Correlates of Depression, Including Overall and Gastrointestinal Functional Status, Among Patients with Systemic Sclerosis

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ABSTRACT. ***Objective.*** Patients with systemic sclerosis (SSc) may develop psychological problems in addition to physiologic symptoms. We investigated whether demographic and clinical factors are associated with comorbid depression.

Methods. From a university hospital's rheumatology clinic, 72 SSc patients who completed 3 questionnaires [Center for Epidemiologic Studies Depression (CES-D) scale, an abbreviated version of a functional status instrument, the Scleroderma Health Assessment Questionnaire (SHAQ), and the Gastrointestinal Quality of Life Index (GIQLI)] during an examination were recruited into the study. Correlations among scores on the 3 questionnaires [including upper and lower gastrointestinal (GI) tract subscales of the GIQLI] were calculated, and associations between CES-D scores and a variety of demographic and clinical characteristics were examined using stepwise linear regression.

Results. Higher CES-D scores (i.e., more depression symptoms) were significantly correlated with upper ($r = –0.48$, $p < 0.0001$) and lower ($r = –0.41$, $p < 0.001$) GI tract dysfunction and worse overall functional status ($r = 0.51$, $p < 0.0001$). Stepwise regression indicated that higher levels of depression were independently associated with lower levels of education ($p < 0.01$), worse upper GI tract functioning ($p = 0.019$), worse functional status ($p = 0.34$), current corticosteroid use ($p = 0.061$), and cardiac involvement ($p = 0.086$).

Conclusion. Decreased functional status and abnormal GI functioning are significantly correlated with depression among patients with SSc. Other demographic and clinical indicators are also associated with depression. (J Rheumatol 2005;32:51–7)

Key Indexing Terms:
SYSTEMIC SCLERODERMA DEPRESSION GASTROINTESTINAL SYSTEM
QUALITY OF LIFE HEALTH STATUS

Although systemic sclerosis (SSc, scleroderma) is typically characterized by skin thickening and abnormal fibrotic processes affecting a wide variety of organ systems, including the lungs, esophagus and other portions of the gastrointestinal (GI) tract, kidneys, heart, and digital blood vessels, the disease also has significant effects on patients' psychological health and health related quality of life. As noted in previous studies[1-3], about 17% of patients with SSc suffer moderate to severe depression, a finding comparable to that among patients with other chronic diseases[4]. A substantial proportion of SSc patients also experience frequent pain, fatigue, esophageal and other GI problems, and decreased functional status[5-8], all of which have the potential to contribute to a decreased health related quality of life. The potential for significant improvement in SSc patients' lives is improved by studying factors associated with their psychological health and health related quality of life.

Clinicians who treat SSc have recognized the importance of assessing patients' psychological status[9-12], especially symptoms of depression. Comorbid depression can have significant negative effects on patients with chronic illnesses, including the worsening of physical symptoms[9,13] and increased mortality rates[14,15]. Depression also contributes significantly to lost work days and numbers of bed days[16,17]. Researchers have confirmed that depression and pain are significant predictors of social adjustment among patients with SSc[3].

Research into factors associated with depression among SSc patients has been sparse. A Medline search from 1996 through 2003 including the terms "scleroderma, systemic" and "depression" yielded only 4 citations[1-3,18], one of which

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was a letter to the editor. One study[1] did examine potential correlates of depression, including clinical factors [digital ulceration, contracture, amputation, organ involvement (i.e., GI, musculoskeletal, renal, cardiac, pulmonary, skin)]; personality factors; psychosocial adjustment to illness in the domains of healthcare orientation, domestic environment, vocational environment, sexual relations, extended family relations, social environment, and psychological distress; and functional disability. The researchers found that depressive symptoms were more correlated with personality, disability, and adequacy of emotional support than with objective measures of illness severity.

