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The association of pruritus with quality of life and disability in systemic sclerosis.

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ABSTRACT

Objective: No studies have investigated the association of pruritus, which is present in almost half of patients with systemic sclerosis (SSc), with quality of life (QoL) and disability. The objective of this study was to investigate the association of pruritus with QoL and disability in SSc.

Methods: Cross-sectional, multi-center study of 578 SSc patients ≥1 years post-enrollment in the Canadian Scleroderma Research Group Registry. Patients reported whether they experienced pruritus during the past month on most days and underwent clinical histories and medical examinations. QoL was measured using the Mental (MCS) and Physical (PCS) Component Summary scores of the SF-36, and disability was measured with the Health Assessment Questionnaire–Disability Index (HAQ-DI). The association of pruritus with QoL and disability was estimated using linear regression, controlling for sociodemographic and disease variables.

Results: 248 patients (43%) reported pruritus on most days. Patients with pruritus had significantly worse mental and physical function (Hedges's *g*=-0.43, 95% confidence interval [CI] -0.59 to -0.26; Hedges's *g*=-0.51, 95% CI -0.68 to -0.34) and greater disability (Hedges's *g*= 0.46, 95% CI: 0.29 to 0.63) than patients without pruritus. In multivariate analyses, controlling for age, sex, marital status, education, disease duration, skin score, number of tender joints, gastrointestinal symptoms, breathing problems, Raynaud's phenomenon, and finger ulcers, pruritus was independently associated with mental (P=0.017) and physical function (P=0.003), but not disability (P=0.112).

Conclusion: Pruritus is common and associated with QoL in SSc. More attention to pruritus in SSc is needed, including its measurement, etiology, trajectory, and potential methods for intervention.

Systemic sclerosis (SSc), or scleroderma, is a chronic autoimmune connective tissue disorder with heterogeneous symptomatology and significant medical morbidity (1). The disease is characterized by excessive production of collagen, which manifests itself in thickening of the skin and fibrosis of internal organs, including the lungs, kidneys and gastrointestinal tract (2-3). The rate of disease onset is highest between 30-50 years of age with risk for women 4-5 times that for men (4, 5). Median survival after diagnosis is approximately 11 years, and patients are almost 4 times as likely to die within 10 years of diagnosis (45% mortality) than age, sex and race-matched peers (12% mortality) (4, 5).

Because there is no cure for SSc, it is important to identify factors that influence quality of life. A potentially significant, yet overlooked problem for SSc patients is pruritus. Pruritus, or itch, has been operationally defined as “an unpleasant sensation, which provokes the desire to scratch” (6). Patient testimonials and expert reviews suggest that pruritus plays an important role in functioning and quality of life (QoL) for many patients. Pruritus in SSc can disrupt sleep and can lead to excruciating itch-scratch-itch cycles. Some patients report scratching until they bleed (1, 7). A recent study of pruritus in 400 SSc patients from the Canadian Scleroderma Research Group Patient Registry (8) found that almost half of patients (45%) experienced at least some pruritus on most days during the preceding month – a significantly higher rate than that of the general population (8%) (9). Pruritus was associated with severity of breathing problems, finger ulcers, Raynaud’s symptoms and gastrointestinal symptoms, although only gastrointestional systems were independently associated with pruritus in multivariate analysis. Age, gender, education level, marital status, and disease duration were not associated with pruritus in bivariate or multivariate analyses.

Pruritus is an important predictor of psychosocial morbidity and decreased QoL in numerous disorders, including general skin disorders (10-11), psoriasis (12-13), atopic dermatitis (14-15), uremia (16-18) and idiopathic pruritus (19-20). Across conditions, sleep disruption is commonly reported among patients with pruritus, including both difficulties falling asleep and waking up multiple times during the night (13, 15-16). Pruritus is also associated with agitation, poor concentration, and symptoms of anxiety and depression (10, 12, 21-24). No studies have investigated the degree to which pruritus may affect physical and mental health and disability in SSc. The authors of a recent consensus statement on psychological health and well-being in SSc (25) emphasized the need to better understand the extent to which pruritus impacts QoL and function. The objective of this study was to assess the degree to which pruritus in SSc is associated with QoL, as measured by Mental (MCS) and Physical (PCS) Component Summary scores of the Short Form 36 Health Survey Questionnaire (SF-36) (26-27) and disability, as measured by the Health Assessment Questionnaire – Disability Index (HAQ-DI) (28).

