Prevalence and Clinical Correlates of Symptoms of Depression in Patients with Systemic Sclerosis

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ABSTRACT

Objective: To assess the prevalence and predictors of symptoms of depression in a large sample of patients with systemic sclerosis (SSc).

Methods: Cross-sectional, multi-center study of 376 SSc patients from the Canadian Scleroderma Research Group Registry. Patients were assessed with the Center for Epidemiological Studies Depression Scale (CES-D) and through extensive clinical histories and medical examinations. Hierarchical multiple linear regression was used to assess the relationship between sociodemographic and clinical variables with symptoms of depression.

Results: The percentages of patients who scored ≥ 16 and ≥ 23 on the CES-D were 35.1% and 18.1%, respectively. Patients with less education, patients who were not married, patients with higher physician-rated overall disease severity, and patients with more tender joints, more gastrointestinal (GI) symptoms, and more difficulty breathing had significantly higher total CES-D scores. As a group, specific symptom indicators (tender joints, GI symptoms, breathing) predicted the most incremental variance in depressive symptoms ($\Delta R^2 = 14.2\%$, $P < 0.001$) despite being added to the model after demographic, socioeconomic, and global disease duration/severity indicators.

Conclusion: High levels of depressive symptoms are common in patients with SSc and are related to overall SSc disease severity, as well as specific medical symptoms. Screening for depression among patients with SSc is recommended, although more research is needed to determine the best method for doing this. Successfully treating dypsnea, gastrointestinal symptoms, and joint pain may improve mood, although this has not yet been demonstrated.

Systemic Sclerosis (SSc), or scleroderma, is a chronic, multi-system disorder of connective tissue characterized by thickening and fibrosis of the skin, and by involvement of internal organs (1, 2). It affects mainly women in the prime of their life and is associated with significant morbidity and increased mortality (3). There is no known cure. Patients with SSc report high levels of pain, fatigue, and disability and substantially impaired overall physical function (4). Approximately 75% of SSc patients, for instance, report chronic pain (5), which is often refractory to treatment (6). In addition, disfigurement resulting from SSc typically includes changes to the most visible and socially relevant parts of the body, including contractures in the hands, skin tightening around the mouth and nose, facial telangectasias (red spots), and finger amputations. Patients with SSc report more body image distress than even patients hospitalized with burn injuries (7, 8).

Not surprisingly, a recent systematic review of symptoms of depression in patients with SSc found that between 36% and 65% of patients with SSc have clinically significant symptoms of depression (9). The reported rates of depressive symptoms from the 8 studies reviewed were consistently higher than rates in other patient groups when the same assessment instruments and cutoff scores were used (e.g., post-myocardial infarction, congestive heart failure, diabetes, chronic obstructive pulmonary disease, and rheumatoid arthritis). The wide range in estimates across SSc patient samples was attributed to the different assessment methods used and the small number of patients sampled in most of the studies reviewed (9).

Results from studies reviewed that assessed predictors of depressive symptoms were less consistent. Although some studies found that SSc severity was a predictor of depressive symptoms, other studies did not find links with indices of disease severity or duration. The inconsistent results may have been related to small sample sizes, but were also likely related to

relatively weak methodological approaches in some studies (e.g., automated stepwise regression procedures without external validation). No studies used a theoretically-driven model designed explicitly to systematically examine predictors of depressive symptoms across patient demographic (e.g., age, sex), socioeconomic (e.g., education, marital status), and disease related (e.g., disease duration, severity) variables.

The objective of this study was to use a large SSc patient sample from a pan-Canadian registry to report the prevalence of significant symptoms of depression using established cutoffs with the Center for Epidemiological Studies Depression Scale (CES-D) (10) and to identify important demographic, socioeconomic, and disease related correlates of depressive symptoms.