Peveler, *et al* state that clinical depression "is a final common pathway resulting from the interaction of biological, psychological, and social factors" and that depression is strongly associated with physical disease[19]. They report that depression is more common among patients with life-threatening and chronic physical illness, unpleasant and demanding treatment, adverse social circumstances, family history of depression, alcoholism and substance misuse, and certain drug treatments in which depression is a side effect (e.g., antihypertensives, corticosteroids, and chemotherapy agents). Given that GI dysfunction is unpleasant and that it potentially contributes to adverse social circumstances, we began to develop the hypothesis that the consequences of GI dysfunction may have greater impact on depression than had been reported, for example, by Roca, *et al*[1]. Our hypothesis was confirmed through informal discussion with patients. Roca, *et al* did not find GI involvement was a significant independent correlate of depression; however, the GI variable included in their statistical models was simply a yes/no indicator of whether or not the patient had GI involvement. This indicator did not differentiate between upper GI tract involvement and lower GI tract involvement, nor did they differentiate the magnitude of GI involvement.

We examined correlates of depression in SSc patients with specific emphasis on GI dysfunction and functional status.

MATERIALS AND METHODS

This study was a cross-sectional analysis of patients visiting the Medical University of South Carolina (MUSC) rheumatology clinic between July 2001 and March 2003. All patients who completed 3 questionnaires during a clinic visit were included in the analysis [Center for Epidemiologic Studies Depression (CES-D) scale[20]; an abbreviated version of the Scleroderma Health Assessment Questionnaire (SHAQ)[21], a modification of a more general functional status instrument, the HAQ-DI[22]; and the Gastrointestinal Quality of Life Index (GIQLI)[23]]. Patients also had to satisfy the American College of Rheumatology criteria for systemic sclerosis[24]. The study was approved by the university's Institutional Review Board, and all patients consented to the questionnaires and to the release of their medical data.

In addition to the data gathered on the questionnaires, a variety of clinical data were also obtained from a routine database for all scleroderma patients treated at MUSC. Data included age, race, sex, years of education, age at first onset of non-Raynaud's symptoms, disease classification (limited, diffuse), total skin score, organ system involvement, other clinical manifestations (alveolitis, pulmonary hypertension, digital pitting, digital ulcers), and current use of antidepressant medications, GI related medications, corticosteroids, antihypertensives and chemotherapy agents. The clinical manifestations were obtained by a rheumatologist during the patient evaluation. Alveolitis was diagnosed if there was evidence of ground-glass opacity on high resolution computed tomography (CT) scan and/or by bronchoalveolar lavage (71% and 43% of patients with alveolitis, respectively). Cardiac involvement included the presence of pericarditis, congestive heart failure, arrhythmias, myocarditis, or any other cardiac symptom deemed related to the patient's disease. GI tract involvement was indicated if the patient reported GI symptoms during the physical examination and/or if there was radiographic or endoscopic evidence of GI involvement (100%, 11%, and 29% of patients with GI tract involvement, respectively). Pulmonary fibrosis was determined by chest radiograph and/or CT scan (50% and 75% of patients with pulmonary fibrosis, respectively). Pulmonary hypertension was defined as having a PA pressure $\geq$ 30 mm Hg by echocardiogram and/or a mean PA $\geq$ 25 mm Hg by cardiac catheterization (96% and 5% of patients with pulmonary hypertension, respectively). Renal involvement was determined by patient history, abnormal blood urea nitrogen (> 20 mg/dl), and/or elevated creatinine (> 1.4 mg/dl) (25%, 50%, and 75% of patients with renal involvement, respectively). Serologic involvement included the presence of antibodies including antinuclear, anticentromere, anti-Scl-70, anti-DNA, anti-Smith, anti-RNP, anti-SSA, anti-SSB, and anti-Jo1.

The CES-D is a 20 item self-report questionnaire used as a screening tool for depression in the general population[20]. A total composite score, ranging from 0 to 60, can be calculated, with higher scores being indicative of more severe depressive symptomatology. Scores higher than 16 suggest the need to be evaluated for depression[25].

