3 (most or all of the time) with a total score ranging from 0 to 60 with higher scores indicating more severe depressive symptoms. Reliability and validity of the CES-D in patients with SSc has been tested and is well supported (127). The CES-D cut-off for clinically significant depressive symptoms is 16 (126); and this CES-D score was used as a binary variable in the present study for descriptive purposes. The CES-D total score, however, was analyzed as a continuous variable in multivariable analyses, with higher scores representing more severe depressive symptoms.

Comorbidities - Patients with SSc may also have other concurrent rheumatic conditions like osteoarthritis and/or chronic low back pain; osteoarthritis and chronic low back are each associated with pain; and they are not on the causal pathway between SSc disease manifestations and pain. Painful comorbidities were defined in the present study as the presence of either patient-reported osteoarthritis or chronic low back pain and were coded as a single binary variable.

RESPONSE VARIABLE

Pain severity - The present study used an 11-point numerical rating scale, which was adapted from the pain visual analogue scale of the HAQ-PVAS. The HAQ-PVAS has been shown to be reliable, valid and sensitive to change in SSc clinical trials (94, 128, 129). Numerical rating scales, however, are simpler to

complete and score compared to VAS scales and have been shown to be as reliable and responsive as a visual analogue scale in patients with ankylosing spondylitis (130) and even more reliable for assessing pain than a VAS in patients with rheumatoid arthritis (131). The patient case report form included the following question with matching numerical rating scale: "In the past week, how much pain have you had because of your illness?" and patients were instructed to place an X in the numbered box that corresponded to the level most appropriate ranging from 0 (no pain) to 10 (very severe pain). Studies in cancer and musculoskeletal pain groups have used ratio intervals on the NRS of 0, 1-4, 5-7, and 8-10 to designate no pain, mild pain, moderate pain and severe pain, respectively (132, 133). A categorical variable reflecting these cut-offs was used for descriptive purposes while the continuous total score was used as a measure of the response-pain in all crude and multivariable analysis, with higher scores representing more severe pain. The continuous pain score was emphasized in order to maximize the usable data for regression analyses and to potentially avoid any serious total misclassification if theoretical cut-offs used for pain were inappropriate (78).

4.5 Statistical Analysis

Standard descriptive statistics for continuous and binary variables were used to summarize demographic and clinical characteristics of the whole SSc sample, the sample of limited cases and the sample of diffuse cases, respectively.

Prevalence and Severity of Pain - Prevalence of pain symptoms was estimated with a categorical variable reflecting the number and proportion of patients with SSc who reported no pain (NRS score =0), mild pain (NRS score = 1 to 4), moderate pain (NRS score = 5 to 7) and severe pain (NRS score = 8 to 10), in all patients with SSc and separately in samples of limited and diffuse cases. Mean (SD) pain scores were used to describe the distribution of pain severity in the whole sample of patients with SSc and separately for limited and diffuse sub-samples.

Difference in Pain Severity between Limited and Diffuse Cases - Differences in pain between subsets were estimated by calculating the mean difference in pain scores between limited and diffuse cases ($mean_{diffuse} - mean_{limited}$) and respective 95% confidence interval (CI). The raw mean difference in pain and Hedges' g, a standardized measure of effect size estimated by calculating the mean difference in pain scores between limited and diffuse samples divided by a variant of their pooled standard deviation with degrees of freedom rather than total n in the denominator (134), were used to interpret the magnitude of the difference in pain severity between SSc clinical subsets. Effect sizes were interpreted based on Cohen's definitions for small, medium and large effect sizes (small = 0.2, medium = 0.5, large = 0.8) (135).

Associations between Clinical Variables and Pain - Separate linear regression analyses for each independent variable with pain as the response were performed to calculate unadjusted regression coefficient estimates and 95% CIs. A multivariable linear regression model was performed entering all independent

variables simultaneously to calculate adjusted regression coefficient estimates and 95% CIs. Results of descriptive analyses were examined to identify variable ranges that were either inconsistent with background knowledge of SSc, or had too much measurement error or too little variability to contribute usefully to multivariable analysis (136).

Associations between SSc Clinical Variables and Pain in Limited and Diffuse Subsets - Separate multivariable linear regressions were performed in the sample of patients with limited SSc and in the sample of patients with diffuse SSc using the same pre-specified independent variables from the multivariable analysis in the whole sample of patients with SSc. Regression estimates in limited and diffuse sub-samples were then compared by estimating regression coefficient differences and 95% CIs for the difference (137). Separate subgroup analyses rather than tests for interactions were performed for two reasons: 1) Patients with limited and diffuse disease have different clinical and serologic profiles suggesting that separate analyses would be appropriate; and 2) no previous studies have examined sources of pain in limited and diffuse subsets therefore there is no prior evidence for which to select potential relevant interactions and exploratory tests for interactions were felt to lack scientific rigour.

Sensitivity Analyses - Whether higher depressive symptoms are a cause or consequence of pain symptoms is unclear. Given this temporal ambiguity, sensitivity analysis including and excluding depressive symptoms were performed. Patients with SSc may also have other conditions that can lead to pain (osteoarthritis or chronic low back pain). Unfortunately, the patients reported comorbidity questionnaire used to asses these conditions was removed from

CSRG case-report forms in order to reduce patient burden in 2007. In order to include the maximum number of subjects in the present study, a multivariable model adjusting for painful comorbidities in a sub-sample of patients with SSc who completed this information was performed as a sensitivity analysis. Multivariate Imputation by Chained Equations (138) was performed to examine potential differences in exposure effects due to deleting cases with missing observations. The MICE and MITOOLS packages in R were used to generate 5 complete copies of the data and the "MICOMBINE" command was used to generate averaged multivariable regression coefficients and adjusted 95% CIs across the 5 generated datasets. Lastly, given that the present study included multiple centers, a multi-level random effects linear model was performed with a random parameter for center as a sensitivity analysis to examine any potential bias due to center-level clustering using the PROC MIXED function in SAS (139).

Analysis diagnostics: Graphical methods (plots of each covariate against the response pain and residual plots of multivariable analyses) were used to verify that linear regression assumptions were met. Correlation coefficients between independent variables and variance inflation factors were examined to assess any potential issues of multicollinearity (118).

Statistical significance was set at $p < 0.05$. All statistical procedures were performed using the Statistical Package for the Social Sciences (SPSS) version 13, R: A Language and Environment for Statistical Computing version 2.8.1, and the Statistical Analysis System (SAS) version 9.1.

CHAPTER 5

Results

5.1 Patient sample

The present study included patients enrolled in the CSRG Registry between September 2004 and November 2008, which included information from 877 patients with SSc. SSc disease subset status was not recorded for 26 (3%) patient records. Of the 851 patient records with SSc subset information, 25 (3%) patients had a diagnosis of sine scleroderma and were ineligible for the present analysis. Of the 826 eligible patient records, 585 (71%) were complete for all of the variables analyzed in the main analysis of the present study.

Descriptive statistics for the whole SSc, limited SSc and diffuse SSc samples are presented in Table 5.1. The mean (SD) age in the whole SSc sample was 56 (12) years; 506 (87%) patients were female; 523 (89%) patients were white; 279 (48%) patients had at least one year of post-secondary education. The median (inter-quartile range [IQR]) disease duration was 9 (4 to 15) years. Five-hundred and thirty-six (92%) patients met ACR criteria for SSc. Three-hundred and fifty-eight patients had limited SSc (61%) and 227 (39%) had diffuse SSc.

Patients with diffuse SSc were on average more likely to be younger (mean 53 years vs. 57 years), male (18% vs. 10%) and have a shorter median disease duration (7 years vs. 10 years), higher median skin score (17 vs. 4), active digital tip ulcers (13% vs. 6%), active other ulcers (29% vs. 11%), finger contractures (53% vs. 23%), other joint contractures (36% vs. 8%), tendon friction rubs (30% vs. 9%) and screen positive for clinically significant depressive symptoms (CES-D ≥ 16) (43% vs. 32%), than patients with limited SSc. Patients with limited SSc were more likely to have synovitis (19% vs. 13%), and report having comorbid osteoarthritis or back pain (48% vs. 35%).

Partial respondents excluded from the present study (N =241) were similar to full respondents included in this study (N =585) with respect to the n (%) meeting ACR criteria for SSc of 217 (90%), demographic variables (mean (SD) age: 56 (12); n (%) female: 205 (85%); n (%) white race: 215 (89%); n (%) post-secondary education: 104 (43%)) and median (IQR) disease duration in years: 8 (3 to 15). Slightly more excluded patients were classified as diffuse SSc (diffuse excluded: 106 [44%] vs. diffuse included 228 [39%]).

Table 5.1. Demographic and Clinical Characteristics of the CSRG Sample

Variables	*All SSc (N=585)*	*Limited SSc (N=358)*	*Diffuse SSc (N=227)*
Age (18-88 years), mean (SD)	56 (12)	57 (12)	53 (11)
Female, n (%)	506 (87%)	321 (90%)	185 (82%)
Race – white, n (%)	523 (89%)	326 (91%)	197 (87%)
Post-secondary education, n (%)	279 (48%)	171 (48%)	108 (48%)
Disease duration years, median (IQR)	9 (4 to 15)	10 (4 to 17)	7 (3 to 14)
Skin score (MRSS 0-51), median (IQR)	7 (4 to 15)	4 (2 to 8)	17 (11 to 25)
Episodes of Raynaud's, median (IQR)	4 (1 to 7)	4 (1 to 7)	3 (1 to 7)
Active digital-tip ulcers, n (%)	52 (9%)	23 (6%)	29 (13%)
Active other ulcers (not digital-tips), n (%)	105 (18%)	40 (11%)	65 (29%)
Calcinosis, n (%)	175 (30%)	109 (30%)	66 (29%)
Finger contractures, n (%)	201 (34%)	81 (23%)	120 (53%)
Other joint contractures, n (%)	108 (19%)	27 (8%)	81 (36%)
Synovitis, n (%)	98 (17%)	68 (19%)	30 (13%)
Tendon friction rubs, n (%)	99 (17%)	31 (9%)	68 (30%)
Abnormal creatinine kinase (CK), n (%)	16 (3%)	8 (2%)	8 (4%)
Total gastrointestinal symptoms, median (IQR)	2 (1 to 4)	2 (1 to 4)	2 (1 to 4)
Problems swallowing, n (%)	325 (56%)	197 (55%)	128 (56%)
Acid reflux, n (%)	386 (66%)	226 (63%)	160 (71%)
Heartburn, n (%)	258 (44%)	152 (43%)	106 (47%)
Stomach bloating, n (%)	224 (38%)	138 (39%)	86 (38%)
Constipation, n (%)	164 (28%)	95 (27%)	69 (30%)
Diarrhea, n (%)	134 (23%)	77 (22%)	57 (25%)
Depressive Symptoms (CESD 0-60), mean(SD)	14 (10)	13 (10)	15 (10)
Depression Screen Positive (CESD≥16), n (%)	211 (36%)	113 (32%)	98 (43%)
Pain Condition (osteoarthritis/ back pain), n (%)	218 (43%)	149 (48%)	69 (35%)

5.2. Prevalence and Severity of Pain in Patients with Systemic Sclerosis

The prevalence of pain in the present sample of patients with SSc is presented in Table 5.2. Four-hundred and eighty-four (83%) patients with SSc reported pain related to their illness in the last week, with more than a third reporting pain in the moderate or severe range (*mild pain (NRS 0-4)*: 268 (46%), *moderate pain (NRS 5-7)*: 155 (27%) and *severe pain* (NRS 8-10): 61(10%)). Mean (SD) pain score for the whole SSc sample was 3.6 (2.8).

5.3 Difference in Pain Severity between Limited and Diffuse Subsets

Mean (SD) pain severity score was 3.9 (2.8) in patients with diffuse SSc and 3.4 (2.7) in patients with limited SSc. The mean difference ($mean_{diff}$) in pain severity score between patients with limited and diffuse SSc was statistically significant, $mean_{diff} = 0.51$, 95% CI for $mean_{diff}$: 0.06 to 0.97. However, the effect size for this difference was small (Hedges' g = 0.18, 95% CI 0.01-0.35).

