Arch Rheumatol 2019;34(3):253-261
doi: 10.5606/ArchRheumatol.2019.7111

ORIGINAL ARTICLE

Prevalence, Risk Factors and Assessment of Depressive Symptoms in Patients With Systemic Sclerosis

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ABSTRACT

Objectives: This study aims to evaluate the prevalence of depressive symptoms among systemic sclerosis (SSc) patients using the Major Depression Inventory (MDI), identify possible risk factors, and analyze the current standard of care to raise awareness and improve clinical care for SSc patients.

Patients and methods: The study included 94 SSc patients (12 males, 82 females; mean age 58.3±13.6 years; range, 28 to 83 years) who completed the MDI, Short Form 36 Health Survey, Scleroderma Health Assessment Questionnaire, Brief Fatigue Inventory and Physical Activity Questionnaire. Clinical parameters were assessed according to standardized procedures. Discharge letters were analyzed for evaluation of depressive symptoms.

Results: The prevalence of depressive symptoms was 22.3%. It correlated with female sex (p=0.047), underweight (p=0.002), fatigue (p<0.001), decreased quality of life (p<0.001) and less physical activity (p=0.048). The latter three were confirmed as independent risk factors in a multivariable regression analysis. The analysis of the current standard of care revealed no assessment of depressive symptoms in the majority of patients (89.4%), including 19 with depressive symptoms according to the MDI score.

Conclusion: This study confirms the high prevalence of depressive symptoms in SSc patients. There is an unmet need of regular assessment of mental health during SSc consultations. Fatigue, decreased quality of life and reduced physical activity were ascertained as independent risk factors, while special attention should also be paid to weight loss and underweight.

Keywords: Depression; fatigue; quality of life; systemic scleroderma.

Systemic sclerosis (SSc) is a connective tissue disease, which is characterized by a combination of vasculopathy, autoimmune-mediated inflammation and organ fibrosis.[1] The etiology of the disease is still unknown and no therapy exists to reverse or halt disease progression. Previous studies have shown that patients with SSc have a higher risk to develop depressive symptoms than the average population and various disease-specific factors such as the disfiguring and disabling course of disease have been proposed. The frequency ranges from 20 to 68% in different studies.[2-11] This compares to a frequency of 8.1% among the average German population according to a survey by the Robert Koch-Institute.[12] Lack of emotional support,[4] low ability to work, pain,[3] disability,[13,14] disease severity,[5,11] fatigue, fear of progression,[15] being lower educated and unmarried[5,16] have been identified as potential risk factors in previous studies.

Received: August 08, 2018 ***Accepted:*** October 29, 2018 ***Published online:*** January 28, 2019

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Citation:
March C, Huscher D, Preis E, Makowka A, Hoeppner J, Buttgereit F, et al. Prevalence, risk factors and assessment of depressive symptoms in patients with systemic sclerosis. Arch Rheumatol 2019;34(3):253-261.

Many studies on depression in SSc patients used the Beck Depression Inventory.[3,4,6,7,11,17] In those studies, the prevalence of depressive symptoms was high with 46 to 65% with the exception of 20% in a study by Baubet et al.[17] Almost all of these studies had a sample size ≤100[3,4,8-10,17] or ≤150.[6,7,11] A larger Canadian study analyzed 376 SSc patients using the Center for Epidemiological Studies Depression Scale (CES-D) to detect depressive symptoms and found a prevalence of 35%.[5] The same level (36%[9] and 38%[10]) were detected with the CES-D9 and the Hospital Anxiety and Depression Scale 10 by two other studies with a sample size ≤100.[9,10]

Our study examined the prevalence of depressive symptoms in SSc patients at our German center by using the Major Depression Inventory (MDI). We investigated the impact of sex, weight, fatigue, quality of life, disability and physical activity on the development of depressive symptoms and assessed the current standard of care, which has not been addressed by previous studies. Additionally, we evaluated the correlation with other comorbidities such as fatigue, using the Brief Fatigue Inventory (BFI), quality of life, using the Short Form 36 Health Survey (SF-36®) and physical activity, using the Physical Activity Questionnaire (IPAQ). Considering the high prevalence of depressive symptoms among SSc patients[2] and a general underdiagnosis of depression in primary care,[18] there is a potentially increased risk for secondary comorbidities such as coronary heart disease[19] and an altered pain perception.[20] Hence, it is of great importance for the comprehensive treatment of SSc not to miss any signs of depression in SSc patients and to know how depressive symptoms in these patients are assessed and treated best in a clinical routine setting. Therefore, in this study, we aimed to evaluate the prevalence of depressive symptoms among SSc patients using the MDI, identify possible risk factors, and analyze the current standard of care to raise awareness and improve clinical care for SSc patients.