The SHAQ includes 20 items from the HAQ-DI[26], covering 8 domains of functional disability (dressing and grooming, arising, eating, walking, hygiene, reaching, gripping, and other daily activities) plus patient-rated visual analog scales (VAS) pertaining to individual organ system involvement, vascular problems (Raynaud's phenomenon), digital ulcers, GI symptoms, lung symptoms (usually shortness of breath), and overall disease severity. Due to time constraints within our hospital clinic, subjects were asked to complete an abbreviated version of the SHAQ. This version, which has not been tested for reliability and validity, included questions from 3 domains: reaching, gripping, and other daily activities. Subjects also completed 2 VAS of the SHAQ: for the degree to which Raynaud's interfered with daily activities, and for overall assessment of disease severity on the day of questionnaire administration. The abbreviated SHAQ score combines the reaching, gripping, and other daily activity scores and ranges from 0 to 3, providing an overall measure of functional status, with higher scores indicating more severe functional status impairment. The VAS scores, which also range from 0 to 3, were treated separately in the analyses.

The GIQLI is a 36-item self-report questionnaire that has been tested to be reliable and valid to measure overall health related quality of life among patients with some form of GI disease[23]. It contains questions about GI symptoms, general physical symptoms, general psychological symptoms, and social activities. A composite score is calculated, which ranges from 0 to 144 (higher scores on the GIQLI indicate better GI function). In addition to the composite score, we wished to determine whether upper GI tract symptoms (esophagus and stomach problems such as heartburn, reflux, swallowing problems, and regurgitation) or lower GI tract symptoms (bowel problems such as diarrhea, constipation, flatulence) were differentially associated with subjects' depressive symptoms. Thus we constructed 2 GIQLI subscales measuring upper and lower GI symptoms. The upper GI subscale comprised 9 items (1, 2, 3, 5, 6, 27, 29, 33, and 35) and ranged from 0 to 36, while the lower GI subscale comprised 7 items (4, 7, 30, 31, 32, 34, and 36) and ranged from 0 to 28. The remaining questions on the GIQLI are more general and are similar in content to questions included in the CES-D.

A variety of statistical techniques were used to examine the correlations between patients' CES-D depression scores and the other variables of inter-

est. Pearson correlations among the scores on the 3 questionnaires (including upper and lower GI subscales of the GIQLI) were calculated, and the associations between CES-D scores and a variety of demographic and clinical characteristics were examined using a 2-step modeling process. In the first step, t scores from unadjusted regression analyses allowed us to identify variables that had the potential to be independently and significantly associated with depression, and those variables, referred to as "candidate predictors," were then entered into a forward stepwise regression analysis. In the unadjusted analyses, a p value of 0.20 was chosen as the cutoff for a variable to be considered a candidate predictor in a stepwise linear regression model (step 2). In the stepwise regression model, the significance level criterion for variables to both enter and remain in the model was 0.15. Although there was high correlation between patients' CES-D and overall GIQLI scores, we did not include the overall GIQLI score in the stepwise regression procedure because it was so highly correlated with its upper and lower GI subscales. Because the VAS measuring the patient's overall self-assessment of disease severity was so strongly correlated with depression and may likely serve as a surrogate for depression (i.e., by being a direct measure of the patient's overall sense of well being including their mental status), we did not include this variable in the stepwise regression procedure. Also, in order that the final model would converge properly, clinical characteristics that were present (or absent) in less than 5 subjects (i.e., presence of pleural pain) were not included in the stepwise procedure. Thus the final regression model comprises those demographic and clinical variables that are most strongly and independently associated with patients' depression scores. Because 72 subjects were available for analysis and because of Harrell's rule that 10 observations are required for each independent variable included in a multivariate model[27], only a maximum of 7 variables exhibiting the strongest independent association with depressive symptoms were included in the final model.