Table 5.2. Prevalence of Pain in Patients with Systemic Sclerosis

Variables	*All SSc (N =585)*	*Limited SSc (N =358)*	*Diffuse SSc (N =227)*
No Pain (NRS 0), n (%)	101 (17%)	67 (19%)	34 (15%)
Mild Pain (NRS 1-4), n (%)	268 (46%)	171 (48%)	97 (43%)
Moderate Pain (NRS 5-7), n (%)	155 (27%)	87 (24%)	68 (30%)
Severe Pain (NRS 8-10), n (%)	61 (10%)	33 (9%)	28 (12%)

5.4 Associations of Clinical Variables with Pain in Systemic Sclerosis

Results of bivariable and multivariable linear regression in all patients with SSc are summarized in Table 5.3. Crude associations between all clinical variables examined and pain were statistically significant. However, only regression estimates for more frequent episodes of Raynaud's phenomenon (unstandardized regression coefficient: 0.029, 95% CI: 0.006 to 0.051), presence of other active ulcers (unstandardized regression coefficient: 1.007, 95% CI: 0.423 to 1.591), higher swollen joint count (unstandardized regression coefficient: 0.119, 95% CI: 0.037 to 0.200), and more gastrointestinal symptoms (unstandardized regression coefficient: 0.461, 95% CI: 0.340 to 0.582) were associated with pain in multivariable analyses. Since few (9%) patients had active digital-tip ulcers, its CI was wide and did not reach statistical significance (unstandardized regression coefficient: 0.400, 95% CI: -0.360 to 1.158).

Descriptive statistics showed that only 3% of the present sample had elevated levels of creatinine kinase indicative of possible muscle involvement which was not enough variability to enter in regression analyses and obtain interpretable regression estimates. Therefore, an index of muscle involvement was not included in regression analyses (revisited in more detail in the discussion). The point estimates for calcinosis in crude (unstandardized regression coefficient: -0.139, 95% CI: -0.629 to 0.351) and multivariable linear regression analyses (unstandardized regression coefficient: -0.426, 95% CI: -0.909 to 0.570), were not significant and in the wrong direction. Therefore calcinosis was not retained in any of the regression models presented (revisited in more detail in the discussion).

Table 5.3. Crude and Adjusted Linear Regression Coefficients of Clinical Variables with Pain in all Patients with Systemic Sclerosis (N=585)

	Crude Regression Coefficients		*Adjusted Regression Coefficients*		
Variables	Beta	95% CI for Beta	Standardized Beta	Beta	95% CI for Beta
Age (18-88 years)	-0.022	(-0.041, -0.004)	-0.036	-0.008	(-0.027, 0.010)
Sex, female	0.006	(-0.650, 0.662)	0.002	0.015	(-0.602, 0.632)
Race, white	-0.844	(-1.570, -0.118)	-0.083	-0.741	(-1.428, -0.058)
Post-secondary education	-0.476	(-0.923, -0.028)	-0.113	-0.623	(-1.052, -0.194)
Disease duration, years	-0.007	(-0.033, 0.018)	-0.060	-0.019	(-0.044, 0.006)
Skin score (MRSS 0-51)	0.037	(0.013, 0.059)	-0.011	0.000	(-0.031, 0.025)
Episodes of Raynaud's	0.035	(0.012, 0.059)	0.099	0.029	(0.006, 0.051)
Active Digital-tip ulcers	0.903	(0.118, 1.689)	0.041	0.400	(-0.360, 1.158)
Active Other ulcers	1.207	(0.631, 1.784)	0.140	1.007	(0.423, 1.591)
Finger contractures (FTP)	0.194	(0.079, 0.308)	0.040	0.057	(-0.064, 0.178)
Other joint contractures	0.254	(0.098, 0.410)	0.060	0.117	(-0.058, 0.292)
Swollen joint count (0-28)	0.124	(0.039, 0.209)	0.113	0.119	(0.037, 0.200)
Tendon friction rubs	0.810	(0.215, 1.405)	0.047	0.343	(-0.254, 0.945)
Gastrointestinal symptoms	0.495	(0.375, 0.616)	0.295	0.461	(0.340, 0.582)

5.5 Associations of Clinical Variables with Pain in Limited and Diffuse Subsets

Results of bivariable and multivariable linear regression in limited and diffuse subsets are summarized in Table 5.4. More gastrointestinal symptoms were significantly associated with pain in limited (unstandardized regression coefficient: 0.558, 95% CI: 0.407 to 0.709) and diffuse (unstandardized regression coefficient: 0.300, 95% CI: 0.082 to 0.518) subsets. Higher swollen joint count was significantly associated with pain among patients with limited disease (unstandardized regression coefficient: 0.151, 95% CI: 0.040 to 0.263) while the presence of other active ulcers was significantly associated with pain among patients with diffuse disease (unstandardized regression coefficient: 0.1.158, 95% CI: 0.323 to 1.993). Regression point estimates and 95% confidence intervals for episodes of Raynaud's Phenomenon in samples of patients with limited (unstandardized regression coefficient: 0.026, 95% CI: -0.001 to 0.053) and diffuse (unstandardized regression coefficient: 0.039, 95% CI: -0.003 to 0.082) disease were just shy of reaching statistical significance but were in a similar range to the estimates reported in the whole sample (unstandardized regression coefficient: 0.029, 95% CI: 0.006 to 0.051). Overall, however, differences in regression coefficient estimates between patients with limited and diffuse SSc for the clinical variables examined were small, and none were statistically significant.

Table 5.4. Multivariable Linear Regression Coefficients of Clinical Variables with Pain in Limited and Diffuse Subsets

	Limited SSc (N =358)		*Diffuse SSc (N =227)*		*Difference between Limited and Diffuse*	
Variables	Beta	95% CI	Beta	95% CI	$Beta_{diff}$‡	95% CI
Intercept	2.557	(0.948, 4.167)	4.868	(2.522, 7.215)	2.311	(-0.519, 5.141)
Age (18-88 years)	-0.007	(-0.030, 0.0167)	-0.012	(-0.046, 0.020)	0.005	(-0.036, 0.046)
Sex, male	0.534	(-0.373, 1.440)	-0.470	(-1.364, 0.424)	1.001	(-0.267, 2.269)
Race, white	-0.572	(-1.527, 0.382)	-1.150	(-2.191, -1.109)	0.578	(-0.827, 1.983)
Post-secondary education	-0.358	(-0.906, 0.189)	-1.039	(-1.745, -0.327)	0.681	(-0.212, 1.574)
Disease duration, years	-0.016	(-0.045, 0.012)	-0.036	(-0.087, 0.016)	0.020	(-0.039, 0.079)
Skin score (0-51)	0.034	(-0.033, 0.102)	0.012	(-0.054, 0.0293)	0.022	(-0.036, 0.080)
Episodes of Raynaud's	0.026	(-0.001, 0.053)	0.039	(-0.003, 0.082)	0.013	(-0.045, 0.071)
Active Digital-tip ulcers	0.042	(-1.061, 1.145)	0.815	(-0.293, 1.922)	0.773	(-0.783, 2.329)
Active Other ulcers	0.846	(-0.018, 1.710)	1.158	(0.323, 1.993)	0.312	(-0.884, 1.508)
Finger contractures (FTP)	0.069	(-0.097, 0.235)	0.006	(-0.180, 0.191)	0.063	(-0.184, 0.310)
Other joint contractures	0.092	(-0.397, 0.581)	0.158	(-0.042, 0.357)	0.066	(-0.461, 0.593)
Swollen joint count (0-28)	0.151	(0.040, 0.263)	0.089	(-0.035, 0.212)	0.062	(-0.104, 0.229)
Tendon friction rubs	0.206	(-0.749, 1.161)	0.377	(-0.418, 1.173)	0.171	(-1.065, 1.407)
Gastrointestinal symptoms	0.558	(0.407, 0.709)	0.300	(0.082, 0.518)	0.258	(-0.007, 0.523)

$Beta_{diff}$‡: Regression coefficient difference between limited and diffuse sub-samples.

5.6 Sensitivity Analysis

The same clinical variables (more frequent episodes of Raynaud's phenomenon, other active ulcers, higher swollen joint count and more gastrointestinal symptoms) remained significant after adjusting for depressive symptoms and comorbid conditions (Table 5.5.). Adjusted regression results for all clinical variables with pain were very similar in models adjusting for depressive symptoms as a continuous variable and as a binary variable (using a threshold of 16 for clinically significant depressive symptoms). Only the model adjusting for depressive symptoms as a continuous variable is presented here for simplicity. Results were also similar after multiple imputation, with the exception that the effect estimate for active digital-tip ulcers reached statistical significance (unstandardized regression coefficient: 0.666, 95% CI: 0.038 to 1.294) (Table 5.6). Lastly, the parameter estimate for center in the multilevel analysis (unstandardized regression coefficient = 0.099, 95% CI: -0.193 to 0.391) was small and not significant (Table 5.8, Appendix 9).

Table 5.5. Multivariable Regression Models of Clinical Variables with Pain Adjusting for Depressive Symptoms and Comorbid Conditions in all Patients with Systemic Sclerosis

	Adjusting for Depressive Symptoms (N =585)		*Adjusting for Comorbid Conditions (n=508)*	
Variables	Beta	95% CI	Beta	95% CI
Intercept	2.218	(0.944, 3.494)	3.077	(1.713, 4.441)
Age (18-88 years)	-0.004	(-0.022, 0.014)	-0.008	(-0.027, 0.012)
Sex, male	0.082	(-0.507, 0.671)	0.139	(-0.526, 0.803)
Race, white	-0.582	(-1.237, 0.073)	-0.819	(-1.574, -0.063)
Post-secondary education	-0.380	(-0.794, 0.034)	-0.685	(-1.138, -0.232)
Disease duration, years	-0.019	(-0.043, 0.005)	-0.019	(-0.045, 0.007)
Skin score (MRSS 0-51)	0.001	(-0.029, 0.025)	0.007	(-0.023, 0.036)
Episodes of Raynaud's	0.026	(0.004, 0.047)	0.028	(0.004, 0.052)
Active Digital-tip ulcers	0.484	(-0.240. 1.208)	0.430	(-0.354, 1.216)
Active Other ulcers	0.810	(0.251, 1.370)	1.163	(0.544, 1.781)
Finger contractures (FTP)	0.033	(-0.082, 0.149)	0.022	(-0.102, 0.147)
Other joint contractures	0.074	(-0.093, 0.241)	0.113	(-0.068, 0.293)
Swollen joint count (0-28)	0.108	(0.030, 0.185)	0.120	(0.038, 0.202)
Tendon friction rubs	0.304	(-0.266, 0.873)	0.196	(-0.428, 0.820)
Total gastrointestinal symptoms	0.337	(0.217, 0.457)	0.444	(0.314, 0.575)
Depressive symptoms (CESD 0-60)	0.079	(0.058, 0.010)		
Pain Condition (osteoarthritis/ back pain)			0.692	(0.230, 1.154)

Table 5.6. Multivariable Linear Regression Coefficients of Clinical Variables with Pain after Multiple Imputation of Missing Observations in all Patients with Systemic Sclerosis

	Multiple Imputation of Cases with Missing Observations (N=826)	
Variables	$Beta_{av}$ ‡	95% CI
Intercept	2.576	(1.399, 3.752)
Age (18-88 years)	-0.003	(-0.020, 0.015)
Sex, male	0.298	(-0.261, 0.856)
Race, white	-0.287	(-0.906, 0.332)
Post-secondary education	-0.608	(-0.982, -0.233)
Disease duration, years	-0.011	(-0.034, 0.013)
Skin score (MRSS 0-51)	0.004	(-0.020, 0.028)
Episodes of Raynaud's	0.035	(0.014, 0.056)
Active Digital-tip ulcers	0.666	(0.038, 1.294)
Active Other ulcers	0.586	(0.050, 1.122)
Finger contractures (FTP)	0.036	(-0.076, 0.147)
Other joint contractures	0.112	(-0.043, 0.267)
Swollen joint count (0-28)	0.121	(0.054, 0.187)
Tendon friction rubs	0.327	(-0.202, 0.856)
Total gastrointestinal symptoms	0.465	(0.358, 0.572)

$Beta_{av}$: Averaged unstandardized regression coefficients.

5.7 Analysis Diagnostics

Assumptions for linear regression (linearity, normality and constant variance) were verified by examining plots of each covariate with the response pain (Figures 5.1., 5.2., Appendix 5,6) and examining residual plots from multivariable analysis (Figure 5.3. Appendix 7). These assumptions were not found to be violated. Inter-correlations between predictor variables were examined to assess potential issues of multicollinearity (Table 5.7. Appendix 8). Only the correlation between skin score and other joint contractures was in the moderate range (r = 0.52). However both these variables were continuous and variance inflation factors in multivariable analysis including all pre-specified variables ranged from 1.1 to 1.7, suggesting that multicollinearity was likely not a concern.

