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Disease-related and psychosocial factors associated with depressive symptoms in patients with systemic sclerosis, including fear of progression and appearance self-esteem

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ABSTRACT

Objective: The prevalence of depressive symptoms is high in patients with systemic sclerosis (SSc, scleroderma). This study was conducted to determine which disease-related and psychosocial factors are associated with depressive symptoms, independent of sociodemographic factors.

Methods: In total, 215 patients with SSc completed questionnaires on sociodemographics, physical functioning (HAQ-DI), pain (VAS), fatigue (CIS), psychosocial characteristics (CISS, ICQ, PRQ, ASE, FoP-Q-SF) and depressive symptoms (CES-D). Disease characteristics (disease duration, disease subtype, modified Rodnan Skin Score) were collected. Hierarchical linear regression analyses were conducted to assess associations with depressive symptoms.

Results: The mean CES-D score was 12.9 (SD = 9.7) and the prevalence of patients scoring ≥ 16 and ≥ 19 were 32.1% and 25.1%, respectively. The variance explained by sociodemographics and disease characteristics was negligible ($R^2 \leq .09$). Fatigue and pain were independently associated with depressive symptoms (R^2 change = .35). After adding psychological factors (R^2 change = .21), satisfaction with social support, emotion-focused coping and helplessness were also significantly associated with depressive symptoms. Higher fear of progression was associated with more depressive symptoms ($P \leq .01$), and appearance self-esteem showed a marginally significant association ($P = .08$).

Conclusion: Depressive symptoms were common in the present sample of patients with SSc and were independently associated with pain, fatigue, social support, emotion-focused coping, helplessness and fear of progression. Results suggest that, in addition to assessment of disease characteristics, attention should be given also to psychosocial factors found to be associated with depressive symptoms. For the development and trialling of psychological interventions, fear of progression could be an important target.

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Introduction

Psychological consequences in patients with rheumatic diseases are increasingly recognised. Many studies focus on patients with rheumatoid arthritis and other inflammatory rheumatic diseases. Recently, the literature on psychological problems in patients with systemic sclerosis (scleroderma, SSc) is growing [1]. However, much is still unknown about the psychological problems of patients with SSc and their relationship with the disease.

Systemic sclerosis is a rare connective-tissue disease, with an estimated prevalence of 8.9 per 100,000 adults in the Netherlands and an estimated incidence of .77 per 100,000 [2]. The disease is

characterized by thickening of the skin as a result of fibrosis. Furthermore, SSc can lead to severe dysfunction and failure of almost any internal organ [3], and Raynaud's phenomenon is common. Although there is considerable heterogeneity in SSc manifestation, it has serious consequences in many patients. SSc confers a high mortality risk, with standardized mortality ratios of 1.5 to 7.2 [4]. The presence of anti-topoisomerase I antibodies and internal organ involvement are important determinants of mortality [4]. No effective treatments are available yet, and existing treatments mainly focus on symptom reduction.

As a consequence of the disease, patients with SSc report impairments in their physical as well as mental health-related quality of life [5]. Fatigue and pain are often reported by patients with SSc [6,7] and SSc causes increased disability over time [8]. Elevated levels of depressive symptoms were observed in 35–65% of the patients with SSc [9].

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Unlike most other rheumatic diseases, SSc is a potential life-threatening disease. Fear of progression of the disease (FoP) is often reported as a major concern for patients with SSc and is related to mental health in diverse medical conditions [6,7,10–13]. However, there are no studies examining the relationship of FoP and psychological distress in SSc.

SSc also differs from other rheumatic diseases in terms of the changes in appearance it may cause. Most affected parts are the face and hands [14]. Previous studies of body image satisfaction and appearance self-esteem (ASE) in patients with SSc suggest that changes in the hands, fingers and face are most relevant in predicting overall ASE [15,16]. Low appearance self-esteem is related to psychological variables [15–17], and it is suggested that ASE is a mediator of the relationship between skin thickening and psychological distress [16].