RESULTS

During the timeframe of the study, a total of 125 patients with SSc were eligible to participate, and of these patients, 72 (58%) completed all 3 questionnaires and provided written consent. The study group included 58 women and 14 men. Participants were not significantly ($p > 0.05$) different from nonparticipants for age; race; sex; education; work status; marital status; disease classification; age at onset; disease duration; total skin score; systolic or diastolic blood pressure; or current use of antidepressants, GI medications, corticosteroids, or chemotherapeutic agents. However, participants were significantly ($p < 0.05$) more likely than nonparticipants to have pulmonary hypertension (26.4% vs 9.6%, respectively), to have serologic involvement (87.5% vs 73.1%), to report joint pain (55.6% vs 26.9%), and to be taking antihypertensive medication (79.2% vs 38.5%). Table 1 lists characteristics of the study group, including descriptive statistics of their scores on each of the questionnaires and associated subscales. Table 2 lists the frequencies associated with various clinical symptoms and organ involvement. Tables 1 and 2 also indicate the direction and significance of the association between the characteristics and clinical symptoms with depressive symptomatology (i.e., CES-D score). A total of 36.1% of patients could be classified as needing further evaluation for depression by a trained professional, based on having scored 16 or higher on the CES-D; 26.4% had scores of 19 or higher, the cutoff value that has been found to be the best predictor of major depression among patients with rheumatoid arthritis[28]. Interestingly, only 19.2% of the patients classified as having clinically relevant depression were currently taking antidepressant medication.

Depression was highly and significantly correlated with the functional status and GI function measures, as shown in Table 3. Greater levels of functional impairment and worse functioning of the upper and lower GI tracts were each associated with greater levels of depression. Functional status and GI function were also significantly correlated with one another, with greater levels of functional impairment being associated with worse GI function. Figures 1 and 2 illustrate how patients' scores on the CES-D are associated with their quartile groupings for the SHAQ functional status scores and GIQLI upper and lower GI scores, respectively.

Results of the linear regression model for the patient's level of depression as scored on the CES-D are shown in Table 4. Independent associations were found between more depression symptoms and the following variables in order of influence: lower levels of education ($p < 0.001$), worse upper GI tract functioning ($p = 0.019$), worse functional status as indicated by the overall abbreviated SHAQ score ($p = 0.034$), current corticosteroid use ($p = 0.061$), and cardiac involvement ($p = 0.086$). Although total skin score, lower GI tract GIQLI subscale, and serologic involvement were found to be significantly associated with CES-D scores in bivariate (unadjusted) analyses, these variables did not explain a significant proportion of the variation in CES-D scores over and above the amount explained by the variables that were included in the final multivariate model. The overall model R-squared statistic was 49.5%, indicating that the independent variables included in the model explained a relatively high proportion of the variation in participants' CES-D scores.

DISCUSSION

This study confirms the observation that depressive symptoms are quite common among patients with SSc. Analysis of CES-D scores indicates that 36.1% of these patients are likely to have clinically relevant depression, and yet only 19.2% of these patients report current antidepressant treatment. Several demographic and clinical factors were independently and significantly associated with depression scores, including years of education, upper GI tract function, overall functional status, and, to a lesser extent, corticosteroid use and cardiac involvement.

Although this report identifies variables that are significantly associated with depression among SSc patients, we do not suggest that the factors are causal. That is, it remains unclear whether factors such as diminished GI functional status play a role in causing patients to develop depressive symptoms, or whether patients' depressive symptoms play a role in causing a decline in GI function. As with depression in other chronic illnesses, there may be some combination of

Table 1. Characteristics of the study sample and unadjusted associations with CES-D depression scores.