PATIENTS AND METHODS

Patient Sample. The study sample consisted of patients enrolled in the Canadian Scleroderma Research Group Registry from September 2004 through August 2006. Patients in this 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 $\geq$ 18 years of age, and be fluent in English or French. Registry patients undergo extensive clinical history, physical evaluation, and laboratory investigations and complete a series of self-report questionnaires. Patients from all sites provided informed consent, and the research ethics board of each study site approved the data collection protocol.

Measures. Analyses included self-reported sociodemographic data (age, sex, marital status, education), symptoms of depression as measured by the CES-D, and SSc related variables (disease duration and severity, number of tender joints, number of gastrointestinal symptoms, skin involvement, respiratory problems).

Symptoms of depression. The CES-D (10) is a 20-item measure designed to assess the presence and severity of depressive symptomatology. The frequency of occurrence of each symptom during the past week is rated on a 0-3 Likert-type scale (*rarely or none of the time* to *most or all of the time*), and total scores range from 0 to 60. Standard cutoffs are ≥ 16 for "possible depression" and ≥ 23 for "probable depression" (10).

Disease related variables. SSc disease duration was determined as the time from onset of non-Raynaud's symptoms based on a clinical history obtained by study physicians. SSc global disease severity was rated by study physicians on a 0-10 numerical rating scale, which has been shown to be a valid method in SSc (11). Skin involvement was assessed using the modified Rodnan skin score ranging from 0 to 51 (12). Tender joint count was recorded by study physicians using a 28-joint count (13). Shortness of breath was assessed by the patient on a 0-10 numerical rating scale (14). The number of gastrointestinal symptoms was determined by patient report from a 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. Finger to palm distance was measured by physicans as the distance from the tip of the finger pad of the third finger to the distal palmar crease in full flexion. The interdental distance was measured with the mouth opened as wide as possible and was the midpoint interincisor measurement to the nearest millimeter. Limited skin disease was defined as skin involvement limited to distal to the elbows and knees with or without face involvement. Active digital ulcers were defined as ulcers distal to the proximal interphalangeal (PIP) joint on the volar aspect of the finger, including denuded area with defined border and loss of epithelialization, loss of epidermis and dermis, but excluding fissures, paronychia, and extrusion of calcium or ulcers proximal to the PIP.

Data Analyses. Patients who scored at least 16 on the CES-D were compared with patients who scored < 16 on the CES-D on demographic and SSc-related disease variables for illustrative purposes. Categorical variables were compared using the χ^2 statistic and continuous variables with 2-tailed *t* tests.

The associations between demographic (step 1), socioeconomic (step 2), global disease (step 3), and specific disease factors (step 4) with depressive symptoms were assessed with hierarchical multiple linear regression. Age and sex were entered in step 1. Marital status (married or living as married versus single/divorced/widowed) and education (> high school versus high school or less) were entered in step 2. Disease duration and physician-rated global severity were entered in step 3. Total skin score, number of tender joints, number of gastrointestinal symptoms, and breathing problems were entered in step 4. The distribution of CES-D scores was significantly positively skewed (+7.2). Thus, a square root transformation was carried out in order to meet regression assumptions of linearity and normality of regression residuals (15). The assumptions of homoscedasticity and normality of residuals were checked with residual plots and quantile-quantile plots. All tolerance values were between 0.61 and 0.98, and all bivariate correlations between variables included in the model were < 0.56, indicating that multicollinearity was not an issue. All analyses were conducted using SPSS version 15.0 (Chicago, IL), and all statistical tests were 2-sided with a $p < .05$ significance level.

RESULTS

Sample Characteristics. A total of 376 patients completed the measures used in the study. Table 1 shows patient demographics and disease variables. Approximately 87% of the sample was female and approximately 80% was White, which is consistent with North American samples from previous reports (3). The mean age of the sample was 55.4 years, and the mean

time since onset of non-Raynaud's Symptoms was 10.8 years. Mean time since diagnosis of SSc was 8.6 years.