As of now, it is hard to come to a conclusion as to which factors are of importance and could be targeted in treating depressive symptoms in SSc patients. Previous studies examining variables related to depressive symptoms revealed varying results [18–22]. This is to some extent due to the fact that different concepts were included. Some studies report that SSc severity or physical functioning are associates of depressive symptoms [19,20], but this finding was not always replicated in other studies [18,21]. Some studies [18,21,22] included physical as well as psychological measures e.g., aspects of personality [18,22], adequacy of emotional or social support [18,21], and acceptance, and found these [21] to be independently associated with depressive symptoms. None of the previous studies included fear of progression and appearance self-esteem, which are both often found as highly distressing to patients with SSc [6,7,11,17].

For a more systematic approach, this study was conducted to determine the independent association of sociodemographic variables, health status and psychological variables with depressive symptoms, as was recommended in the review of depression in SSc by Thombs et al. [9]. Factors included were derived from literature on associates of depression as well as factors patients reported as distressing in previous studies (appearance self-esteem, fear of progression). Examining all these variables in one model might provide us with starting points for developing (interdisciplinary) interventions for patients with SSc and symptoms of depression.

Method

Patients and procedure

Data were collected in the baseline assessment of the cohort study “Psychological factors in scleroderma,” including patients with a definitive diagnosis of SSc according to the preliminary ARA classification criteria [23] under treatment in the Sint Maartenskliniek or Radboud University Medical Center Nijmegen, the Netherlands. The main objective of the cohort study is to determine which psychological variables (e.g., coping, cognitions, social support) predict psychological distress. Patients in the cohort study complete sets of physical and psychological questionnaires every 6 months over 3 years. Furthermore, a number of disease characteristics were assessed by a rheumatologist (e.g., modified Rodnan Skin Score (mRSS)). Exclusion criteria for participation in the cohort were a life expectancy of less than a year (because of the burden of the study), acute serious complications (e.g., acute renal crisis), severe psychiatric comorbidity (e.g., severe substance abuse, psychosis or dementia), other serious comorbidities (e.g., cancer) and insufficient knowledge of the Dutch language. The attending rheumatologist assessed whether a patient met one or more of the exclusion criteria based on clinical experience, using a checklist stating the exclusion criteria. Data on the reasons for exclusion for individual patients are not available. All eligible patients in both clinics were invited to participate in the study by their attending rheumatologist. After they read the written patient information, they had the

opportunity to ask questions to their rheumatologist or the researcher. Informed consent was obtained before the patients completed their first questionnaire at home. The study was approved by the local medical ethical board (CMO 2008/109). In total, 279 patients were invited to participate, of whom 215 completed the baseline questionnaire (response rate 77.1%). Non-responders did not differ from responders regarding age and gender. Data were collected between June 2008 and February 2010.

Measures

Sociodemographics

The sociodemographic variables assessed were: age, sex, marital status, education and current employment status.

Disease characteristics

The attending rheumatologist assessed disease duration (time since onset of first non-Raynaud's symptoms), SSc disease subtype (limited or diffuse), and mRSS. Furthermore, auto-antibodies (ANA, ACA, Anti-TOPO, Anti-RNP) were assessed to describe our sample.

Physical functioning

Patients completed the Dutch version of the Scleroderma Health Assessment Questionnaire (SHAQ). The SHAQ consists of the Health Assessment Questionnaire (HAQ) and Visual Analogue Scales measuring perceived severity of six disease symptoms. The Disability Index score consists of 20 items, measuring 8 dimensions of functioning (dressing and grooming, ability to get up, eating, walking, personal hygiene, reach, grip strength and activities). The score of each dimension ranges from 0 (best function) to 3 (worst function), and the mean of these scores can be calculated as an indicator of overall physical functioning (HAQ-DI) with higher scores depicting worse functioning. The HAQ was originally developed for use in rheumatoid arthritis [24] but has demonstrated good reliability and validity in patients with SSc [25].

Pain was assessed using a Visual Analogue Scale (VAS) of 10 cm, ranging from 0 (no pain) to 100 (severe pain).

Fatigue was assessed with the “subjective experience of fatigue” subscale of the Checklist Individual Strength [26]. This subscale consists of 8 items, scored on a 7-point Likert scale. Higher scores depict higher levels of fatigue. The CIS has shown to be valid and reliable across different settings [26].