PATIENTS AND METHODS

Patient Sample. The study sample consisted of patients enrolled in the Canadian Scleroderma Research Group Registry who completed their second annual follow-up visit and responded to an item, described below, assessing the presence of pruritus on most days in the past month. The item is administered at follow-up Registry visits, but not at the initial Registry visit. Patients in the Registry were recruited from 15 centers across Canada. To be eligible for the Registry, patients must have a diagnosis of SSc made by the referring rheumatologist, be 18 years of age or older, and be fluent in English or French. There were no other inclusion or exclusion criteria. Registry patients undergo an extensive clinical history, physical evaluation,

and laboratory investigations and complete a series of self-report questionnaires. Patients from all centers provided informed consent, and the research ethics board of each center approved the data collection protocol.

Measures. The presence of pruritus was evaluated with a dichotomously scored item, *I have or I have had in the past month itchiness in my skin, on most days*. Although this item has not been validated in patients with SSc, similar questions have been used to establish the prevalence of pruritus in dermatologic diseases (15). Mental and physical health aspects of QoL were assessed with the MCS and PCS of the SF-36 (26-27), and disability was assessed with the HAQ-DI (28). Covariates in multiple regression models that evaluated the association of pruritus with MCS, PCS, and HAQ-DI scores included sociodemographic variables (e.g., age, sex, marital status, education) and disease variables (e.g., disease duration, number of tender joints, number of gastrointestinal symptoms, skin involvement, respiratory problems, Raynaud's phenomenon, finger ulcers).

Demographic and Disease Variables: Demographic information was based on self-report. Patients' medical histories and disease characteristics were obtained via clinical histories and examinations by study physicians. Limited skin disease was defined as skin involvement distal to the elbows and knees with or without face involvement (29). SSc disease duration was determined as the time from onset of non-Raynaud's symptoms based on a clinical history obtained by study rheumatologists. Because pruritus was measured only at annual follow-up visits and not the initial Registry visit, disease duration for all patients was at least 1 year. Skin involvement was assessed using the modified Rodnan skin score, with scores ranging from 0-51 (30). Tender joint count was recorded by study physicians using a 28-joint count (31). The

number of gastrointestinal symptoms was determined by patient report from a 14-item checklist that included weight loss, anorexia, dysphagia, reflux, pyrexia, choking at night, early satiety, bloating, nausea/vomiting, constipation, diarrhea, malabsorption, fecal incontinence, antibiotics for bacterial overgrowth, and hyperalimentation. Severity of breathing problems (*In the past week how much have your breathing problems interfered with your daily activities?),* severity of Raynaud's phenomenon (*In the past week how much have the Raynaud's attacks interfered with your daily activities?),* and severity of finger ulcers (*In the past week how much have your finger ulcers interfered with your daily activities?)* were assessed by patients on 0-10 numerical rating scales (32).

The Short Form 36 Health Survey Questionnaire (SF-36): The SF-36 (26-27) is the most widely used and evaluated health outcomes measure and has extensive evidence for its validity and reliability in multiple populations (33). It consists of 8 domains, including physical functioning, social functioning, role limitations related to physical problems, role limitations related to emotional problems, mental health, vitality, bodily pain, and general health perceptions. Each domain can be scored separately, with scores ranging from 0 (the worst health state) to 100 (the best health state). Domain scores can also be summarized into the MCS and PCS summary scores. The MCS and PCS are scored using norm-based scoring based on a general population sample to produce T scores for each patient (mean of 50 and standard deviation of 10). Version 2 of the SF-36 was used in this study. The SF-36 has been shown to be responsive to change in SSc (34).