Characteristic	All Patients, n = 72	Unadjusted p*	Direction of Association†
Age, yrs, mean ± SD	51.3 ± 12.4	0.489	NA
Race, % Caucasian	75.3	0.331	NA
Female, %	80.6	0.943	NA
Education, yrs, mean ± SD	14.6 ± 2.6	< 0.0001	Less education
Work status, %		0.472	NA
Working/student	38.8		
Disabled	20.4		
Other	40.8		
Married, %	45.2	0.780	NA
Disease classification, %		0.238	NA
Limited	30.6		
Diffuse	61.1		
Other	8.3		
Age at onset of non-Raynaud's symptoms, yrs mean ± SD	45.0 ± 12.3	0.564	NA
Duration, yrs, mean ± SD	6.2 ± 7.6	0.830	NA
Total skin score, mean ± SD	16.6 ± 12.2	0.043	Higher skin scores
Systolic blood pressure, mm/Hg, mean ± SD	121.3 ± 23.7	0.598	NA
Diastolic blood pressure, mm/Hg, mean ± SD	68.6 ± 23.7	0.985	NA
Current use of antidepressant medications, %	15.1	0.481	NA
Current use of GI medications, %	67.1	0.373	NA
Current use of corticosteroids, (%)	27.8	0.011	Currently taking
Current use of antihypertensive medication, %	77.8	0.236	NA
Current use of chemotherapeutic agents, %	12.5	0.431	NA
Overall abbreviated SHAQ, mean ± SD	0.89 ± 0.65	< 0.0001	More disability
SHAQ Raynaud's interference, VAS	0.84 ± 0.83	0.218	NA
SHAQ overall disease severity, VAS	1.48 ± 0.90	< 0.0001	More severe
GIQLI overall, mean ± SD	97.0 ± 22.3	< 0.0001	Worse GI function
GIQLI lower tract, mean ± SD	23.3 ± 4.5	< 0.001	Worse GI function
GIQLI upper tract, mean ± SD	28.6 ± 6.3	< 0.0001	Worse GI function

* P values were derived from t test. † For moderately significant ($p < 0.2$) associations, the direction of the association is indicated by listing the characteristics of the subjects with greater depressive symptomatology. VAS: visual analog scale, NA: not applicable, since the association was not moderately significant ($p > 0.20$). GI: gastrointestinal.

both influences[29-31]. Regardless of whether depression worsens SSc patients' functional status or whether their diminished functional status increases their likelihood of developing depressive symptoms, clinicians who treat SSc patients, including primary care physicians, rheumatologists, and gastroenterologists, should recognize that depression is a serious threat to their quality of life. Given the relatively infrequent use of antidepressant medications in this study sample, more aggressive treatment of depressive symptoms is warranted. Although the use of GI pharmaceutical agents was high among these SSc patients (67.1%), more aggressive treatment of GI dysfunction may also increase their quality of life.

Because depression is strongly associated with physical disease, part of the purpose of our analyses was to determine what physical symptoms were associated with depression in our population. While the CES-D does not offer any specific adjustment *per se* to account for the fact that certain patient populations have increased rates of physical symptoms, we have accounted for important physical symptoms in the regression model. In reviewing each of the items in the CES-D, there are several questions (about appetite, fatigue, and sleep) that are likely to be worse in the SSc population because of their physical symptoms. To test whether the variables we identified as being significantly associated with depression were associated with the psychological depressive symptoms, we ran our regression model against a revised overall CES-D score in which 4 items were removed (no. 2: poor appetite; no. 7: everything was an effort; no. 11: restless sleep; and no. 20: could not "get going"), and our findings were relatively unchanged.

This study has several strengths and limitations. The study examined a relatively large number of patients with SSc, and it addresses an area that has been understudied in the past. The use of the GIQLI questionnaire is novel in this population, and the results have brought to light a largely unaddressed need among SSc patients, namely the lack of treatment with antidepressant medications. Some limitations should be noted. First, the response rate (58%) was moderate, and the prevalence of depression may have been

Table 2. Clinical symptoms of the study sample and unadjusted associations with CES-D depression scores.