Depressive mood

The Center for Epidemiologic Studies- Depression Scale (CES-D) was used to assess depressive mood. The CES-D was originally developed to measure depressive symptomatology in the general population [27]. Recently, the scale has shown to be a reliable and valid measure of depressive symptoms in patients with SSc [28]. The CES-D is a 20-item measure, with the frequency of each depressive symptom rated on a 4-point Likert scale ranging from 0 to 3 (“rarely or none of the time” to “most or all of the time”). A score of ≥ 16 on the CES-D is considered as the cut-off for possible depression [27], while the cut-off ≥ 19 is identified as the most accurate cut-off for identifying major depression in arthritis [29].

Social support was measured using the Personal Resources Questionnaire 85-Part2 (PRQ85) [30]. Part 2 of the PRQ85 consists of 25 items measuring the patient's perceived level of social support. Items are scored on a 7-point Likert scale, ranging from 1 (strongly disagree) to 7 (strongly agree). Higher scores on the PRQ85 depict greater availability of and satisfaction with social support. The questionnaire has shown to be reliable and valid in healthy adults [31]. Furthermore, some support for the validity of the PRQ85 in patients with SSc was provided by Moser et al. [32].

Coping strategies were assessed using the Coping Inventory Stressful Situations (CISS) [33]. The CISS consists of 48 items, measuring

three coping strategies: problem-focused coping, emotion-focused coping and avoidance. Items are scored on a 5-point Likert scale, ranging from 1 (not at all) to 5 (very much). The CISS showed good psychometric properties in diverse samples [33,34].

Disease cognitions were measured using the Illness Cognition Questionnaire (ICQ) [34]. The ICQ consist of 18 items, measuring helplessness, acceptance and disease benefits. Participants rate their agreement with the statements on a 4-point Likert scale, ranging from 1 (not at all) to 4 (completely). Higher scores on subscales reflect higher levels of agreement with that particular illness cognition. The scale has excellent construct and internal validity in chronic diseases [35]. In this study we only used the subscales acceptance and helplessness.

Satisfaction with appearance was measured using the 6-item subscale 'Appearance self-esteem' of the State Self Esteem Scale [36]. The items are scored from 1 (not at all) to 5 (extremely). Higher scores depict more satisfaction with appearance. A previous study in patients with SSc using this questionnaire demonstrated good internal consistency reliability [16].

Fear of progression was measured using the Short Form of the Fear of Progression Questionnaire (FoP-Q) [12]. The FoP-Q was developed to measure the fear of disease progression in patients with chronic illnesses. The original questionnaire comprises 43 items. The Short Form is a 12-item measure based on the FoP-Q. Each item is scored from 1 (never) to 5 (very often). The reliability and validity of the FoP-Q-SF in patients with breast cancer appears to be good [13]. As far as we know, this questionnaire was not previously used in patients with SSc. Higher scores depict more fear of progression.

All questionnaires showed good internal consistency in our sample, Cronbach's α ranging from .77–.92.

Statistical analysis

Descriptive statistics are provided as means and standard deviations (SD) for continuous variables and percentages for categorical variables. Univariate associations of all sociodemographic and study variables with depressive symptoms were calculated. Hierarchical multiple regression analyses were conducted to determine the associations of the disease-related stressors with depressive mood. CES-D scores were used as the dependent variable. The independent variables were entered in the regression equation in five steps. Following the model of Thombs et al. [20], step 1 contained demographics (age, sex) and step 2 contained socioeconomic status (education, married/cohabiting). In step three, disease characteristics were added (limited/diffuse disease, disease duration, mRSS). Step 4 consisted of physical functioning variables (HAQ, pain, fatigue). In the fifth step, psychological variables were added (disease cognitions, social support, coping, appearance self-esteem, fear of progression). We chose to include all psychological variables together in one step, as there is no consensus on the order of coping and cognitions [37,38]. Given the fact that fatigue is an important characteristic of depression, and the relatively high correlation of fatigue with depressive symptoms, as a sensitivity analysis (to examine the robustness of our findings), step 4 and 5 were repeated omitting fatigue.

The assumption for the regression analysis (normal distribution of residuals) was tested using a normal probability plot. There were no indications of violation of this assumption. Furthermore, correlations between independent variables and tolerances were calculated to check for multicollinearity. All tolerance values were between .36 and .92, and all correlations were $\leq .58$, indicating multicollinearity was not an issue [39]. All statistical analyses were conducted using Stata/IC 10.1 software (StataCorp LP, College Station, TX).