CHAPTER 6

Discussion

6.1 Summary of Main Findings

Results from the present study show that pain complaints are highly prevalent in SSc with 5 of every 6 patients (> 83%) reporting pain related to their illness. Moreover, although overall mean (SD) pain severity in the present sample of 3.6 (2.8) can be interpreted as falling in the mild pain range (≤ 4); a sizeable proportion of patients (37%) reported pain complaints falling in the moderate or severe pain range. After adjusting for demographic variables, depressive symptoms and comorbid conditions, specific SSc clinical variables significantly associated with pain included more frequent episodes of Raynaud's phenomenon, other active ulcers, more swollen joints (worse synovitis) and a higher number of gastrointestinal symptoms. Digital tip ulcers were also significantly associated with pain after multiple imputation. Patients with diffuse disease reported only minimally higher pain levels than patients with limited disease; differences between limited and diffuse subsets in the clinical predictors of pain were small and not significant.

6.2 Relating Results from the Present Study to the Literature in the Field

PREVALENCE AND SEVERITY OF PAIN

Few studies in SSc include assessments of pain. This lack of focus on pain in SSc may, in part, be related to the fact that pain appears to be assessed and treated less often in SSc compared to other rheumatic diseases (54). However, results from the present study show that pain is common in SSc. Moreover, cumulative evidence from the present study and other studies in SSc suggests that pain complaints in SSc are more severe than those in the general population and are comparable to those observed in reports of other rheumatic diseases where pain is a widely recognized concern.

There are currently no published data on pain assessed by a numerical scale in the general population that could be used as a direct comparison with results from the present study. However, Georges et al. (53) found that mean bodily pain scores on the SF-36 in 89 patients with SSc were approximately one standard deviation worse in SSc than in US and French normative samples. Similarly, a study by Del Rosso et al. (72) found that mean SF-36 bodily pain scores in 24 patients with SSc were also approximately one standard deviation worse than in 24 age and sex matched non-diseased controls.

The high prevalence of pain complaints observed in the present large sample study was even higher than estimates from 3 earlier studies in SSc with small samples (N's = 19, 49, 142) (49, 50, 67) that reported pain prevalence ranging from 60-75%. This suggests that pain may be more common in SSc than previously suspected. Moreover, the estimate of 37% of patients reporting pain in

the moderate or severe range in the present study was higher than in an earlier study (N=142) (67), in which only 10% of SSc patients reported pain beyond mild pain or discomfort (pain assessed with a verbal rating scale ranging from 0 [no pain] to 5 [excruciating]). This again suggests that the proportion of patients experiencing more severe pain in SSc may be greater than previously suspected.

As further evidence of the high levels of pain in SSc, pain severity in the present sample of patients with SSc (mean 3.6, SD 2.8) was comparable with that reported in a recent Canadian study of RA patients (N = 60) (140) seeking specialty care for pain assessed with a 10cm VAS (mean: 4.3, SD: 2.7). Two earlier studies compared patients with SSc to patients with other rheumatic diseases and reported comparable or somewhat higher levels of pain in patients with SSc. Danieli et al. (71) reported similar SF-36 bodily pain scores (range 0-100) in 76 SSc patients (median 61, interquartile range 41-77) and 118 RA patients (median 51, interquartile range 41-74). Moreover Johnson et al. (54), reported mean HAQ-PVAS scores (range 0-3) in 43 SSc patients (mean 1.4, 95% CI 1.1 to 1.6) that was similar to 82 psoriatic arthritis patients (mean 1.2, 95% CI 1.0 to 1.4) and higher than in 42 RA patients (mean 1.0, 95% CI 0.8 to 1.7).

Results from the present large sample study confirm preliminary findings from earlier small sample studies in SSc demonstrating that pain is highly prevalent in SSc, and there is compelling evidence that pain is as severe in SSc as in other rheumatic diseases where pain is commonly assessed and treated.

DIFFERENCES IN PAIN BETWEEN LIMITED AND DIFFUSE SUBSETS

Earlier studies that assessed pain separately in SSc subsets all reported higher pain scores in patients with diffuse disease than in patients with limited disease, (49, 54, 66, 67, 72, 73); however, effect sizes were negligible to small and not statistically significant in 5 of 6 studies. Results from the present study showed that patients with diffuse disease reported higher pain than patients with limited disease and that the difference observed between clinical subsets was statistically significant ($mean_{difference}$: 0.51, 95% CI: 0.06 to 0.97). In terms of clinical decision making, however, it is important to ascertain whether statistical differences between subsets are clinically meaningful. In the context of the present study we examined potential clinically meaningful differences between subsets by estimating an effect size for the difference, as well as, comparing the estimated $mean_{difference}$ between subsets to a threshold of what would be considered a minimal clinically important difference (MCID) based on what is suggested in the literature on pain measures. Although the difference in pain scores between limited and diffuse subsets was statistically significant, the effect size for this difference was 0.18 and would be interpreted as small (<0.2) (135). Furthermore, studies describing MCIDs for pain in SSc and other rheumatic diseases suggest that a 10-20% difference in pain measures, equivalent to approximately a 1 to 2 point difference on the NRS, would correspond to a clinically meaningful difference (141, 142). The raw mean difference in pain between patients with limited and diffuse disease in this study was only half a point, and would therefore not meet the MCID threshold to be considered a

clinically meaningful difference. In addition, there were also no significant differences between SSc subsets in terms of potential clinical predictors of pain.

Evidence from the present large sample study therefore, suggests that defining subsets according to the extent of skin involvement is not clinically relevant in terms of addressing pain complaints in patients with SSc.

ASSOCIATIONS BETWEEN CLINICAL VARIABLES AND PAIN

The present study found statistically significant associations between more frequent episodes of Raynaud's phenomenon, other active ulcers, higher swollen joint count and more gastrointestinal symptom involvement and pain after adjusting for all prespecified covariates. These observations are consistent with reports from prior qualitative and unadjusted quantitative studies in smaller samples of patients with SSc (50, 54, 75).

According to standardized regression coefficient estimates presented in Table 5.3, relative to all other clinical covariates included in the multivariable model, gastrointestinal symptoms (standardized regression coefficient = 0.295) and other active ulcers (standardized regression coefficient = 0.140) had the largest associations with pain. Significant but slightly more modest standardized coefficients were observed for the associations of Raynaud's phenomenon (standardized regression coefficient = 0.099) and swollen joint count (standardized regression coefficient = 0.113) with pain. Similarly, in light of the magnitude of the unstandardized regression coefficient estimates and confidence intervals from multivariable analysis (Table 5.3), 2-3 or more gastrointestinal

symptoms and other active ulcers would reasonably be considered to have independent clinically meaningful effects on pain (i.e. would be associated with ≥ 1 point difference in pain scores). Effect estimates for more frequent episodes of Raynaud's phenomenon and higher swollen joint count were also statistically significant; however, patients would need to experience ≥ 30 Raynaud's episodes per week and have ≥ 8 swollen joints to be associated with a 1 point difference, respectively. This suggests that only severe Raynaud's symptoms and moderate or severe synovitis would be associated with a clinically meaningful difference in pain complaints.

We expected to find a strong and significant positive association between active digital tip ulcers and pain. This expected association was observed in crude regression analysis (unstandardized regression coefficient: 0.903, 95% CI: 0.118 to 1.689). Only 52 (9%) patients in the present study, however, had active digital tip ulcers, so there was fairly little variability. Therefore, the confidence interval for this variable in adjusted analyses that were limited to patients with complete observations was wide and included 0 (unstandardized regression coefficient: 0.400, 95% CI: -0.360 to 1.158). It was statistically significant, however, after multiple imputation was performed (unstandardized regression coefficient: 0.666, 95% CI: 0.038 to 1.294). The fact that all point estimates were relatively large for digital tip ulcers, regardless of the model, and that estimated confidence intervals included values that would be associated with independent clinically meaningful differences in pain, suggests that the association between digital tip ulcers and pain is plausibly clinically meaningful, however, the small proportion of patients

with these active ulcers in the present study made it difficult to obtain precise estimates.

Two published studies (50, 66) have reported associations between skin involvement and pain. While the present study found a significant association between severity of skin involvement and pain in crude regression analysis, this association was no longer significant after adjusting for all other covariates in multivariable analysis. Inconsistent results between the present study and earlier studies may be due to differences in sample sizes, differences in study design, analytic techniques and control of confounding. The first study to report an association between skin involvement and pain was a qualitative study of 19 patients with SSc that recorded anecdotal statements from patients regarding manifestations of their SSc they described as painful. Of the 19 cases included, 18 were categorized as diffuse disease; these patients would therefore be assumed to have more severe skin involvement and problems related to skin may have been more salient to these patients. In addition, due to the qualitative design, this study could not provide any estimate of the magnitude of the association between severity of skin involvement and pain nor could it provide any control of confounding. The second study used the same skin scoring method as the present study and included a quantitative multivariable analysis; however, its sample size constraints did not allow for rigorous data analysis and did not include measures of the full range of clinical covariates included in the present study.

6.3 Study Limitations

Several limitations should be considered when interpreting results from this study. Results were based on cross-sectional analyses, therefore limitations with respect to **determining temporality** (given that measures of the exposures and the response were collected at the same single time point) and **problems sampling early cases, cases with more severe disease and specific demographic groups**, were present leading to difficulties in causal interpretation and generalizibility (124). Careful consideration, however, was used to select and examine associations between only clinical variables that temporally precede the response and could have a plausible causal relationship with pain. Therefore information from the present study regarding the clinical predictors examined would help to advance causal reasoning about potential sources of pain in SSc.

Limitations determining temporality were an issue with respect to potential mediating relationships between clinical predictor variables that could not be verified in the context of the present study. Bias, either towards or away from the null, can be introduced if multivariable analysis include adjustment for clinical variables that are on the causal pathway between other clinical variables and the response (143). Given what is known about the clinical variables examined, such a bias could potentially apply to the reported adjusted association between skin score and pain. Severe skin thickening may be a component or even sufficient cause of finger and other bodily contractures as well as the micro-trauma associated with the development of other ulcers which in turn may cause pain. If this were true then including these variables in the same analysis with skin

score as was done in the multivariable analysis here would have been inappropriate. Therefore, in this scenario, the crude association between skin score and pain may be closer to the true association than the adjusted. However, even the crude association of skin score and pain reported in Table 5.3 (unstandardized regression coefficient: 0.037, 95% CI: 0.013 to 0.059) was very small, and only a difference of at least 25 points on the MRSS (range 0-51) would be associated with a clinically meaningful difference in pain score.

Limitations determining temporality were also an issue in the decision of whether or not to adjust for certain confounders such as depressive symptoms whose temporal relationship with pain is not well established and could not be verified in the context of the present study. However, sensitivity analyses in the present study that examined differences in model estimates between models that included and excluded depressive symptoms as a predictor of pain showed that the observed associations of the clinical predictor variables with pain are not substantively changed with or without adjustment for depressive symptoms.

The present study was based on a convenience sample of patients with SSc. Limitations, therefore associated with this sampling strategy should be considered. The present sample of SSc patients generally had stable disease (median disease duration 9 years). Patients that are not being cared for by a rheumatologist and patients with very severe SSc that were too sick to participate or that died earlier in their disease course, were not included in the present study. This may have resulted in an over-representation of healthier patients in our SSc sample (survival cohort), and results may therefore not be generalizable to the full spectrum of SSc. One solution could have been to attempt to sample cases of

early disease as well as more severe / end stage disease early on in order to obtain finer slices of duration and severity that would enable us to examine whether observed associations remain constant. Nonetheless, even in this potentially healthier sample the prevalence and severity of pain were high.

Proportions of female (female: male ratio = 6:1) and white patients (white: non-white 8:1) were somewhat higher in the present sample than in published SSc samples from the US (US female: male ratio = 3-4:1, US white: non-white ratio = 4:1) (26, 27). The present sample may therefore be more representative of white female cases of SSc. The distribution of limited / diffuse disease in the present study of 61% / 39%, however, is generally consistent with US studies when taking in to account racial differences for limited and diffuse disease (US white - limited / diffuse = 73% / 27%, US non-white limited / diffuse = 40% / 60% (26). Moreover, gender and limited/ diffuse distributions were very similar to another predominantly white European sample that included ≥ 3000 SSc cases (females: males = 6:1, limited / diffuse disease: 62% / 38%) (144). Differences between our Canadian and the European sample vs. the US may be partially explained by sampling artifacts and/or racial differences associated with different clinical profiles of SSc.