Health Assessment Questionnaire – Disability Index (HAQ-DI): The HAQ-DI is a 20 item self-administered measure intended to assess functional ability in patients with arthritis (30). Questions can be divided into 8 categories (dressing, standing, eating, walking, toileting,

reaching, gripping, and instrumental activities), and the use of assistive aids and devices to help with function is recorded. Scores are derived as the average of the score for the most abnormal activity in each of the 8 categories, taking into account the use of assistive aids and devices. Scores range from 0 (no disability) to 3 (severe disability) (35).The HAQ has been validated as a measure of disability in SSc (32, 34, 36).

Data Analyses. Standard descriptive statistics were used to describe the sample, and Pearson's correlations were used to assess bivariate associations of sociodemographic and disease variables with the MCS, PCS, and HAQ-DI. The magnitude of the differences in MCS, PCS and HAQ-DI between pruritic patients and non-pruritic patients was estimated by calculating Hedges's *g*, a measure of standardized effect size (37). Effect sizes were interpreted based on Cohen's operational guidelines for small, medium and large effect sizes (small = 0.2, medium = 0.5, large = 0.8) (38).The associations between sociodemographic and disease covariates and pruritus with the MCS, PCS, and HAQ-DI were assessed using hierarchical multiple linear regression models. All model covariates were selected *a priori* based on previous published models of physical health, mental health, and disability among Canadian Scleroderma Research Group patients (39-40). Age, sex, marital status ("married or living as married" versus "single or divorced or widowed"), education (high school or more versus high school or less), disease duration, skin score, number of tender joints, number of gastrointestinal symptoms, severity of breathing problems, severity of Raynaud's symptoms, and severity of finger ulcers were entered in step 1. Presence or absence of pruritus was entered in step 2. The contribution of pruritus to the overall variance explained was calculated by subtracting the variance explained in step 1 from variance explained in step 2. The assumptions of homoscedasticity and normality of

residuals were checked with residual plots and quantile-quantile plots. All tolerance values were between .90 and .99, and all bivariate correlations between variables included in the model were ≤ .38 except for severity of finger ulcers with severity of raynaud's phemomenon (r = .52), indicating that multicollinearity was not an issue. Analyses were conducted using PASW statistics version 18.0 (Chicago, IL), and statistical tests were 2-tailed with a $P < 0.05$ significance level. Based on the numbers of patients with and without pruritus this study had 80% power to detect a bivariate correlation between pruritus and continuous outcome variables of 0.11 or greater.

RESULTS

Sample Characteristics. A total of 578 patients completed all measures included in regression models. Mean age in the sample was 56.3 years (SD = 11.9, range: 19 - 86). Approximately 89% (n = 513) were female, 95% (n = 515) were white (35 of the 578 patients had missing data for race/ethnicity), 71% (n = 415) were married or living as married, and 48% (n = 279) had more than post-secondary education. Of all patients, 40% (n = 219) had diffuse SSc (27 of the 578 patients had missing data for disease classification) and 43% (n = 248) reported experiencing pruritus during the past month on most days.. Patients reported a mean of 49.0 on the MCS (SD = 11.6, range: 7.6 – 69.6), 37.9 on the PCS (SD = 10.8, range: 11.3 – 59.8) and 0.8 on the HAQ-DI (SD = 0.7, range: 0 – 3). Table 1 shows sociodemographic and disease variables, including associations with the MCS, PCS, and HAQ-DI.

Pruritus, QoL, and Disability. As shown in Table 1, pruritus was negatively associated, indicating worse function, with the MCS (r = -.21, $P < 0.01$) and the PCS (r = -.25, $P < 0.01$)