Of the 376 patients in the study, 132 (35.1%) scored 16 or higher on the CES-D, and 68 (18.1%) scored 23 or higher. Among patients with CES-D ≥ 16 and CES-D < 16, 23 of 132 (17.4%) and 16 of 244 (6.6%), respectively, reported that they were receiving treatment for depression, although the specific type of treatment (e.g., antidepressant medication, psychological treatment) was not specified. As shown in Table 1, patients who scored at least 16 on the CES-D were significantly ($P < .05$) less likely to be married or to have education beyond high school compared to patients with CES-D < 16. Patients who scored ≥ 16 on the CES-D were also significantly younger, more likely to have diffuse SSc, and had higher disease severity ratings, number of tender joints, number of gastrointestinal symptoms, and breathing problems.

Predictors of Symptoms of Depression. Results from the hierarchical multiple linear regression are shown in Table 2. Neither age nor sex was a significant predictor, and the combination of the variables in step 1 did not predict a meaningful amount of variance in depressive symptoms ($P = 0.460$). Education and marital status together incrementally added approximately 8% to predicted variance in depressive symptoms (step 2). Patients with a high school education or less ($P = 0.001$) and patients who were not married ($P < 0.001$) had significantly higher scores, reflecting more depressive symptoms, based on their coefficients in the final model (step 4). Global disease indicators (duration and severity) predicted an additional 4.9% of the total variance, and both physician-rated severity ($P < 0.001$) and time since the onset of non-Raynaud's symptoms ($P = 0.030$) were significant predictors in step 3. Specific indicators of disease factors were more robust predictors than global indicators, however. As a group, they predicted 14.2% of total variance in CES-D scores above and beyond the variance predicted by

sociodemographic factors and global disease indicators (step 4). Tender joint count (P = 0.033), breathing problems (P < 0.001), and number of gastrointestinal symptoms (P < 0.001) were all significantly related to depressive symptoms. When these indicators were included in the model in step 4, disease duration was no longer independently predictive of symptoms of depression (P = 0.411), although the global severity score continued to predict CES-D scores (P = 0.013). After the initially-specified regression model was run, several other variables were added to the model individually to explore whether they were related to symptoms of depression, but none were significant: White/non-White (P = 0.929), income (P = 0.164), finger to palm distance (P = 0.205), interdental distance (P = 0.613), and active digital ulcers (P = 0.512). In addition, we ran the model using diffuse/limited status instead of the total skin score, but this did not change results meaningfully (P = 0.494).

DISCUSSION

This is the first study to assess the prevalence of symptoms of depression among SSc patients in a relatively large, multi-center patient sample. Based on standard cutoffs on the CES-D, 35% of patients scored ≥ 16 and 18% of patients scored ≥ 23. The rates of depressive symptoms at each cutoff in this study were highly similar to rates from the only previous study of patients with SSc that used the CES-D (N = 72, CES-D ≥ 16 = 36%, CES-D ≥ 19 = 26%) (16). The level of similarity across the two studies is consistent with findings from a review of prevalence among cardiology patients that rates tend to be highly consistent across samples when the same assessment instruments and cutoff levels are used, but that standard cutoffs on commonly used screening tools (e.g., CES-D, Beck Depression Inventory (BDI) (17), Hospital Anxiety and Depression Scale (HADS-D)) (18) tend to produce markedly different estimates (19). Indeed, 4 studies that have used the BDI to assess patients with SSc have reported rates

from 46% to 65% (20-23), whereas 1 study (N = 49) that used the HADS-D reported 17% or 38% depending on the cutoff used (24). More work is needed to determine how best to screen for depression among patients with SSc. Nonetheless, the rates reported here based on a CES-D cutoff of 16 or greater are on the high end of rates reported in other patient groups when the same criteria is used, including 22% to 42% in patients with COPD (25), CHF (26-28), and rheumatoid arthritis (29).