In addition, missingness could have affected the generalizibility of our results. Approximately 29% of the CSRG sample had incomplete observations and were excluded from main analyses. Partial respondents could possibly have differed systematically from full respondents included in the present study. Partial respondents; however; were similar to full respondents with respect to demographic variables, disease duration and proportion meeting ACR criteria for

SSc, and there was only a slight discrepancy (< 5%) in the proportion of patients classified as limited and diffuse SSc. Furthermore, regression estimates from sensitivity analysis that used multiple imputation to fill in missing observations did not differ substantively from regression estimates that deleted missing observations, other than by improving precision of model estimates so that effects for digital-tip ulcers reached statistical significance.

Variables reflecting muscle involvement and calcinosis were not included in multivariable analysis. Detailed and precise measurements of muscle involvement such as electromyogram (EMG), muscle imaging, and muscle biopsy are invasive and/or not readily accessible. These measures are therefore not part of the CSRG clinical assessment. Subsequently, the only available measure of muscle involvement was levels of creatinine kinase muscle enzymes. Abnormal elevated creatinine kinase would be indicative of an inflammatory muscle condition such as the presence of myositis. Only 16 (3%) patients however had elevated values of creatinine kinase, which were too few to obtain reasonable and interpretable model estimates in regression analysis. One possible explanation is that patients with an inflammatory muscle condition were likely treated prior to the CSRG assessment when laboratory results for the present study were obtained. Inflammatory myositis, however, by and large, is relatively uncommon in patients with SSc (< 15%) (121). Perhaps more useful than a measure of inflammatory muscle disease would have been a measure of patient myopathy which is suspected to be more common in SSc (121, 145) and may be found to be a more pertinent source of pain complaints.

In preliminary regression models that included a measure of calcinosis, the point estimate for calcinosis in crude (unstandardized beta: -0.139, 95% CI: -0.629 to 0.351) and multivariable linear regression analysis (unstandardized beta: -0.426, 95% CI: -0.909 to 0.0.57), though not significant, was negative, which was cause for scrutiny. A possible explanation may be that the measure used in the present study (a single binary variable reflecting the presence of visible or palpable calcinosis anywhere on the body recorded by the examining physician) was likely not a specific measure that was restricted to calcinosis that would be expected to cause pain. That is, rheumatologists may have reported calcinosis uncovered during the physical exam (i.e. when palpating arms or legs) that the patient may not have even previously noticed, as opposed to reporting only calcinosis reported to be bothersome to the patient (tender calcinosis). It is also possible that location of calcinosis, particularly in those areas subject to constant pressure (i.e. calcinosis on the fingers, hands and toes), may be relevant to record in the context of studies of pain in patients with SSc. In this study, classification of calcinosis did not take into account location.

Other measurement constraints should also be considered when interpreting study estimates. The present study used a crude measure of race (binary variable reflecting white vs. non-white race). Given, however, that the CSRG sample was predominantly white (90%), a more inclusive measure of race would have provided too few observations in each additional racial category to obtain reasonable and interpretable model estimates in regression analysis.

An important advantage of analyzing data from the CSRG is their standardized detailed clinical assessment which consists of measures that meet the

most recent recommendations for measures used to assess patients with SSc. That said, there is some debate about the use of the current standard measure of finger contracture severity, which was used in the present study. Medsger et al. (146) describe important limitations of the FTP measure including that it is a non-standardized measure with somewhat poor reliability. Moreover the measure does not distinguish between patients with fixed exaggerated flexion who have no range of motion and therefore have significant impairment versus patients whose fingers are not fixed forward but have minimal impairment and are just short of being able to form a perfect fist. They rationalize, however, that FTP is the only current measure with an established reference range, is the best available measure of joint contracture severity, and should be used until a better measure is developed. The following is the direct commentary provided in Medsger et al. (146) (p. S-44):

> "The subcommittee members felt that a more precise / reliable measure of finger contracture would be most desirable, and thus issues a challenge for clinical investigators to develop such a measure. In the future, another alternative would be a patient-completed hand function questionnaire or practical test. However, for the present we recommend retaining the FTP measurement as described in the severity scale publication, without any changes."

Therefore results from the present study reporting that there was no significant association between finger contracture severity and pain should be interpreted with caution.

Similarly, the MRSS is the best available and only skin scoring method recommended for use in SSc clinical trials (95), however, reliability of the MRSS can be an issue, for the most part in untrained and inexperienced rheumatologists

with the skin score (102). Inter-observer reliability of the MRSS for CSRG rheumatologists has not been formally assessed however, CSRG rheumatologists are all considered to be the top specialists in SSc in Canada and have all undergone standardized training in the MRSS assessment for purposes of standardizing CSRG procedures, therefore it is unlikely that reliability of the MRSS was an issue that would have substantively impacted on results in the present study.

Measures of episodes of Raynaud's phenomenon, gastrointestinal symptoms, depressive symptoms and comorbidities were patient-reported, so it is possible that there was some misclassification with these measures. However, Raynaud's phenomenon is episodic and involves certain subjective elements such as tingling and numbness that would require patient-based data collection. Therefore, the present study used the current standard for measuring Raynaud's phenomenon in studies of SSc patients; the number of patient-reported episodes (95). More objective tests exist for assessing gastrointestinal involvement but these are invasive, and patient reports of gastrointestinal symptoms have been shown to be reliable and valid in SSc (77). Interviews based on DSM-IV criteria are currently the gold standard for assessing depression. However, they are less feasible in the context of epidemiologic studies as they would require trained interviewers and add significantly to the length of the patient assessment. The CES-D questionnaire used in the present study is easy to administer and has been validated in patients with SSc as a measure of symptom severity. Physician reported diagnoses of osteoarthritis and back pain obtained from patient charts would have been a more valid measure of comorbidity than patient reports.

However, most patients would know whether they had such common and chronic conditions as osteoarthritis and/or back pain, and it would therefore be reasonable to assume that misclassification would be minimal.

Lastly, there are many individual and contextual factors (both known and unknown) that affect the way patients respond to pain (56). The present study attempted to assess intensity/ severity of SSc-related pain. Subsequently, an appropriate pain intensity/ severity scale, a pain numerical rating scale (NRS), which has been shown to be reliable and valid was selected as the primary outcome measure. None the less, individual and contextual factors in addition to SSc-related pain stimuli may have influenced response ratings. Moreover, there were two implicit assumptions in using the pain NRS: i) pain responses on the NRS reflected patient SSc-related pain and, ii) patient-rated pain in the past week was an accurate reflection of patient general SSc pain status. These assumptions, however, would not hold true if NRS responses were contaminated by other sources of pain unrelated to their scleroderma, if pain fluctuated in SSc over time and if responses reflected pain complaints on the current day rather than an average across the past week. In order to avoid contamination by other sources of pain, case report forms explicitly asked patients to rate the intensity/ severity of pain related to their illness in the past week. Furthermore, painful comorbid conditions were included in sensitivity analysis and were found not to substantively change any reported associations. Therefore although contamination is a potential concern that cannot be ruled out, contamination was likely minimized by the phrasing of the question and the sensitivity analysis performed. Another source of bias might have been the relatively short reference period of

one week used with the pain NRS. Shorter reference periods may not yield a valid estimate of the patient pain status because of the variability of chronic pain over time (147, 148). Furthermore, there is no way to ascertain if the referral period was actually respected and patients were not responding based on how they felt the day the case report form was completed. However, pain assessment based on a longer reference period might have resulted in poorer recall and increasing the frequency of pain assessment was not feasible given the framework of this study.

6.4 Study Strengths

The reported results were derived from large multi-center data collected using standardized procedures consistent with the most recent recommendations and rigorous data analysis, and are therefore likely robust. Results from this study confirmed earlier findings based on small samples of SSc patients, and showed that pain is highly prevalent in these patients and is as severe in SSc as in other rheumatic diseases. This was the first study to rigorously examine multiple potential sources of pain in SSc and results showing significant associations of more frequent episodes of Raynaud's phenomenon, active ulcers, synovitis and gastrointestinal symptoms with pain suggest that these may potential represent clinical intervention targets. This was the first study to examine whether differences in severity of pain complaints between SSc disease subsets were clinically meaningful. It was also the first study to systematically examine whether predictors of pain differ between subsets and showed that subsetting by the extent of skin involvement does not appear to be important insofar as pain is concerned.

6.5 Directions for Future Research

Future longitudinal studies of pain in SSc with multiple waves of data collection examining effects of time-varying clinical covariates on pain and adjusting for informative missingness would provide compelling evidence for causal interpretation. These studies should also include specific measures of tender calcinosis, muscle involvement, sicca symptoms, fibromyalgia and dependent oedema that were unavailable in the present study. More research clarifying the pathophysiologic mechanisms of pain in SSc as well as psychosocial risk/ protective factors for pain will be needed to improve the understanding of pain in order to help develop and implement optimal interventions (149). The role of inflammation in sensitizing pain pathways is an emerging area in the rheumatic disease (150). However, research aimed at uncovering pathogenetic processes specific to SSc-related pain is lacking. Multiple psychosocial interventions for pain have been developed and tested primarily in arthritis, including cognitive behavioural therapy, relaxation, biofeedback and meditation (151), but the efficacy of such interventions in patients with SSc remains unknown. Lastly, research identifying patient and physician facilitators/ barriers to pain assessment and treatment in SSc can help to improve health service delivery for pain in patients with SSc.

CHAPTER 7

Conclusion

7.1 Summary, Conclusions and Key Messages

SSc is a chronic rheumatic disease with no cure characterized by vascular, immune system and fibrotic changes that largely affects young adult women and has a severe impact on multiple areas of quality of life. Improvement in pain management has been shown to be of the highest priority to patients with rheumatic disease, and, although pain complaints are widely assessed and treated in most rheumatic diseases, pain has received relatively little attention in SSc. Current understanding of pain in SSc is based on very few descriptive studies with small samples. Thus, clinicians do not have good research on which to base their understanding of prevalence, severity, and potential sources of pain in these patients.

Robust estimates from the present study confirm that pain is more common and even more severe than previously suspected based on earlier published data. Some level of pain is present in 5 of every 6 SSc patients, and pain is as severe in SSc as in other rheumatic disease where pain is widely

assessed and treated. Although defining clinical subsets according to the extent of skin involvement has been shown to provide important prognostic information, results from the present study showed that this classification was not meaningfully associated with pain severity or with clinical predictors of pain. Clinical predictors of pain in the present study included more frequent episodes of Raynaud's phenomenon, active ulcers, worse synovitis and more gastrointestinal symptoms, and these may represent potential clinical intervention targets.

KEY MESSAGES

- Pain is highly prevalent in SSc and is as severe as in other rheumatic diseases.
- Specific SSc clinical variables associated with pain were: *more frequent episodes of Raynaud's phenomenon, active ulcers, worse synovitis and more gastrointestinal symptoms,* which may represent potential clinical targets for intervention.
- Defining subsets according to the extent of skin involvement does not appear to be important insofar as pain is concerned.
- More attention to pain and how to best manage it is needed in SSc.

1. Charles C, Clements P, Furst DE. Systemic sclerosis: hypothesis-driven treatment strategies. Lancet 2006;367:1683-91.

2. Haustein UF. Systemic sclerosis-scleroderma. Dermatol Online J 2002;8:3.

3. Mayes M. The Scleroderma Book. 2 ed. Ney York: Oxford University Press, Inc.; 2005.

4. Denton CP, Black CM. Scleroderma and related disorders: therapeutic aspects. Baillieres Best Pract Res Clin Rheumatol 2000;14:17-35.

5. Flavahan NA, Flavahan S, Mitra S, Chotani MA. The vasculopathy of Raynaud's phenomenon and scleroderma. Rheum Dis Clin North Am 2003;29:275-291.

6. Ho KT, Reveille JD. The clinical relevance of autoantibodies in scleroderma. Arthritis Res Ther 2003;5:80-93.

7. Kissin EY, Korn JH. Fibrosis in scleroderma. Rheum Dis Clin North Am 2003;29:351-369.

8. Gayraud M. Raynaud's phenomenon. Joint Bone Spine 2007;74:e1-8.

9. Chizzolini C. Update on pathophysiology of scleroderma with special reference to immunoinflammatory events. Ann Med 2007;39:42-53.

10. Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. N Engl J Med 2009;360:1989-2003.

11. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Arthritis Rheum 1980;23:581-90.

12. Lonzetti LS, Joyal F, Raynauld JP, Roussin A, Goulet JR, Rich E, et al. Updating the American College of Rheumatology preliminary classification criteria for systemic sclerosis: addition of severe nailfold capillaroscopy abnormalities markedly increases the sensitivity for limited scleroderma. Arthritis Rheum 2001;44:735-6.

13. Medsger TA, Jr. Comment on scleroderma criteria cooperative study. In: Black CM MA, editor. Current topics in rheumatology: systemic sclerosis (scleroderma). New York: Gower; 1985. p. 16–7.

14. Valentini G. The assessment of the patient with systemic sclerosis. Autoimmun Rev 2003;2:370-6.

15. Clements PJ. Systemic sclerosis (scleroderma) and related disorders: clinical aspects. Baillieres Best Pract Res Clin Rheumatol 2000;14:1-16.

16. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA, Jr., et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 1988;15:202-5.

17. Medsger Jr 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;29:255-273.

18. Denton CP. Systemic sclerosis:clinical features and management. medicine 2006;34:480-488.

19. Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. Arthritis Rheum 2008;58:15-25.

20. Mayes MD. Scleroderma epidemiology. Rheum Dis Clin North Am 2003;29:239-54.

21. Chifflot H, Fautrel B, Sordet C, Chatelus E, Sibilia J. Incidence and prevalence of systemic sclerosis: a systematic literature review. Semin Arthritis Rheum 2008;37:223-35.

22. Englert H, Joyner E, Bade R, Thompson M, Morris D, Chambers P, et al. Systemic scleroderma: a spatiotemporal clustering. Intern Med J 2005;35:228-33.

23. Valesini G, Litta A, Bonavita MS, Luan FL, Purpura M, Mariani M, et al. Geographical clustering of scleroderma in a rural area in the province of Rome. Clin Exp Rheumatol 1993;11:41-7.

24. Silman AJ, Howard Y, Hicklin AJ, Black C. Geographical clustering of scleroderma in south and west London. Br J Rheumatol 1990;29:93-6.

25. Arnett FC, Howard RF, Tan F, Moulds JM, Bias WB, Durban E, et al. Increased prevalence of systemic sclerosis in a Native American tribe in Oklahoma. Association with an Amerindian HLA haplotype. Arthritis Rheum 1996;39:1362-70.

26. Mayes MD, Lacey JV, Jr., Beebe-Dimmer J, Gillespie BW, Cooper B, Laing TJ, et al. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. Arthritis Rheum 2003;48:2246-55.

27. Steen VD, Oddis CV, Conte CG, Janoski J, Casterline GZ, Medsger TA, Jr. Incidence of systemic sclerosis in Allegheny County, Pennsylvania. A twenty-year study of hospital-diagnosed cases, 1963-1982. Arthritis Rheum 1997;40:441-5.

28. Medsger TA, Jr. Epidemiology of systemic sclerosis. Clin Dermatol 1994;12:207-16.

29. Laing TJ, Gillespie BW, Toth MB, Mayes MD, Gallavan RH, Jr., Burns CJ, et al. Racial differences in scleroderma among women in Michigan. Arthritis Rheum 1997;40:734-42.

30. Al-Dhaher FF, Pope JE, Ouimet JM. Determinants of Morbidity and Mortality of Systemic Sclerosis in Canada. Semin Arthritis Rheum 2008;in press.

31. Denton CP, Black CM. Pulmonary hypertension in systemic sclerosis. Rheum Dis Clin North Am 2003;29:335-49, vii.

32. White B. Interstitial lung disease in scleroderma. Rheum Dis Clin North Am 2003;29:371-390.

33. Steen VD. Scleroderma renal crisis. Rheum Dis Clin North Am 1996;22:861-78.

34. Deswal A, Follansbee WP. Cardiac involvement in scleroderma. Rheum Dis Clin North Am 1996;22:841-60.

35. Khanna D, Melikterminas E. Gastrointestinal involvement in systemic sclerosis. Indian J Rheumatol 2008;3:13-20.

36. Varga E, Field EA, Tyldesley WR. Orofacial manifestations of mixed connective tissue disease. Br Dent J 1990;168:330-1.

37. Randone SB, Guiducci S, Cerinic MM. Musculoskeletal involvement in systemic sclerosis. Best Pract Res Clin Rheumatol 2008;22:339-50.

38. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. Ann Rheum Dis 2007;66:940-4.

39. Ioannidis JP, Vlachoyiannopoulos PG, Haidich AB, Medsger TA, Jr., Lucas M, Michet CJ, et al. Mortality in systemic sclerosis: an international meta-analysis of individual patient data. Am J Med 2005;118:2-10.

40. Bryan C, Knight C, Black CM, Silman AJ. Prediction of five-year survival following presentation with scleroderma: development of a simple model using three disease factors at first visit. Arthritis Rheum 1999;42:2660-5.

41. Ferri C, Valentini G, Cozzi F, Sebastiani M, Michelassi C, La Montagna G, et al. Systemic sclerosis: demographic, clinical, and serologic features and survival in 1,012 Italian patients. Medicine 2002;81:139-53.

42. McNearney TA, Reveille JD, Fischbach M, Friedman AW, Lisse JR, Goel N, et al. Pulmonary involvement in systemic sclerosis: associations with genetic, serologic, sociodemographic, and behavioral factors. Arthritis Rheum 2007;57:318-26.

43. Bernatsky S, Hudson M, Panopalis P, Clarke AE, Pope J, Leclercq S, et al. The cost of systemic sclerosis. Arthritis Rheum 2009;61:119-23.

44. Maetzel A, Li LC, Pencharz J, Tomlinson G, Bombardier C. The economic burden associated with osteoarthritis, rheumatoid arthritis, and hypertension: a comparative study. Ann Rheum Dis 2004;63:395-401.

45. Wilson L. Cost-of-illness of scleroderma: the case for rare diseases. Semin Arthritis Rheum 1997;27:73-84.

46. Belotti Masserini A, Zeni S, Cossutta R, Soldi A, Fantini F. Cost-of-illness in systemic sclerosis: A retrospective study of an italian cohort of 106 patients. [Italian]. Reumatismo 2003;55:245-255.

47. Haythornthwaite JA, Heinberg LJ, McGuire L. Psychologic factors in scleroderma. Rheum Dis Clin North Am 2003;29:427-39.

48. Joachim G, Acorn S. Life with a rare chronic disease: the scleroderma experience. J Adv Nurs 2003;42:598-606.

49. 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.

50. Suarez-Almazor ME, Kallen MA, Roundtree AK, Mayes M. Disease and symptom burden in systemic sclerosis: a patient perspective. J Rheumatol 2007;34:1718-26.

51. 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.

52. Hyphantis TN, Tsifetaki N, Pappa C, Voulgari PV, Siafaka 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.

53. Georges C, Chassany O, Toledano C, Mouthon L, Tiev K, Meyer O, et al. Impact of pain in health related quality of life of patients with systemic sclerosis. Rheumatology (Oxford) 2006;45:1298-302.

54. Johnson SR, Gladman DD, Schentag CT, Lee P. Quality of life and functional status in systemic sclerosis compared to other rheumatic diseases. J Rheumatol 2006;33:1117-1122.

55. Hudson M, Steele R, Taillefer S, Baron M. Quality of life in systemic sclerosis: psychometric properties of the World Health Organization Disability Assessment Schedule II. Arthritis Rheum 2008;59:270-8.

56. Sokka T. Assessment of pain in patients with rheumatic diseases. Best Pract Res Clin Rheumatol 2003;17:427-49.

57. Katz WA, Rothenberg R. Section 2: The importance of improving function in patients with pain. J Clin Rheumatol 2005;11:S6-9, discussion S9-10.

58. Kazis LE, Meenan RF, Anderson JJ. Pain in the rheumatic diseases. Investigation of a key health status component. Arthritis Rheum 1983;26:1017-22.

59. Anderson JJ, Baron G, van der Heijde D, Felson DT, Dougados M. Ankylosing spondylitis assessment group preliminary definition of short-term improvement in ankylosing spondylitis. Arthritis Rheum 2001;44:1876-86.

60. Bellamy N, Kirwan J, Boers M, Brooks P, Strand V, Tugwell P, et al. Recommendations for a core set of outcome measures for future phase III clinical trials in knee, hip, and hand osteoarthritis. Consensus development at OMERACT III. J Rheumatol 1997;24:799-802.

61. Felson D, Anderson,JJ., Boers,M., Bombardier,C., Furst,D., Goldsmith,C., Katz,LM., Lightfoot Jr,R., Paulus,H., Strand,V., Tugwell,P., Weinblatt,M., Williams,J., Wolfe,F., Kieszak,S. American college of rheumatology preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 2005;38:727 - 735.

62. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. Arthritis Rheum 1990;33:160-72.

63. Taylor WJ. Preliminary identification of core domains for outcome studies in psoriatic arthritis using Delphi methods. Ann Rheum Dis 2005;64:ii110-2.

64. Heiberg T, Kvien TK. Preferences for improved health examined in 1,024 patients with rheumatoid arthritis: pain has highest priority. Arthritis Rheum 2002;47:391-7.

65. Sultan N, Pope JE, Clements PJ. The health assessment questionnaire (HAQ) is strongly predictive of good outcome in early diffuse scleroderma: results from an analysis of two randomized controlled trials in early diffuse scleroderma. Rheumatology (Oxford) 2004;43:472-8.

66. Malcarne VL, Hansdottir 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.

67. Benrud-Larson LM, Haythornthwaite JA, Heinberg LJ, Boling C, Reed J, White B, et al. The impact of pain and symptoms of depression in scleroderma. Pain 2002;95:267-75.

68. Hudson M, Thombs BD, Steele R, Watterson R, Taillefer S, Baron M. Clinical correlates of quality of life in systemic sclerosis measured with the World Health Organization Disability Assessment Schedule II. Arthritis Rheum 2008;59:279-84.

69. Carreira PE. 'Quality of pain' in systemic sclerosis. Rheumatology (Oxford) 2006;45:1185-6.

70. Malcarne VL, Greenbergs HL. Psychological adjustment to systemic sclerosis. Arthritis Care Res 1996;9:51-9.

71. Danieli E, Airo P, Bettoni L, Cinquini M, Antonioli CM, Cavazzana I, et al. Health-related quality of life measured by the Short Form 36 (SF-36) in systemic sclerosis: correlations with indexes of disease activity and severity, disability, and depressive symptoms. Clin Rheumatol 2005;24:48-54.

72. Del Rosso A, Boldrini M, D'Agostino D, Placidi GP, Scarpato A, Pignone A, et al. Health-related quality of life in systemic sclerosis as measured by the Short Form 36: relationship with clinical and biologic markers. Arthritis Rheum 2004;51:475-81.

73. Rannou F, Poiraudeau S, BereznÃ© A, Baubet T, Le-Guern V, Cabane J, et al. Assessing disability and quality of life in systemic sclerosis: construct validities of the Cochin Hand Function Scale, Health Assessment Questionnaire (HAQ), Systemic Sclerosis HAQ, and Medical Outcomes Study 36-Item Short Form Health Survey. Arthritis Rheum 2007;57:94-102.

74. Korn JH, Mayes M, Matucci Cerinic M, Rainisio M, Pope J, Hachulla E, et al. Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist. Arthritis Rheum 2004;50:3985-93.

75. Merkel PA, Herlyn K, Martin RW, Anderson JJ, Mayes MD, Bell P, et al. Measuring disease activity and functional status in patients with scleroderma and Raynaud's phenomenon. Arthritis Rheum 2002;46:2410-20.

76. Toffolo SR, Furtado RN, Klein A, Watanabe S, Andrade LE, Natour J. Measurement of upper limb ulcers in patients with systemic sclerosis: reproducibility and correlation with pain, function, and quality of life. Nurs Res 2008;57:84-92.

77. Khanna D, Hays RD, Park GS, Braun-Moscovici Y, Mayes MD, McNearney TA, et al. Development of a preliminary scleroderma gastrointestinal tract 1.0 quality of life instrument. Arthritis Rheum 2007;57:1280-6.

78. Harrell Frank E, Jr,. Regression Modelling Strategies With Applications to Linear Models, Logistic Regression, and Survival Analysis New York: Springer-Verlag New York, Inc; 2001.