Clinical Manifestations	All Patients, n = 72	Unadjusted p*	Direction of Association†
Abdominal pain, %	11.1	0.629	NA
Alveolitis, %	9.7	0.680	NA
Cancer, %	6.9	0.398	NA
Cardiac involvement**, %	9.7	0.062	Having involvement
Dialysis, %	2.8	0.301	NA
Digital gangrene, %	0.0	—	NA
Digital pitting scars, %	45.8	0.562	NA
Digital ulcers, %	12.5	0.581	NA
Digital/lower extremity amputation, %	0.0	—	NA
Digital/upper extremity amputation, %	4.2	0.470	NA
GI tract involvement, %	77.8	0.237	NA
Joint contracture, %	40.3	0.299	NA
Joint pain, %	55.6	0.222	NA
Lower extremity ulcer, %	0.0	—	NA
Proximal muscle weakness, %	20.8	0.246	NA
Pericardial pain, %	2.8	0.842	NA
Pleural pain, %	4.2	0.017	Pain reported
Pulmonary fibrosis, %	16.7	0.982	NA
Pulmonary hypertension, %	26.4	0.565	NA
Raynaud's phenomenon, %	90.3	0.815	NA
Renal involvement, %	5.6	0.301	NA
Serological involvement***, %	86.1	0.115	Having no involvement
Ulcers over PIP, MCP, elbow, %	6.9	0.918	NA

* P values derived from t tests. † For moderately significant ($p < 0.2$) associations, the direction of the association is indicated by listing the characteristics of the subjects with greater depressive symptomatology. ** Cardiac involvement was defined as the presence of pericarditis, congestive heart failure, arrhythmias, myocarditis, or any other cardiac symptom deemed related to the patient's disease. *** Serological involvement was defined as including the presence of any of the following antibodies: antinuclear, anticentromere, anti-Scl-70, anti-DNA, anti-Smith, anti-RNP, anti-SSA, anti-SSB, or anti-Jo1. NA: not applicable, since the association was not moderately significant ($p > 0.20$). PIP: proximal interphalangeal, MCP: metacarpophalangeal.

Table 3. Pearson correlations (r) and p values (p) of the CES-D, abbreviated SHAQ, and GIQLI.

	CES-D	Overall Abbreviated SHAQ	GIQLI (overall)	GIQLI (upper GI)	GIQLI (lower GI)
CES-D	NA	r = 0.51 p < 0.0001	r = –0.73 p < 0.0001	r = –0.48 p < 0.0001	r = –0.41 p = 0.0003
Overall abbreviated SHAQ		NA	r = –0.65 p < 0.0001	r = –0.49 p < 0.0001	r = –0.27 p = 0.024
GIQLI (overall)			NA	r = 0.83 p < 0.0001	r = 0.69 p < 0.0001
GIQLI (upper GI)				NA	r = 0.62 p < 0.0001
GIQLI (lower GI)					NA

NA: not applicable

upwardly biased. However, we do not believe that the associations between patients' depression scores and other variables of interest were heavily influenced by the lack of response. Another limitation is that certain patient characteristics thought to be associated with depression were not obtained in this study, including social support and disease coping mechanisms. Such detailed analysis of psychological factors was beyond the scope of this investigation. The GIQLI, an important tool in this study, has not been formally validated in a population with SSc. However, it was originally validated in a group of patients with various forms of GI disease, and it is unlikely that the associations reported in