Results

Participants

In total, 69 men and 146 women completed the baseline questionnaires. Most patients (74.1%) were married or cohabitating. Sociodemographic and disease characteristics are displayed in Table 1. The mean depression score was 12.9 (SD 9.7) and the

prevalence of patients scoring ≥ 16 in our sample was 32.1%. The prevalence of probable depression (CES-D ≥ 19) was 25.1%.

Hierarchical regression analysis

Table 2 shows the results from the hierarchical multiple regression analysis. In step 1 to 3, the variance explained was negligible ($R^2 \leq .09$). Sex and marital status were significantly associated with depressive symptoms. Of the disease characteristics (disease type, disease duration, mRSS) added in step 3, only mRSS showed a borderline significant association with depressive symptoms ($P = .09$). Of the physical function measures added in step 4, fatigue and pain were significant correlates, while HAQ score was not. Patients who experienced more fatigue or pain, reported more depressive symptoms ($P < .01$ and $P = .03$, respectively). After adding these physical functioning measures, sex was no longer significantly associated with depressive symptoms. The amount of variance explained increased remarkably (+35%) in step 4. Psychological factors were added in step 5. In this final model, significant correlates were pain ($P = .05$), fatigue ($P < .01$), social support ($P = .01$), emotion-focused coping ($P < .01$), helplessness ($P = .03$) and fear of progression ($P < .01$). The total explained amount of variance in depressive symptoms was 64.7%. Patients who were more satisfied with their social network reported less depressive symptoms, while patients using emotion-focused coping as an important strategy, had higher depression scores. Feelings of helplessness were associated with more depressive symptoms. Higher fear of progression was associated with more depressive symptoms. The p-value of appearance self-esteem indicated a trend ($P = .08$), suggesting that patients with higher appearance self-esteem reported less depressive symptoms.

The sensitivity analysis omitting fatigue revealed highly similar results (not shown). Differences with the original model were, that in step 4 (adding HAQ-DI and pain), the HAQ-DI was now significantly associated with depressive symptoms ($B = 2.38$, $P = .03$), and R^2 was substantially lower ($R^2 = .21$). In the final model, the only difference was the significance level of appearance self-esteem ($B = -.37$,

Table 1

Sociodemographic variables (N = 215), disease variables, study variables, and univariate associations with depressive symptoms (CES-D, range 0–60).

Variables	Value	Correlation ^a	P
<i>Demographic</i>			
Gender (% female)	146 (67.9%)	-.17	.01
Mean age in years	56.4 (SD = 12.0, range 17.9–86.7)	-.08	.23
<i>Socioeconomic status</i>			
Higher education (> 12 yrs)	87 (41.2%)	-.05	.51
Currently employed	70 (32.6%)	-.10	.13
Married/ cohabitating	162 (75.4%)	-.16	.02
<i>Disease characteristics</i>			
Time since onset first Non-Raynaud symptom, yrs	9.2 (SD = 7.9, range 0.2–51.8)	.07	.34
Patients with limited SSC	158 (74.9%)	.02	.74
Mean mRSS	6.4 (SD = 5.9, range 0–37)	.06	.36
ANA positive	196 (91.2%)		
ACA positive	54 (25.1%)		
Anti-TOPO positive	57 (26.6%)		
Anti-RNP positive	14 (6.5%)		
<i>Physical functioning</i>			
HAQ-DI (0–3)	1.04 (SD = .74)	.35	<.01
Pain visual analogue scale (0–100)	28.6 (SD = 24.5)	.37	<.01
Fatigue (CIS) (7–56)	36.2 (SD = 12.6)	.62	<.01
<i>Psychosocial factors</i>			
Social support (PRQ)(25–175)	131.5 (SD = 20.2)	-.36	<.01
Helplessness (ICQ)(6–24)	12.7 (SD = 4.3)	.59	<.01
Acceptance (ICQ)(6–24)	16.4 (SD = 4.1)	-.43	<.01
Problem-focused coping (CISS)(16–80)	50.6 (SD = 11.0)	.02	.81
Emotion-focused coping (CISS)(16–80)	34.0 (SD = 11.7)	.49	<.01
Avoidance coping (CISS)(16–80)	40.4 (SD = 9.9)	.10	.13
Appearance self esteem (ASE)(6–30)	19.6 (SD = 4.1)	-.43	<.01
Fear of progression (FoP-Q-SF)(1–60)	30.0 (SD = 9.0)	.58	<.01

mRSS, modified Rodnan Skin Score; ANA, antinuclear antibody; ACA, anticentromere antibody; anti-TOPO, antitopomerase antibody; anti-RNP, antiribonuclear protein antibodies.