79. Bombardieri S, Medsger TA, Jr., Silman AJ, Valentini G. The assessment of the patient with systemic sclerosis. Introduction. Clin Exp Rheumatol 2003;21:S2-4.

80. Akesson A, Fiori G, Krieg T, van den Hoogen FH, Seibold JR. Assessment of skin, joint, tendon and muscle involvement. Clin Exp Rheumatol 2003;21:S5-8.

81. Kahaleh B, Meyer O, Scorza R. Assessment of vascular involvement. Clin Exp Rheumatol 2003;21:S9-14.

82. Clements PJ, Becvar R, Drosos AA, Ghattas L, Gabrielli A. Assessment of gastrointestinal involvement. Clin Exp Rheumatol 2003;21:S15-8.

83. Matucci-Cerinic M, D'Angelo S, Denton CP, Vlachoyiannopoulos P, Silver R. Assessment of lung involvement. Clin Exp Rheumatol 2003;21:S19-23.

84. Ferri C, Emdin M, Nielsen H, Bruhlmann P. Assessment of heart involvement. Clin Exp Rheumatol 2003;21:S24-8.

85. Steen VD, Mayes MD, Merkel PA. Assessment of kidney involvement. Clin Exp Rheumatol 2003;21:S29-31.

86. McHugh NJ, Distler O, Giacomelli R, Riemekasten G. Non organ based laboratory markers in systemic sclerosis. Clin Exp Rheumatol 2003;21:S32-8.

87. Valentini G, Silman AJ, Veale D. Assessment of disease activity. Clin Exp Rheumatol 2003;21:S39-41.

88. Medsger TA, Jr., Silman AJ, Steen VD, Black CM, Akesson A, Bacon PA, et al. A disease severity scale for systemic sclerosis: development and testing. J Rheumatol 1999;26:2159-67.

89. Bombardieri S, Medsger TA, Jr., Silman AJ, Valentini G. Manual of signs, symptoms, methods and procedures for the assessment of the patient with SSc. Clin Exp Rheumatol 2003;21:S49-56.

90. Boers M, Brooks P, Simon LS, Strand V, Tugwell P. OMERACT: an international initiative to improve outcome measurement in rheumatology. Clin Exp Rheumatol 2005;23:S10-3.

91. Wolfe F, Lassere M, van der Heijde D, Stucki G, Suarez-Almazor M, Pincus T, et al. Preliminary core set of domains and reporting requirements for longitudinal observational studies in rheumatology. J Rheumatol 1999;26:484-9.

92. 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.

93. Kahaleh MB, Sultany GL, Smith EA, Huffstutter JE, Loadholt CB, LeRoy EC. A modified scleroderma skin scoring method. Clin Exp Rheumatol 1986;4:367-9.

94. Furst DE, Khanna D, Mattucci-Cerinic M, Silman AJ, Merkel PA, Foeldvari I. Scleroderma--developing measures of response. J Rheumatol 2005;32:2477-80.

95. Merkel PA, Clements PJ, Reveille JD, Suarez-Almazor ME, Valentini G, Furst DE. Current status of outcome measure development for clinical trials in systemic sclerosis. Report from OMERACT 6. J Rheumatol 2003;30:1630-47.

96. Clements PJ, Lachenbruch PA, Ng SC, Simmons M, Sterz M, Furst DE. Skin score. A semiquantitative measure of cutaneous involvement that improves prediction of prognosis in systemic sclerosis. Arthritis Rheum 1990;33:1256-63.

97. Clements PJ, Hurwitz EL, Wong WK, Seibold JR, Mayes M, White B, et al. Skin thickness score as a predictor and correlate of outcome in systemic sclerosis: high-dose versus low-dose penicillamine trial. Arthritis Rheum 2000;43:2445-54.

98. Steen VD, Medsger TA, Jr. Improvement in skin thickening in systemic sclerosis associated with improved survival. Arthritis Rheum 2001;44:2828-35.

99. DeMarco PJ, Weisman MH, Seibold JR, Furst DE, Wong WK, Hurwitz EL, et al. Predictors and outcomes of scleroderma renal crisis: the high-dose versus low-dose D-penicillamine in early diffuse systemic sclerosis trial. Arthritis Rheum 2002;46:2983-9.

100. Brennan P, Silman A, Black C, Bernstein R, Coppock J, Maddison P, et al. Reliability of skin involvement measures in scleroderma. The UK Scleroderma Study Group. Br J Rheumatol 1992;31:457-60.

101. Clements P, Lachenbruch P, Siebold J, White B, Weiner S, Martin R, et al. Inter and intraobserver variability of total skin thickness score (modified Rodnan TSS) in systemic sclerosis. J Rheumatol 1995;22:1281-5.

102. Czirjak L, Nagy Z, Aringer M, Riemekasten G, Matucci-Cerinic M, Furst DE. The EUSTAR model for teaching and implementing the modified Rodnan skin score in systemic sclerosis. Ann Rheum Dis 2007;66:966-9.

103. Dziadzio M, Denton CP, Smith R, Howell K, Blann A, Bowers E, et al. Losartan therapy for Raynaud's phenomenon and scleroderma: clinical and biochemical findings in a fifteen-week, randomized, parallel-group, controlled trial. Arthritis Rheum 1999;42:2646-55.

104. Wigley FM, Korn JH, Csuka ME, Medsger TA, Jr., Rothfield NF, Ellman M, et al. Oral iloprost treatment in patients with Raynaud's phenomenon secondary to systemic sclerosis: a multicenter, placebo-controlled, double-blind study. Arthritis Rheum 1998;41:670-7.

105. Milio G, Corrado E, Genova C, Amato C, Raimondi F, Almasio PL, et al. Iloprost treatment in patients with Raynaud's phenomenon secondary to systemic sclerosis and the quality of life: a new therapeutic protocol. Rheumatology (Oxford) 2006;45:999-1004.

106. Hettema ME, Zhang D, Bootsma H, Kallenberg CGM. Bosentan therapy for patients with severe Raynaud's phenomenon in systemic sclerosis [1]. Annals of the Rheumatic Diseases 2007;66(10):1398-1399.

107. Chung L, Fiorentino D. Digital ulcers in patients with systemic sclerosis. Autoimmun Rev 2006;5:125-8.

108. Boulman N, Slobodin G, Rozenbaum M, Rosner I. Calcinosis in rheumatic diseases. Semin Arthritis Rheum 2005;34:805-812.

109. Clements PJ, Wong WK, Hurwitz EL, Furst DE, Mayes M, White B, et al. Correlates of the disability index of the health assessment questionnaire: a measure of functional impairment in systemic sclerosis. Arthritis Rheum 1999;42:2372-80.

110. Poole JL, Steen VD. The use of the Health Assessment Questionnaire (HAQ) to determine physical disability in systemic sclerosis. Arthritis Care Res 1991;4:27-31.

111. Ashida R, Ihn H, Mimura Y, Jinnin M, Asano Y, Kubo M, et al. Clinical features of scleroderma patients with contracture of phalanges. Clin Rheumatol 2007;26:1275-7.

112. Baron M, Lee P, Keystone EC. The articular manifestations of progressive systemic sclerosis (scleroderma). Ann Rheum Dis 1982;41:147-52.

113. Scott DL, Antoni C, Choy EH, Van Riel PC. Joint counts in routine practice. Rheumatology (Oxford) 2003;42:919-23.

114. Fuchs HA, Brooks RH, Callahan LF, Pincus T. A simplified twenty-eight-joint quantitative articular index in rheumatoid arthritis. Arthritis Rheum 1989;32:531-7.

115. Scott DL, Houssien DA. Joint assessment in rheumatoid arthritis. Br J Rheumatol 1996;35:14-8.

116. Prevoo ML, van Riel PL, van 't Hof MA, van Rijswijk MH, van Leeuwen MA, Kuper HH, et al. Validity and reliability of joint indices. A longitudinal study in patients with recent onset rheumatoid arthritis. Br J Rheumatol 1993;32:589-94.

117. Smolen JS, Breedveld FC, Eberl G, Jones I, Leeming M, Wylie GL, et al. Validity and reliability of the twenty-eight-joint count for the assessment of rheumatoid arthritis activity. Arthritis Rheum 1995;38:38-43.

118. Mansfield ER, Helms BP. Detecting Multicollinearity. The American Statistician 1982;36:158-160.

119. Mayes M. Systemic Sclerosis A.Clinical Features. In: Klippel JH, Stone JH, Crafford LJ, White PH, editors. Primer on the Rheumatic Diseases. 13 ed. New York: Springer and Arthritis Foundation; 2008. p. 343-350.

120. Steen VD, Medsger TA, Jr. The palpable tendon friction rub: an important physical examination finding in patients with systemic sclerosis. Arthritis Rheum 1997;40:1146-51.

121. Clements PJ, Furst DE, Campion DS, Bohan A, Harris R, Levy J, et al. Muscle disease in progressive systemic sclerosis: diagnostic and therapeutic considerations. Arthritis Rheum 1978;21:62-71.

122. Medsger TA, Jr., Rodnan GP, Moossy J, Vester JW. Skeletal muscle involvement in progressive systemic sclerosis (scleroderma). Arthritis Rheum 1968;11:554-68.

123. Pope JE. Musculoskeletal involvement in scleroderma. Rheumatic Disease Clinics of North America 2003;29:391-408.

124. Rothman KJ, Greenland S, Lash TL. Modern Epidemiology. Third ed. Philadelphia: Lippincott Williams & Wilkins; 2008.

125. Spencer-Green G. Outcomes in primary Raynaud phenomenon: a meta-analysis of the frequency, rates, and predictors of transition to secondary diseases. Arch Intern Med 1998;158:595-600.

126. Radloff L. The CES-D scale: a self-report depression scale for research in the general population. . Applied Psychological Measurement 1977:189-98.

127. Thombs BD, Hudson M, Schieir O, Taillefer SS, Baron M. Reliability and validity of the center for epidemiologic studies depression scale in patients with systemic sclerosis. Arthritis Rheum 2008;59:438-43.

128. Johnson SR, Hawker GA, Davis AM. The Health Assessment Questionnaire Disability Index and Scleroderma Health Assessment Questionnaire in scleroderma trials: an evaluation of their measurement properties. Arthritis Rheum 2005;53:256-262.

129. Steen VD, Medsger Jr TA. The value of the Health Assessment Questionnaire and special patient- generated scales to demonstrate change in systemic sclerosis patients over time. Arthritis Rheum1997;40:1984-1991.

130. Van Tubergen A, Debats I, Ryser L, Londono J, Burgos-Vargas R, Cardiel MH, et al. Use of a numerical rating scale as an answer modality in ankylosing spondylitis-specific questionnaires. Arthritis Rheum 2002;47:242-8.

131. Ferraz MB, Quaresma MR, Aquino LR, Atra E, Tugwell P, Goldsmith CH. Reliability of pain scales in the assessment of literate and illiterate patients with rheumatoid arthritis. J Rheumatol 1990;17:1022-4.

132. Chow E, Doyle M, Li K, Bradley N, Harris K, Hruby G, et al. Mild, moderate, or severe pain categorized by patients with cancer with bone metastases. J Palliat Med 2006;9:850-4.

133. Salaffi F, Stancati A, Silvestri CA, Ciapetti A, Grassi W. Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. Eur J Pain 2004;8:283-91.

134. Hedges LV. Estimation of effect size from a series of independent experiments. Psychol Bull 1982;92:490-499.

135. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum 1988.

136. Greenland S. Invited commentary: variable selection versus shrinkage in the control of multiple confounders. Am J Epidemiol 2008;167:523-9.

137. Zar J. Biostatistical Analysis. 3rd ed. Upper Saddle River: Prentice Hall 1996.

138. Van Buuren S, Oudshoorn K. Flexible multivariate imputation by MICE. . Report. Leiden: Prevention and Health; 1999. Report No.: PG/VGZ/99.054.

139. Singer JD. Using SAS PROC MIXED to Fit Multilevel Models, Hierarchical Models, and Individual Growth Models. J Educ Behav Stat 1998;24:323-355.

140. Fitzcharles MA, Dacosta D, Ware MA, Shir Y. Patient Barriers to Pain Management May Contribute to Poor Pain Control in Rheumatoid Arthritis. J Pain 2008;in press.

141. Farrar JT, Young JP, Jr., LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94:149-58.

142. Gazi H, Pope JE, Clements P, Medsger TA, Martin RW, Merkel PA, et al. Outcome measurements in scleroderma: results from a Delphi exercise. J Rheumatol 2007;34:501-509.