and positively associated, indicating greater disability, with the HAQ-DI (r = .22, P < 0.01). The mean MCS score was 46.2 (SD = 12.1, range: 8.6 – 67.2) for the 248 patients with pruritus compared to 51.0 (SD =10.8, range: 7.6 – 69.6) for the 330 patients who did not experience pruritus (mean difference = -4.86, 95% confidence interval [CI] -6.74 to -2.98, Hedges's g = -0.43, 95% CI -0.59 to -0.26). Mean PCS scores were 34.8 (SD = 10.1, range: 11.3 – 57.2) for patients with pruritus and 40.2 (SD = 10.7, range: 11.8 – 59.8) for patients with no pruritus (mean difference = -5.33, 95% CI -7.05 to -3.61, Hedges's g = -0.51, 95% CI -0.68 to -0.34. Mean HAQ-DI scores were 1.0 (SD = 0.7, range: 0 - 3) and 0.7 (SD = 0.7, range: 0 - 3) for patients with and without pruritus, respectively (mean difference = 0.31, 95% CI 0.20 to 0.42, Hedges's g = 0.46, 95% CI: 0.29 to 0.63).

Results from the multiple linear regression models are presented in Tables 2, 3 and 4. As shown in Table 2, the presence of pruritus was significantly associated with MCS scores (P = 0.017). However, the inclusion of pruritus in the model added only 0.8% to predicted variance beyond sociodemographic and other disease variables, which accounted for 21.0% of total variance. In addition to pruritus, younger age, less education, number of gastrointestinal symptoms, and severity of breathing problems were significantly associated with poorer mental health (P < 0.05).

Pruritus was also a statistically significant multivariate correlate of PCS scores (P = 0.003), but only accounted for 1.0% of variance above and beyond the 39.9% attributed to sociodemographic and disease variables (Table 3). In addition to pruritus, age, modified Rodnan skin scores, tender joints, gastrointestinal symptoms, breathing problems and Raynaud's were significantly related to PCS scores (P < 0.05).

The presence of pruritus was associated with HAQ-DI scores on a bivariate basis (Table 1), but not on a multivariate basis (P = 0.112), after controlling for sociodemographic and other disease variables (Table 4). Statistically significant independent correlates of HAQ-DI scores were age, modified Rodnan skin scores, tender joints, gastrointestinal symptoms, breathing problems, Raynaud's, and finger ulcers.

After the initially-specified regression models were run, as a sensitivity analysis, alternative models were run using diffuse/limited status instead of the modified Rodnan total skin score, but this did not change results substantively (data not shown). Additionally, we dicthotomized the gastrointestinal symptoms and breathing problems variables to improve comparability with the pruritus variable and reran the regression models. Again the results did not change substantively (data not shown).

DISCUSSION

This is the first study to investigate the association of pruritus with QoL and disability in systemic sclerosis. The presence of pruritus on most days in the past month was significantly associated with poorer mental and physical function and greater disability with a small effect size difference for disability and medium effect size differences for mental and physical health. Typically, a medium standardized difference effect size (approximately 0.50) is considered to be clinically meaningful (41). After controlling for sociodemographic and other disease variables, the presence of pruritus was significantly associated with mental and physical health, but not disability. The magnitude of the independent association of pruritus with QoL outcomes in multivariate analyses was small, but it is notable that it was significantly associated with QoL

even after controlling for a large number of variables known to have robust associations with QoL and disability in SSc.

The results of this study are consistent with previous studies from other patient groups that have found that pruritus is associated with important aspects of QoL (42-43), including mood, sleep, personal relationships and social function, and daily activities (10-24). In most previous studies, pruritus has been a core symptom of the patient group being studied (e.g., psoriasis, atopic dermatitis, generalized idiopathic pruritus), although not in all cases (e.g., haemodialysis patients). In this study, 43% of patients with SSc experienced pruritus on most days in the last month.

It will be important in future research to determine the degree to which the low explained variance in QoL attributed to pruritus in multivariate models may be due to it being a less important indicator across patients versus it being a very important indicator for some patients, but much less so for other patients. Alternatively, the low explained variance may reflect limitations related to how pruritus was measured in this study. The use of a single, dichotomous item to assess pruritus, although a method that has been used in previous studies, did not allow an assessment of the association between the severity of pruritus and QoL outcomes and did not differentiate between patients who experienced relatively mild pruritus from patients who experienced constant and very severe pruritus, including patients with sleep disturbances due to pruritus or those who scratched enough to cause bleeding, as has been documented in patient testimonials (1, 7). It is possible that the use of dichotomous assessment may have artificially reduced the association of pruritus with QoL and disability in this study and that a continuous measure of pruritus intensity would have found a more robust relationship. On an individual

level, it may be that there is a subset of patients for whom pruritus has a major impact on QoL and disability.