Another important finding from this study was that both sociodemographic and individual disease severity indicators were significantly related to symptoms of depression. Not surprisingly, patients with higher education and patients who were married were less at risk of having high levels of depressive symptoms. Nietert et al. (16) have also reported that education is negatively associated with symptoms of depression measured with the CES-D. The best incremental prediction, however, was related to specific indicators of disease severity, even after controlling for sociodemographic factors and global estimates of SSc severity and duration. Higher tender joint count, number of gastrointestinal symptoms, and breathing difficulties all independently predicted increased symptoms of depression. This is consistent with several other studies of SSc patients that have reported associations between gastrointestinal involvement (16, 30) or dyspnea (31) with depressive symptoms or poorer mental health. These findings underscore the importance of effectively treating disease manifestations. The strong links between discrete medical symptoms and symptoms of depression also raise the question of whether earlier diagnosis of SSc would enhance treatment of both. Currently, many patients in the Registry report that they went undiagnosed for a relatively long period from the onset of non-Raynaud's symptoms (mean = 6.1 years, under review).

It may be surprising that total skin score and diffuse/limited status did not independently predict symptoms of depression since body image distress does predict depressive symptoms (7). This is, however, consistent with results from other studies that have attempted to identify concurrent correlates of symptoms of depression (16, 21-24). It is possible that total skin score is a relatively gross measure that may not capture degree of disfigurement. Another explanation of this findings relates to the highly subjective nature of disfigurement. A review of the literature on psychosocial adjustment to disfigurement found that there was little relationship between clinical and subjective severity of disfigurement and distress (32). One study of patients with disfiguring burn injuries, however, showed that the importance of appearance to patients moderated the relationship between subjectively-rated scar severity and distress. That is, more severe scars produced distress among patients for whom appearance was important, but not among patients who were less concerned about their appearance (33).

Limitations of this study include its cross-sectional design and the use of a self-report questionnaire, rather than a standardized structured clinical interview, to assess depressive symptoms. The concurrent assessment of both predictor and outcome variables did not allow for the evaluation of pathways of influence. Indeed, we intentionally did not include self-reported variables reflecting global distress, such as patient-reported global disease severity, functional disability, pain or fatigue, in the models. Similar to depression, each of these variables reflects the lived experience of patients with SSc. Thus, although there are causal pathways and linkages between these variables, they are all potentially outcomes related to the demographic, socioeconomic, and disease factors that were the focus of this study. In addition, method overlap related to self-reporting of these variables can inflate associations and could have artifactually diminished the roles of the primary medical factors in this study. It is important to note that self-

report method overlap may also explain the relative predictive importance of specific indicators of disease factors since breathing difficulties, number of gastrointestinal symptoms, and tender joint count were all based on patient report. Even though tender joint count was recorded by a physician, it was based on patient-report of tenderness/pain in each joint. It is possible that method effects increased the relation of these factors with depression compared to physician rated/assessed variables, such as total skin score or global severity. The negative thinking patterns characteristic of patients with depression may have also influenced reporting of these variables. Depressed patients typically focus on negative aspects of their experience and report these experiences in a distorted fashion that reflects their mood in addition to the actual experience (34). Thus, more work is needed to refine objective, measurable symptom indicators and to assess longitudinal pathways for distress that include indicators of pain, fatigue, and body image distress.

An additional limitation is that rates of depression among SSc patients could have been inflated due to bias related to overlapping symptoms of SSc and somatic symptoms of depression. Studies of the CES-D in patients with rheumatoid arthritis have found that a small number of items appear to be biased, but that the magnitude of the effect is sufficiently small so that overall measurement is not impacted substantially (35, 36). No studies, however, have assessed the measurement properties of the CES-D among patients with SSc.

In summary, findings from this study emphasize that rates of depressive symptoms are very high among patients with SSc. Patients with less education, patients who are not married, and patients with worse overall disease severity, more difficulty breathing, and higher numbers of tender joints and gastrointestinal symptoms are the most vulnerable. Consistent with recommendations made in an earlier systematic review, routine screening for depression in

patients with scleroderma should be recommended, although more research is needed to determine the most effective screening method (9). Successfully treating dypsnea, gastrointestinal symptoms, and joint pain may improve mood, although this has not yet been demonstrated.