143. Tu YK, West R, Ellison GT, Gilthorpe MS. Why evidence for the fetal origins of adult disease might be a statistical artifact: the "reversal paradox" for the relation between birth weight and blood pressure in later life. Am J Epidemiol 2005;161:27-32.

144. Walker UA, Tyndall A, Czirjak L, Denton CP, Farge D, Kowal-Bielecka O, et al. Geographic variation of disease manifestations in systemic sclerosis - a report from the EULAR Scleroderma Trials And Research (EUSTAR) group data base. Ann Rheum Dis 2009;68:856-862.

145. Ranque B, Authier FJ, Berezne A, Guillevin L, Mouthon L. Systemic sclerosis-associated myopathy. Ann N Y Acad Sci 2007;1108:268-82.

146. Medsger TA, Jr., Bombardieri S, Czirjak L, Scorza R, Della Rossa A, Bencivelli W. Assessment of disease severity and prognosis. Clin Exp Rheumatol 2003;21:S42-6.

147. Turk DC. Handbook of pain assessment; 2001.

148. Jensen MP, McFarland CA. Increasing the reliability and validity of pain intensity measurement in chronic pain patients. Pain 1993;55:195-203.

149. Fitzcharles MA, Shir Y. New concepts in rheumatic pain. Rheum Dis Clin North Am 2008;34:267-83.

150. Kidd BL, Urban LA. Mechanisms of inflammatory pain. Br J Anaesth 2001;87:3-11.

151. Keefe FJ, Somers TJ, Martire LM. Psychologic interventions and lifestyle modifications for arthritis pain management. Rheum Dis Clin North Am 2008;34:351-68.

1980 Criteria for the Classification of Systemic Sclerosis

Table 2. Glossary of clinical terms used in description or classification of systemic sclerosis

1. Typical sclerodermatous skin changes: tightness, thickening, and non-pitting induration, excluding the localized forms of scleroderma (morphea or linear scleroderma)

- **a.** Sclerodactyly: above-indicated changes limited to (fingers and toes)
- **b.** Proximal scleroderma: above-indicated changes proximal to the metacarpophalangeal or metatarsophalangeal joints, affecting other parts of the extremities, face, neck, or trunk (thorax or abdomen); usually bilateral, symmetrical and almost always *including* sclerodactyly

2. Other skin manifestations attributable to systemic sclerosis or comparison disorders

- **a.** Digital pitting scars or loss of substance from the finger pad: depressed areas at tips of digits or loss of digital pad tissue as a result of digital ischemia rather than trauma or exogenous causes
- **b.** Bilateral finger or hand edema: firm but pitting edema, especially involving fingers (includes puffy sausage-like swelling of fingers) or the dorsal aspect of the hands
- **c.** Abnormal skin pigmentation: hyperpigmentation often containing areas of punctate or patchy hypopigmentation or depigmentation ("pepper and salt")
- **d.** Raynaud's phenomenon: at least two-phase color change in fingers and often toes consisting of pallor, cyanosis, and/or reactive hyperemia in response to cold exposure or emotion, as determined by patient's history or physician's observation

3. Visceral manifestations

- **a.** Bibasilar pulmonary fibrosis: bilateral reticular pattern of linear or lineonodular densities which are most pronounced in basilar portions of the lungs on standard chest roentgenogram; may assume appearance of diffuse mottling or "honeycomb lung," and should not be attributable to primary lung disease
- **b.** Lower (distal) esophageal dysphagia: substernal discomfort on swallowing or sensation of food holdup in the retrosternal location
- **c.** Lower (distal) esophageal dysmotility: hypoperistalsis or aperistalsis, as demonstrated by either cine esophagram or fluoroscopy or by manometric study, often accompanied by evidence of decrease in lower esophageal sphincter tone with reflux of gastric contents into the esophagus
- **d.** Colonic sacculations: wide-mouthed diverticula of colon located along the antimesenteric border; found on barium enema examination; these sacculations may also occur in ileum and jejunum

Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980;23:581---90.

Figure 4.1. Canadian Scleroderma Research Group Participating Rheumatologists

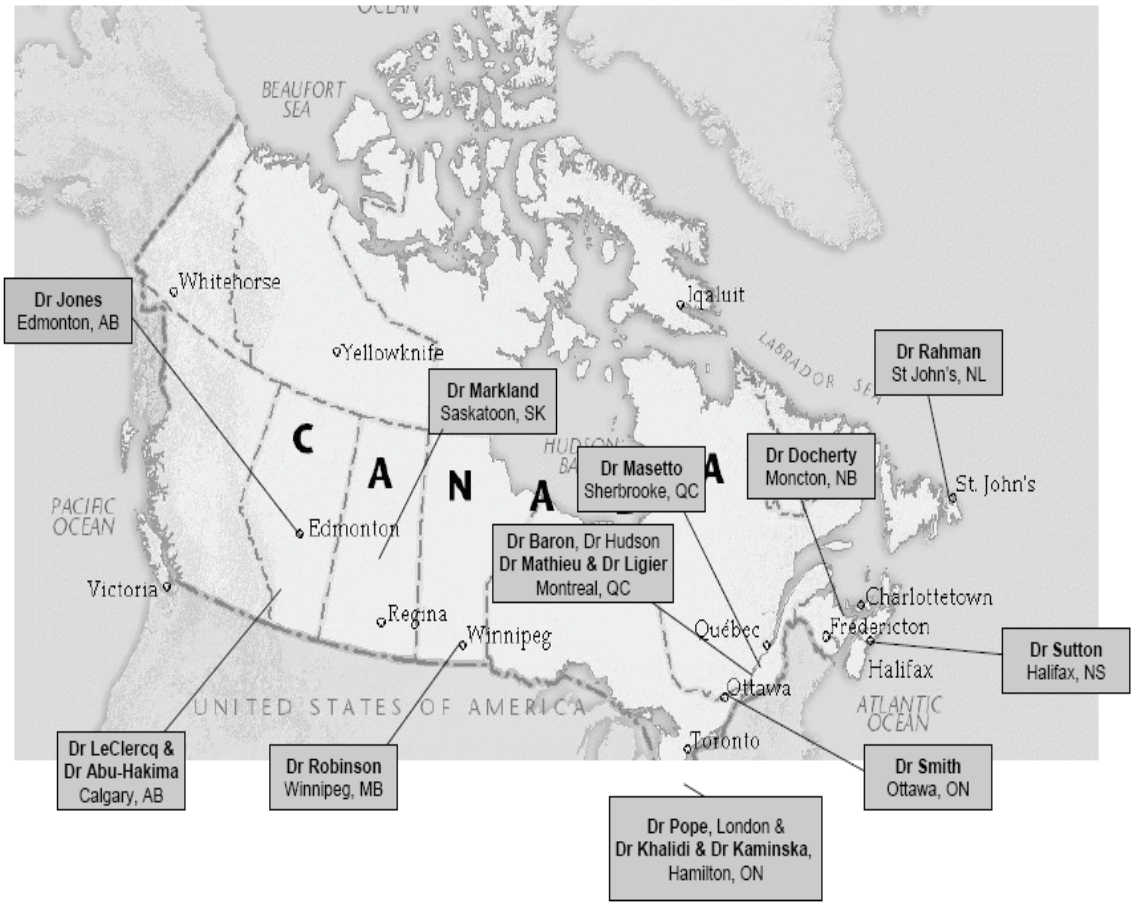


Figure 4.2. Extended Canadian Scleroderma Research Group Team Members

McGill

Faculty of Medicine
3655 Promenade Sir William Osler
Montreal, QC H3G 1Y6

Faculté de médecine
3655, Promenade Sir William Osler
Montréal, QC, H3G 1Y6

Fax/Télécopieur: (514) 398-3595

CERTIFICATION OF ETHICAL ACCEPTABILITY FOR RESEARCH INVOLVING HUMAN SUBJECTS

The Faculty of Medicine Institutional Review Board (IRB) is a registered University IRB working under the published guidelines of the Tri-Council Policy Statement, in compliance with the Plan d'action ministériel en éthique de la recherche et en intégrité scientifique, (MSSS, 1998) and the Food and Drugs Act (17 June 2001); and acts in accordance with the U.S. Code of Federal Regulations that govern research on human subjects. The IRB working procedures are consistent with internationally accepted principles of good clinical practice.

At a full Board meeting on October 06, 2008, the Faculty of Medicine Institutional Review Board, consisting of:

SARIT ASSOULINE, MD	ARTHUR CANDIB, M.ED.
PATRICIA DOBKIN, PHD	ANITA GAGNON, PHD
CATHERINE GARDNER, B.SC.	LAWRENCE HUTCHISON, MD
WILSON MILLER, MD, PHD	ROBERT L, MUNROE, BCL
ROBERTA PALMOUR, PHD	LUCILLE PANET-RAYMOND, BA
LAURIE SNIDER, PHD	MARGARET SWAINE, BA

NELDA SWINTON, B.SC.

Examined the research project **A10-M111-08A** titled *Pain in systemic sclerosis*

As proposed by: Dr. Brett D. Thombs (Applicant) to _____ (Granting Agency, if any)

And consider the experimental procedures to be acceptable on ethical grounds for research involving human subjects.