The development and validation of a short, easily administered and scored, continuous pruritus severity measure is needed. Most existing measurement scales for pruritus tend to be difficult to administer and score and/or are not well-validated (8). The Eppendorf Itch Questionnaire (45), for instance, is commonly used, but takes approximately 30 minutes to complete and is laborious to score. The Questionnaire for the Assessment of Pruritus (QAP) (46), is lengthy, interviewer-administered, laborious to score, and does not generate a single overall summary score. The Itch Severity Scale (ISS) (47) is a self-report version of the QAP, but is complex to score and not well-validated. Recently, a pilot study was conducted among dermatology patients with the ItchyQoL (48) a 22-item, multidimensional tool that is easily scored and provides either a single total score or factor scores for symptoms, functional limitations, and emotions related to pruritus. Only rudimentary validation data are available, however, and we are currently collecting data to refine it for use in SSc and to assess its performance against a single-item pruritus numerical rating scale.

Another potential limitation related to measurement concerns using the number of gastrointestinal symptoms to measure overall gastrointestinal involvement. This method weighs all symptoms equally and does not consider possible non-independence between pairs of symptoms.

An additional limitation of this study was that it was based on a convenience sample of patients with SSc. The median disease duration since the onset of non-Raynaud's symptoms was 10 years, suggesting a sample of patients with generally stable disease. Patients not 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. Despite these limitations, the demographic and clinical characteristics of Canadian Scleroderma Research Group Registry patients in this study were consistent with other outpatient SSc samples that have been reported in the research literature (4). In addition, patient data were drawn from 15 centers across Canada, which is a strength of the study.

In summary, the results of this study found that pruritus was associated with poorer mental and physical health and greater disability. When sociodemographic and other disease variables are accounted for, only the associations with mental and physical health were statistically significant. The findings of this study emphasize the need for research that contributes to the development of a better understanding of pruritus, including its etiology, trajectory, and potential methods for intervention in SSc.

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Table 1. Patient Sociodemographics and Disease Characteristics and Associations with SF-36 MCS, SF-36 PCS, and HAQ-DI.

	All Patients N=578		MCS		PCS		HAQ-DI	
	n	**%**	***r***	***p***	***r***	***p***	***r***	***p***
Female	513	88.8	-.02	.722	.03	.539	.02	.639
White*	515	94.8	-.02	.704	-.03	.548	.02	.579
More than high school education	279	48.3	.12	.005	.11	.008	-.08	.054
Married or living as married	415	71.8	.04	.288	.09	.030	-.010	.020
Diffuse SSc**	219	39.7	.04	.354	-.12	.005	.16	< .001
Pruritus present	248	42.9	-.21	< .001	-.25	< .001	.22	< .001
			MCS		**PCS**		**HAQ-DI**	
	Mean	**SD**	***r***	***p***	***r***	***p***	***r***	***p***
Age (years)	56.3	11.8	-.06	.130	-.16	< .001	.06	.149
Time since onset of non-Raynaud's symptoms (years)	11.8	8.9	-.03	.496	-.03	.512	-.01	.899
Modified Rodnan Total Skin Score (0-51)	9.6	8.8	.01	.990	-.19	< .001	.32	< .001
Number of tender joints (0-28)	1.0	3.3	-.05	.261	-.21	< .001	.17	< .001
Number of gastrointestinal symptoms (0-14)	3.1	2.7	-.37	< .001	-.37	< .001	.41	< .001
Severity of breathing problems (0-10)	1.9	2.6	-.33	< .001	-.52	< .001	.44	< .001
Severity of Raynaud's (0-10)	2.9	2.8	-.27	< .001	-.33	< .001	.34	< .001
Severity of finger ulcers (0-10)	1.8	2.8	-.19	< .001	-.28	< .001	.35	< .001