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Table 1. Patient Demographic and Disease Characteristics

	All Patients (N=376)		Patients With CES-D < 16 (N=244)		Patients With CES-D ≥ 16 (N=132)		Significance
	N	**%**	**n**	**%**	**n**	**%**	**P**
Female	328	87.2	208	85.2	88	90.9	0.116
White	303	80.6	203	83.2	100	75.8	0.082
More than High School Education	172	45.7	123	50.4	49	37.1	0.014
Married or Living as Married	273	72.6	191	78.3	82	62.1	<0.001
Diffuse SSc	182	48.4	109	44.7	73	55.3	0.049
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**P**
Age (years)	55.4	12.7	56.5	12.6	53.4	12.6	0.023
Time Since Onset of Non-Raynaud's Symptoms (years)	10.8	8.7	10.5	7.9	11.3	10.1	0.420
Time Since Diagnosis of Systemic Sclerosis (years)	8.6	7.8	8.7	7.4	8.4	8.4	0.711
Physican-Rated Global Disease Severity (1-10)	2.3	2.0	2.3	2.0	3.4	2.5	<0.001
Modified Rodnan Total Skin Score	11.2	10.4	10.7	10.1	12.1	11.0	0.208
Number of Tender Joints	2.0	4.5	1.5	3.7	3.1	5.6	0.005
Number of Gastrointestinal Symptoms	4.0	2.9	3.3	2.8	5.2	2.8	<0.001
Breathing Problems (1-10)	2.1	2.5	1.5	2.1	3.2	2.9	<0.001

Table 2. Hierarchical Linear Regression Predicting Symptoms of Depression as Measured by CES-D Scores

Step	Variables	B	SE B	β	P	df	R^2	Adjusted R^2	Δ R^2	P
1	**Demographic Variables:**					2, 373	0.004	-0.001	0.004	0.460
	Age	-0.004	0.006	-0.038	0.466					
	Male Sex	-0.243	0.232	-0.054	0.296					
2	**Socioeconomic Variables:**					4, 371	0.086	0.077	0.082	<0.001
	Age	-0.008	0.006	-0.065	0.197					
	Male Sex	-0.247	0.224	-0.055	0.271					
	Education > High School	-0.659	0.152	-0.219	<0.001					
	Married or Living as Married	-0.646	0.167	-0.192	<0.001					
3	**Global Disease Duration/Severity:**					10, 365	0.135	0.121	0.049	<0.001
	Age	-0.008	0.006	-0.071	0.160					
	Male Sex	-0.291	0.219	-0.065	0.185					
	Education > High School	-0.610	0.148	-0.203	<0.001					
	Married or Living as Married	-0.573	0.164	-0.170	<0.001					
	Time Since Onset Non-Raynaud's Symptoms	0.019	0.009	0.110	0.030					
	Physician-rated Disease Severity	0.163	0.037	0.216	<0.001					
4	**Specific Disease Factors:**					12, 363	0.277	0.257	0.142	<0.001
	Age	-0.008	0.006	-0.065	0.181					

Male Sex	-0.273	0.206	-0.061	0.185
Education > High School	-0.456	0.138	-0.151	0.001
Married or Living as Married	-0.536	0.151	-0.160	<0.001
Time Since Onset Non-Raynaud's Symptoms	0.007	0.008	0.039	0.411
Physician-rated Disease Severity (0-10)	0.107	0.043	0.143	0.013
Modified Rodnan Skin Score	-0.003	0.008	-0.018	0.759
Tender Joint Count	0.033	0.015	0.099	0.033
Breathing Problems (0-10)	0.141	0.029	0.237	<0.001
Number of Gastrointestinal Symptoms	0.109	0.025	0.212	<0.001

For each step, individual variable parameters are shown, including raw regression coefficients (B) and their standard errors, as well as standardized regression coefficients (β), and p values. In addition, overall model fit statistics and a P value for the change in variance accounted for (Δ R) are shown for each step.