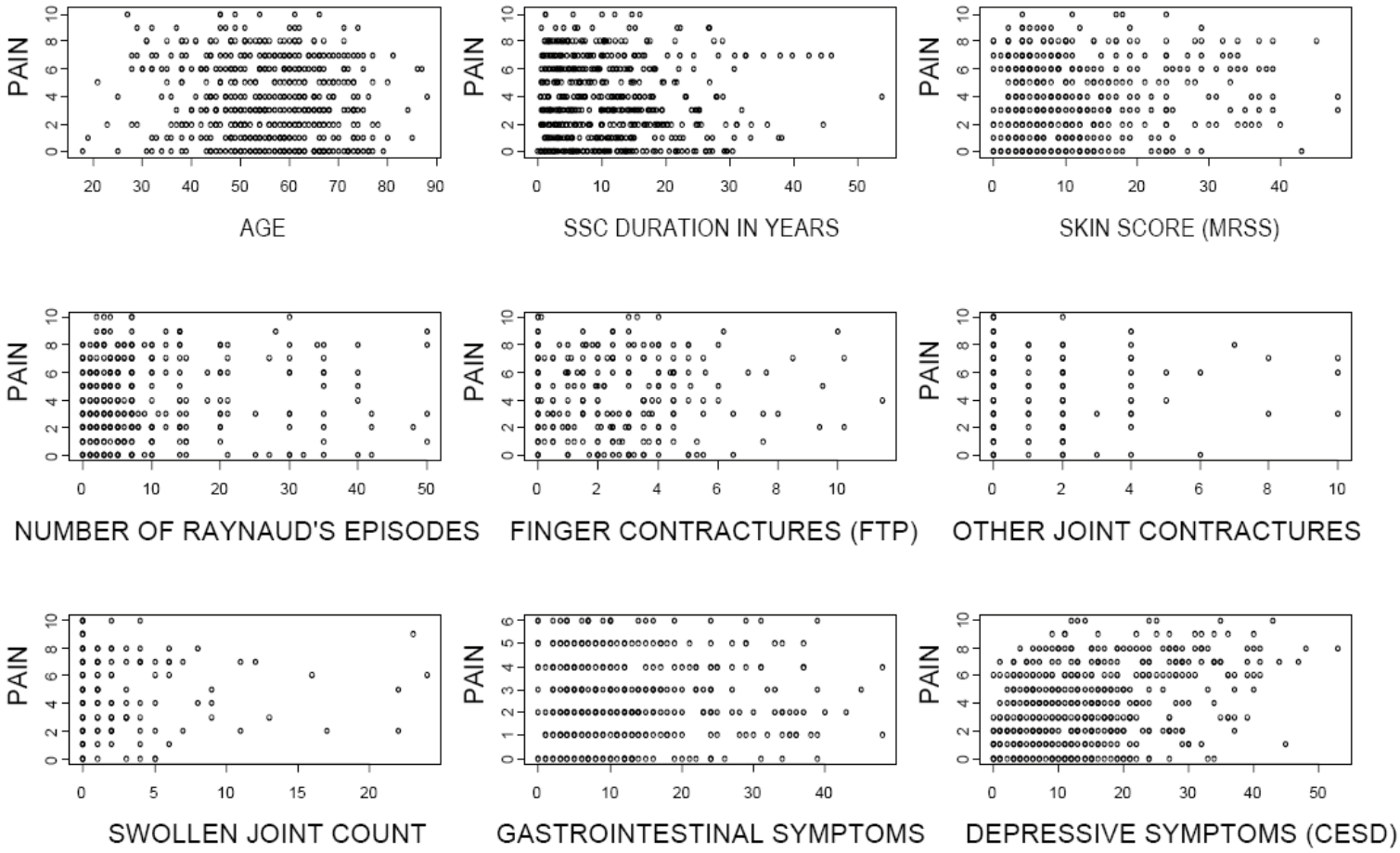
October 06, 2008
Date

Roberta Palmour
Chair, IRB

Dean of Faculty

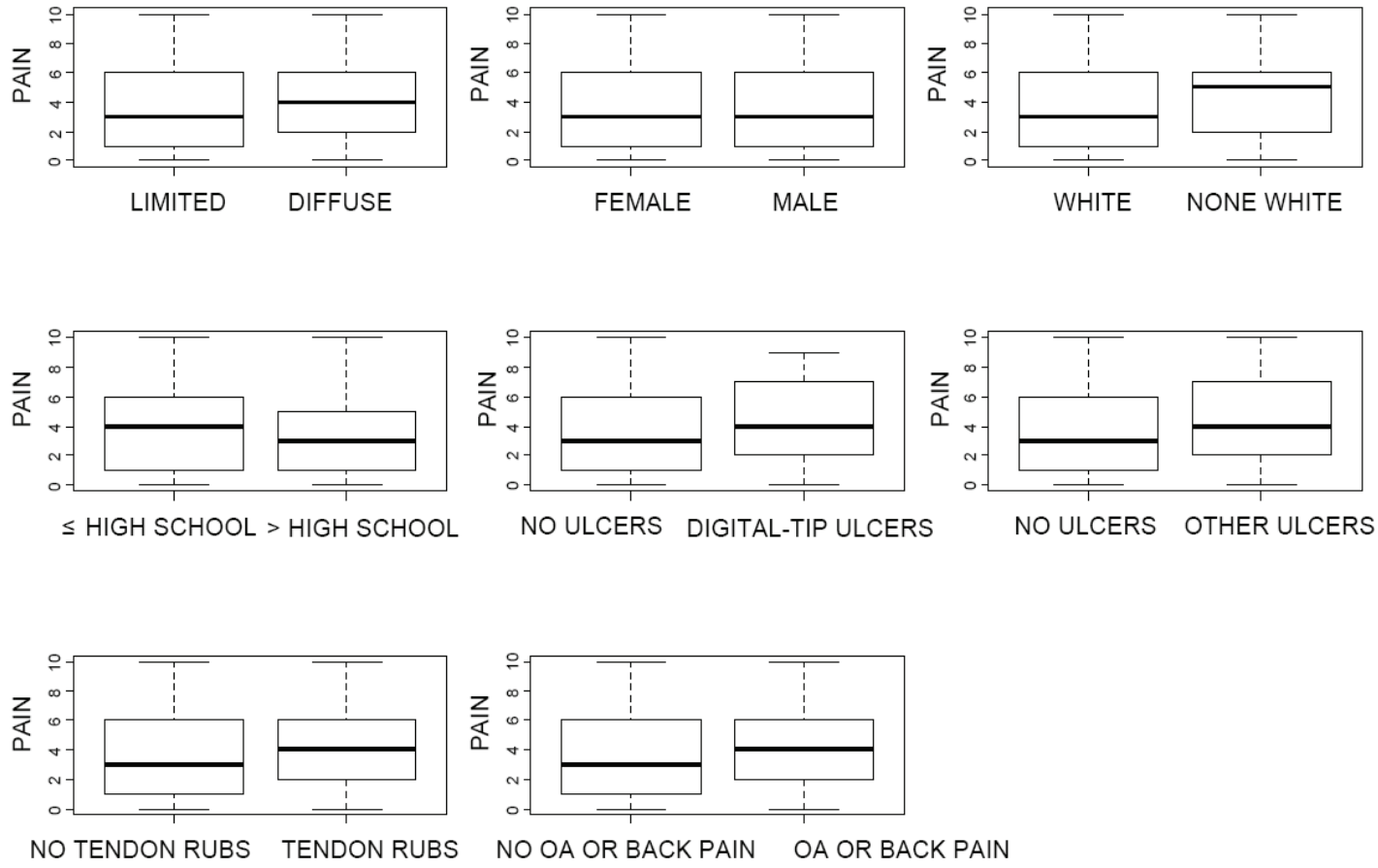
Institutional Review Board Assurance Number: FWA 00004545

Figure 5.1. Scatter Plots of Continuous Independent Variables with the Response Pain in all Patients with Systemic Sclerosis (n=585)



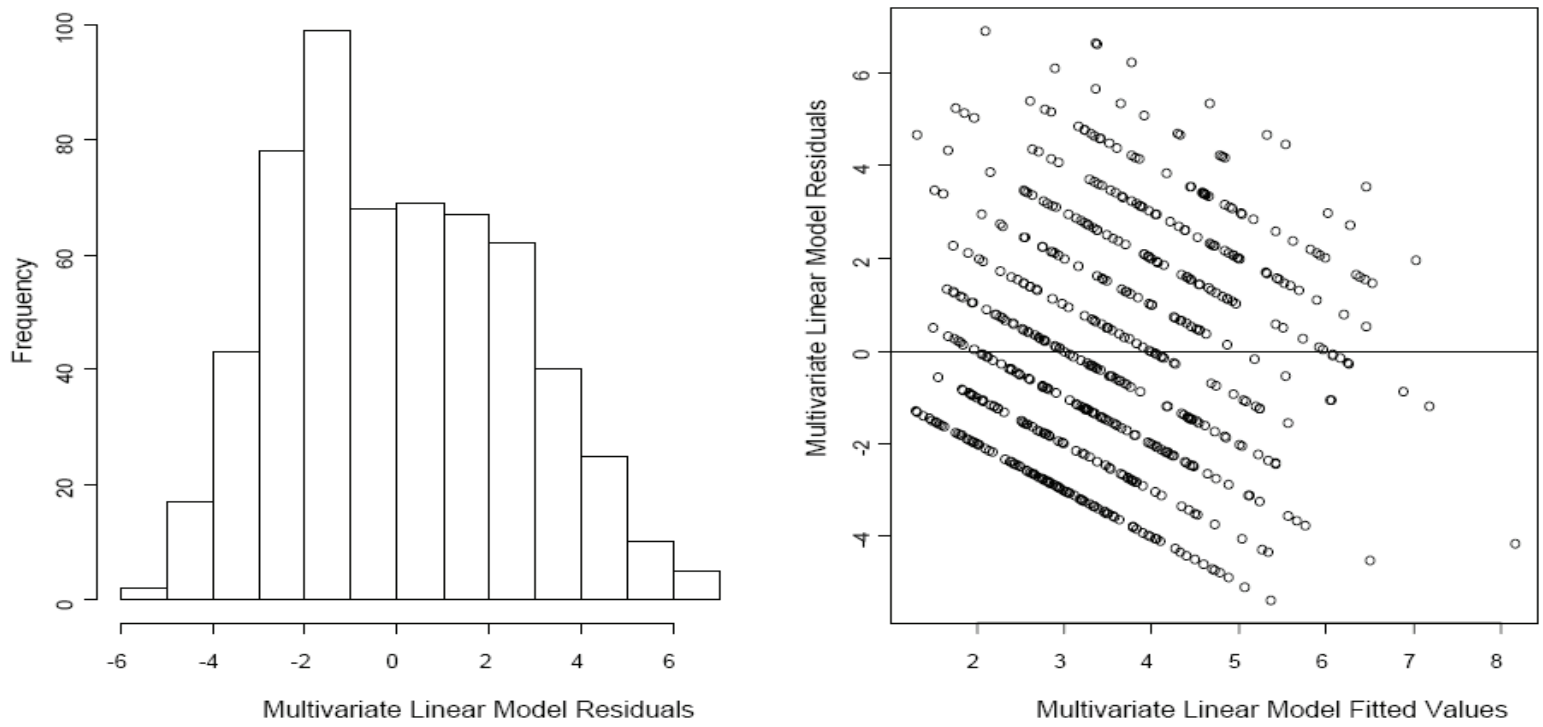
Appendix 6

Figure 5.2. Box Plots of Binary Independent Variables with the Response Pain in all Patients with Systemic Sclerosis (n=585)



Appendix 7

Figure 5.3. Multivariable Linear Regression Residual Plots examining Assumptions of Normality and Constant Variance (N=585)



Appendix 8

Table 5.7 Pearson's Rho Correlation Coefficients between Predictor Variables in all Patients with Systemic Sclerosis (N=585)

	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*
1. Age	1.00														
2. Sex (Male)	-0.09	1.00													
3. Race (White)	0.17	0.01	1.00												
4. Education (Postsecondary)	-0.21	0.01	-0.09	1.00											
5. SSc Duration (years)	0.27	-0.08	0.09	-0.10	1.00										
6. Skin score (MRSS)	-0.19	0.11	0.00	0.02	-0.20	1.00									
7. Episodes of Raynaud's	-0.11	-0.02	0.00	0.17	-0.02	-0.05	1.00								
8. Digital-tip ulcers	-0.15	0.07	0.05	0.01	-0.04	0.18	-0.01	1.00							
9. Other ulcers	-0.12	0.08	-0.01	0.04	0.04	0.32	-0.05	0.23	1.00						
10. Finger contractures (FTP)	-0.09	0.07	-0.03	0.02	-0.09	0.39	0.02	0.19	0.20	1.00					
11. Other Contractures	-0.13	0.18	0.06	-0.02	-0.10	**0.52**	-0.03	0.10	0.22	0.34	1.00				
12. Swollen Joint Count	0.07	-0.08	0.01	-0.02	0.02	0.00	-0.03	-0.02	-0.04	0.23	0.09	1.00			
13. Tendon rubs	-0.10	0.06	0.01	0.04	-0.11	0.38	0.01	0.10	0.16	0.19	0.29	0.04	1.00		
14. GI symptoms	-0.04	-0.09	-0.05	-0.06	0.17	0.03	0.16	0.02	0.01	0.00	0.00	0.00	0.02	1.00	
15. Depressive symptoms	-0.07	-0.03	-0.07	-0.14	0.04	0.09	0.06	0.01	0.11	0.10	0.11	0.05	0.06	0.29	1.00
16. Pain condition (OA or BP)[◊]	0.17	-0.10	-0.01	-0.01	0.08	-0.12	0.08	-0.07	-0.08	-0.03	-0.05	0.12	0.06	0.18	0.08

[◊] OA: osteoarthritis, BP: back pain

Table 5.8. Multi-level Random Effects Model of Clinical Variables with Pain in all Patients with Systemic Sclerosis (N = 585)

Covariance Parameter Estimates

Cov Parm	*Subject*	*Estimate*	*Standard Error*	*Z Value*	*Pr Z*
Intercept	CENTRE_ID	0.09925	0.1494	0.66	0.2533
Residual		6.2914	0.3803	16.54	<.0001

Fit Statistics	
-2 Res Log Likelihood	2777.1
AIC (smaller is better)	2781.1
AICC (smaller is better)	2781.1
BIC (smaller is better)	2782.6

Solution for Fixed Effects

Effect	*Estimate*	*Standard Error*	*DF*	*t Value*	*Pr > |t|*
Intercept	3.4742	0.6672	15	5.21	0.0001
Age	-0.01011	0.009589	555	-1.05	0.2923
Sex, male	0.009308	0.3151	555	0.03	0.9764
Race, white	-0.7429	0.3484	555	-2.13	0.0334
Post-secondary education	-0.6228	0.2186	555	-2.85	0.0045
Disease duration, years	-0.01765	0.01274	555	-1.39	0.1664
Skin score (MRSS 0-51)	-0.00393	0.01438	555	-0.27	0.7848
Episodes of Raynaud's	0.02848	0.01148	555	2.48	0.0134
Active Digital-tip ulcers	0.3826	0.3872	555	0.99	0.3235
Active Other ulcers	1.0349	0.2968	555	3.49	0.0005
Finger contractures (FTP)	0.05549	0.06199	555	0.90	0.3711
Other joint contractures	0.1229	0.08968	555	1.37	0.1712
Swollen joint count (0-28)	0.1244	0.04176	555	2.98	0.0030
Tendon friction rubs	0.3728	0.3085	555	1.21	0.2274
Total gastrointestinal symptoms	0.4652	0.06164	555	7.55	<.0001