***** 35 patients had missing data (N = 543)
****** 27 patients had missing data (N = 551)

Table 2. Linear Regression Analysis: Mental Health (SF-36 MCS)

Variables	B	SE B	β	95% Confidence Interval	*p*
Age	.085	.039	.087	(.008, .166)	.031
Female	-.565	1.386	-.015	(-.059, .090)	.684
Married or living as married	-.104	.973	-.004	(-.078, .070)	.915
Education	1.998	.899	.086	(.010, .162)	.027
Time since onset of non-Raynaud's symptoms	.012	.053	.009	(-.070, .088)	.825
Modified Rodnan Total Skin Score	.099	.054	.075	(-.005, .155)	.067
Number of tender joints	.026	.133	.007	(-.067, .082)	.844
Number of gastrointestinal symptoms	-1.006	.187	-.234	(-.319, -.148)	< .001
Severity of breathing problems	-.902	.189	-.199	(-.281, -.117)	< .001
Severity of Raynaud’s	-.324	.195	-.078	(-.171, .014)	.098
Severity of finger ulcers	-.204	.196	-.049	(-.141, .043)	.299
Presence of pruritus	-2.203	.918	-.094	(-.171, -.017)	.017

Individual variable parameters are shown, including raw regression coefficients (B) and their standard errors, as well as standardized regression coefficients (β), confidence intervals, and p values.

Table 3. Linear Regression Analysis: Physical Health (SF-36 PCS)

Variables	B	SE B	β	95% Confidence Interval	*p*
Age	-.169	.032	-.187	(-.256, -.118)	< .001
Female	.801	1.117	.024	(-.041, .088)	.474
Married or living as married	.858	.784	.036	(-.029, .101)	.274
Education	-.184	.724	-.009	(-.075, .058)	.199
Time since onset of non-Raynaud's symptoms	.058	.043	.048	(-.021, .116)	.175
Modified Rodnan Total Skin Score	-.154	.043	-.126	(-.196, -.057)	< .001
Number of tender joints	-.453	.107	-.139	(-.204, -.074)	< .001
Number of gastrointestinal symptoms	-.532	.151	-.133	(-.208, -.059)	< .001
Severity of breathing problems	-1.592	.153	-.379	(-.451, -.308)	< .001
Severity of Raynaud’s	-.448	.157	-.117	(-.198, -.036)	.005
Severity of finger ulcers	-.201	.158	-.052	(-.132, 0.28)	.205
Presence of pruritus	-2.231	.740	-.103	(-.036, -.170)	.003

Individual variable parameters are shown, including raw regression coefficients (B) and their standard errors, as well as standardized regression coefficients (β), confidence intervals, and *p* values.

Table 4. Linear Regression Analysis: Disability (HAQ-DI)

Variables	B	SE B	β	95% Confidence Interval	*p*
Age	.007	.002	.117	(.048, .187)	.001
Female	.092	.073	.042	(-.024, -.107)	.210
Married or living as married	-.069	.051	-.045	(-.110, .021)	.180
Education	.020	.047	.015	(-.053, .082)	.668
Time since onset of non-Raynaud's symptoms	-.003	.003	-.041	(-.111, .029)	.247
Modified Rodnan Total Skin Score	.020	.003	.251	(.180, .322)	< .001
Number of tender joints	.017	.007	.080	(.014, .146)	.017
Number of gastrointestinal symptoms	.056	.010	.216	(.140, .291)	< .001
Severity of breathing problems	.073	.010	.270	(.198, .343)	< .001
Severity of Raynaud’s	.021	.010	.085	(.003, .167)	.043
Severity of finger ulcers	.029	.010	.115	(.034, .196)	.006
Presence of pruritus	.077	.048	.055	(-.013, .123)	.112

Individual variable parameters are shown, including raw regression coefficients (B) and their standard errors, as well as standardized regression coefficients (β), confidence intervals, and *p* values.