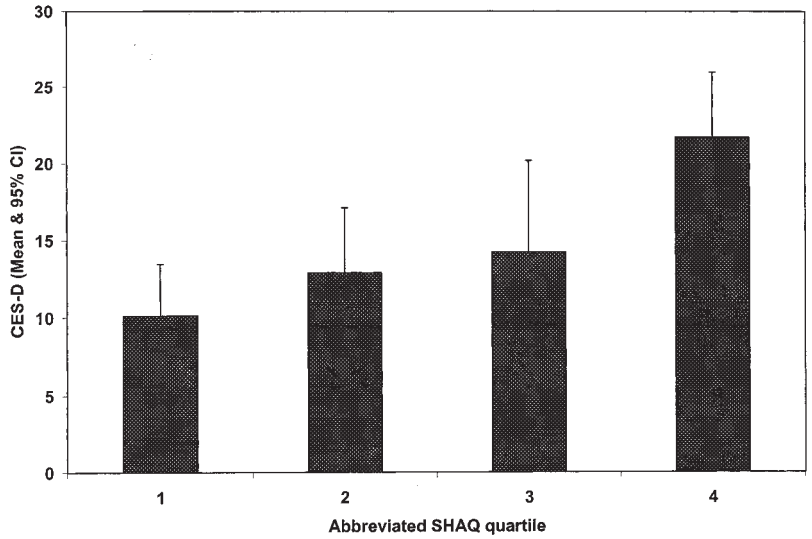

Figure 1. Mean number of depressive symptoms (i.e., CES-D score) by abbreviated Scleroderma Health Assessment Questionnaire quartile.

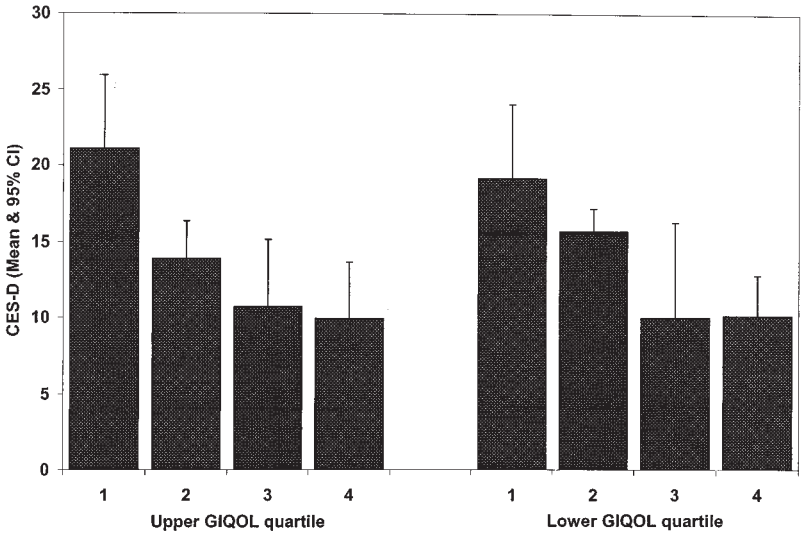

Figure 2. Mean number of depressive symptoms (i.e., CES-D score) by upper and lower GI tract subscale quartiles of the Gastrointestinal Quality of Life Index.

Table 4. Results of the final multivariate regression model with CES-D scores as dependent variable after stepwise selection of independent variables.

Independent Variable	Beta Coefficient Estimate	Standard Error	F Value (1 df)	p
Intercept	40.15	8.19	24.1	< 0.0001
Education	–1.33	0.39	11.6	< 0.01
GIQLI (upper GI)	–0.41	0.17	5.8	0.019
Overall abbreviated SHAQ	0.46	0.21	4.7	0.034
Current corticosteroids	3.98	2.08	3.7	0.061
Cardiac involvement	5.34	3.06	3.0	0.086

this study are unduly influenced by the different patient population. Although the upper and lower GI tract subscales that we created from the GIQLI were not formally validated, categorizing the GIQLI items into these 2 domains does have face validity and highlights the need for further detailed study of GI dysfunction among the SSc population. Finally, although we did find several significant associations between patients' depression scores and their clinical characteristics, the sample was not large enough to determine whether all the variables of interest were significant independent predictors. In other words, had the sample been larger, we would have been able to include more patient characteristics into the final multivariate model.

Future work in this area should focus on finding ways to diminish SSc patients' depressive symptoms, perhaps through a combination of health education, counseling, and antidepressant treatment. Primary care physicians, rheumatologists, and gastroenterologists should recognize that depression and GI dysfunction among SSc patients are common and need to be addressed. Research into interventions to improve depressive and gastrointestinal symptoms in patients with SSc may lead to improvements in quality of life for them.

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