^a Pearson correlations for continuous variables, point-biserial correlations for dichotomous variables.

Table 2
Hierarchical regression analyses of demographics, disease status and psychological variables associated with depressive symptoms (CES-D, range 0–60).

	Variable	B	[95% CI]	P	Beta	Total R ²
Step 1) Demographics	Age	-.05	[-.16,.05]	.33	-.07	.03*
	Sex	-3.35	[-3.00,1.28]	.02	-.16	
Step 2) Socioeconomic status	Age	-.07	[-.19,.04]	.21	-.09	.07
	Male sex	-3.06	[-5.84, -.27]	.03	-.15	
	Higher education	-1.42	[-4.18,1.35]	.31	-.07	
	Married/Cohabiting	-3.92	[-6.97, -.88]	.01	-.17	
Step 3) Disease characteristics	Age	-.08	[-.21,.04]	.20	-.10	.09
	Male sex	-3.95	[-6.93, -.97]	.01	-.19	
	Higher education	-1.41	[-4.32,1.50]	.34	-.07	
	Married/Cohabiting	-3.76	[-7.00, -.52]	.02	-.16	
	Limited disease	-.95	[-4.40,2.50]	.59	-.04	
	Disease duration	.04	[-.13,.21]	.64	.03	
	mRSS	.22	[-.03,.47]	.09	.13	
Step 4) Physical functioning	Age	-.08	[-.18,.02]	.13	-.09	.44**
	Male sex	-1.42	[-3.89,1.06]	.26	-.07	
	Higher education	-.92	[-3.30,1.45]	.44	-.04	
	Married/Cohabiting	-2.48	[-5.08,.12]	.06	-.11	
	Limited disease	.87	[-1.93,3.67]	.54	.04	
	Disease duration	.03	[-.11,.17]	.71	.02	
	mRSS	.11	[-.10,.32]	.32	.07	
	HAQ score	-.52	[-2.45,1.41]	.60	-.04	
	Pain	.06	[.01,.12]	.03	.15	
	Fatigue	.44	[.34,.54]	<.01	.56	
	Step 5) Psychosocial factors ^a	Age	-.04	[-.12,.05]	.37	
Male sex		-.86	[-3.00,1.28]	.43	-.04	
Higher education		-.37	[-2.42,1.69]	.73	-.02	
Married/Cohabiting		-2.0	[-4.41,.43]	.11	-.09	
Limited disease		-.04	[-2.38,2.31]	.98	.00	
Disease duration		.02	[-.10,.14]	.74	.02	
mRSS		.08	[-.10,.26]	.41	.05	
HAQ score		-1.16	[-2.95,.62]	.20	-.09	
Pain		.05	[.00,.09]	.05	.11	
Fatigue		.23	[.13,.33]	<.01	.31	
Social support		-.03	[-.12, -.01]	.01	-.14	
Helplessness		.39	[.04,.75]	.03	.17	
Acceptance		.06	[-.26,.37]	.69	.03	
Problem-focused coping		-.03	[-.12,.07]	.62	-.03	
Emotion-focused coping	.18	[.08,.28]	<.01	.23		
Avoidance coping	.06	[-.05,.16]	.30	.06		
Appearance self esteem	-.23	[-.49,.03]	.08	-.10		
Fear of progression	.20	[.05,.34]	<.01	.18		

^a Final model.

* P-value for the change in variance accounted for (ΔR^2) $\leq .05$.

** P-value for the change in variance accounted for (ΔR^2) $\leq .001$.

$P < .01$). The amount of variance explained was only slightly lower than in the original model ($R^2 = .60$).

Discussion

This study assessed the independent association of sociodemographic, disease, and psychosocial variables, including appearance self-esteem and fear of progression, with depressive symptoms. Depressive symptoms were prevalent in our sample, comparable to those in previous studies [21,28], as was the percentage of patients scoring above the cut-offs for possible and probable depression (32.1% and 25.1%, respectively) [9].

Significant correlates of depressive symptoms were found, in addition to pain and fatigue, mostly in the psychological domain. Depressive symptoms were associated with lower satisfaction with social support, emotion-focused coping, helplessness and higher fear of progression. The variance explained by the sociodemographic measures and disease characteristics assessed in the present study was negligible. Therefore, it is recommended that, in addition to assessment of physical functioning, attention should be paid to pain, fatigue and psychological factors found to be associated with depressive symptoms. A recent study of patients with rheumatoid arthritis showed that long-term patterns of depression are associated with worse function and perceptions of poor health [40]. Appropriate and timely treatment of depressive symptoms might

therefore contribute to an improvement in health outcomes, also for patients with SSC.

To our knowledge, this is the first study that included appearance self-esteem and fear of progression as correlates of depression, in addition to sociodemographics, disease characteristics and physical functioning. Body image concerns as well as fear of the future were identified as important psychological stressors in patients with SSC in many existing studies [6,7,10,11]. Moreover, the present study suggests they both are independently associated with depressive symptoms, although the association of appearance self-esteem with depressive symptoms should be interpreted with caution since it was only marginally significant. More research is needed to confirm our findings on appearance self-esteem.

An important finding from this study was that fear of progression is associated with depression. Because SSC is a serious and potentially life-threatening disease, disease progression is a real concern for most patients. However, although fear of progression may have some basis in reality, patients could overestimate their fear of progression in comparison to the likelihood of actual progression. Decreasing this dysfunctional fear to a more functional level might lead to fewer depressive symptoms and an increased quality of life. A recent study showed that two short psychotherapeutic group interventions in cancer patients were effective in reducing fear of progression in the long term [41]. The authors also found significant improvements in depression, anxiety and health-

related quality of life. Since, in the present study, fear of progression showed a higher association with depressive symptoms than actual indicators of the likelihood of progression (disease type, disease duration, mRSS), this could be an important target of intervention in patients with SSc as well. As of now, it is not clear whether this finding is unique for patients with SSc, or if it is also true for patients with other chronic diseases (like rheumatoid arthritis), for which fear of progression might play an important role as well.

Ideally, psychological interventions for depressive symptoms in SSc should be integrated into interdisciplinary care, taking levels of fatigue and pain into account. Solving sleep problems or changing unhelpful coping behaviour could help patients decrease fatigue levels. In addition, exercises matched to patients' physical abilities could help increase physical condition and reduce fatigue.

Since this study was cross-sectional, no causal relationships could be established. Longitudinal research is needed to identify which factors predict the development of depressive symptoms over time. This study could however be a starting point in determining which variables to include in longitudinal studies. Another limitation is that not all possible physical consequences of SSc were included in the present study. For example, the involvement of specific organs was not taken into account. Furthermore, the use of self-report measures is a limitation of this study. Beyond the lack of validation studies concerning Dutch versions of the instruments used (including the CES-D), in SSc, method overlap can inflate associations between depression scores and other self-report measures. Patients with depressive symptoms might respond to the other self-report measures in a more negative manner as well. Another limitation of the use of self-report measurements in this study is that the association of helplessness and fatigue with depressive symptoms could partly be explained by the fact that both are an important characteristic of depression. Helplessness as used in this study is a cognitive concept, and therefore might have overlapped with the learned helplessness in depression. A recent study by Thombs et al. [42] showed that, although patients with SSc had inflated scores on the somatic items of the CES-D compared to matched controls, this had no substantial impact on the overall score of the measure. Also, the sensitivity analysis omitting fatigue revealed only a minor difference in the variance explained in the final model.

Strengths of the present study were that data were collected in a relatively large and well-defined sample of patients and that a number of physical and psychological variables were examined in a standardized way. All variables were included in the model without preselection, providing us with a precise and valid insight to variables that are independently associated with depressive symptoms. The patients included in the study are comparable with the large Dutch sample in a recent study by Vonk et al. [2] with regard to disease characteristics and demographics, except that our sample included slightly more men, indicating that results are generalizable.

In conclusion, depressive symptoms were common in the present study of patients with SSc and were independently associated with pain, fatigue, social support, emotion-focused coping, helplessness and fear of progression. Results suggest that, in addition to assessment of disease characteristics, attention should be given also to psychosocial factors found to be associated with depressive symptoms. For the development and trialling of psychological interventions, fear of progression could be an important target.

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