PATIENTS AND METHODS

In this study, 94 SSc patients (12 males, 82 females; mean age 58.3±13.6 years; range, 28 to 83 years) from our center at the Department of Rheumatology, Charité University Hospital Berlin, Germany were recruited between April 2013 and October 2015. They met the American College of Rheumatology/European League Against Rheumatism 2013 classification. All patients completed the MDI, SF-36®, Scleroderma Health Assessment Questionnaire (SHAQ), BFI and IPAQ. The study protocol was approved by the Charité University Hospital Berlin Ethics Committee (EA1/013/13). A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

We used the MDI to assess the prevalence of depressive symptoms among SSc patients. The questionnaire is used as a diagnostic instrument for Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) major depression,[21] but also as a depression severity scale. The scale provides information about the severity of depressive symptoms. The MDI contains 10 items with 50 being the highest possible summarized score, which can be transferred into the categories of low (score of 20-24), moderate (score of 25-29) and severe depressive symptoms (score of ≥30).[22]

We measured quality of life using the SF-36®. It results in weighted scores for eight domains and a total value from 0 to 100 with a low score being equivalent to low quality of life.[23] The test has been used in many studies with SSc patients before.[13,24]

The German version of the SHAQ was used to measure the severity of disability arising from SSc. It results in a weighted total score, which can be translated in no to mild disability (DI) (SHAQ-DI >1), moderate (SHAQ-DI 1 to <2) and severe impairment (SHAQ-DI 2 to 3)[25] and it is commonly used and well-validated in SSc.[7] The score correlates positively with the degree of impairment.[25]

The level of fatigue was measured using the BFI. Mild fatigue accounts for values from 10 to 30, moderate from 40 to 60 and severe from 70 to 100 (in decimal steps).[26] Fatigue is a symptom frequently mentioned by SSc patients.[18]

The IPAQ was used to measure physical activity in the categories of work, transportation, work at home and leisure time. It results in a weighted

continuous score and a categorical score reflecting levels of low, moderate and intense activity. A high score in the test shows a more distinct level of physical activity.[27] Additionally, most patients completed the ABILHAND Questionnaire, a tool to assess a patients' ability to perform daily activities with their upper limbs.

Clinical parameters including sex, age, disease duration, cutaneous subsets, type and number of organ involvement, autoantibodies, weight and the resulting body mass index (BMI, kg/m^2) were collected and maximum grip strength was measured with Jamar hand dynamometer® (Patterson Medical by Sammons Preston, Bolingbrook, Illionis, USA).

At the time when the patients were included in the study, discharge letters were analyzed with respect to the assessment of depressive symptoms during their consultation to evaluate current standard of care. We analyzed whether depressive symptoms and mental health were assessed; *(i)* at all, *(ii)* if depression was mentioned in the list of diagnoses or in the examination, and *(iii)* if there was any treatment prescribed or suggested, for example social or psychological intervention or treatment with antidepressants.

Statistical analysis

The data were analyzed using the IBM SPSS version 23.0 program (IBM Corp., Armonk, NY, USA. The data are presented as percentages for categorical variables and means and standard variations for continuous variables. For the analysis of risk factors, patients were divided into two subgroups, those with low to severe (≥20) and those without depressive symptoms (<20) according to the MDI. The subgroups were compared with regard to clinical parameters and results of the patient questionnaires using chi-square and Mann-Whitney U tests to identify potential risk factors with significant differences between the two subgroups. In order to detect any potential association between the MDI score and clinical characteristics or results of the questionnaires, we conducted a multivariable

Table 1. Clinical characteristics of our cohort of 94 systemic sclerosis patients

Variables	n	%	Mean±SD
Age (years)			58.3±13.6
Gender			
Female	82	87.2	
Weight (kg)			67.3±16.3
Body mass index (kg/m^2)			24.5±5.4
Overweight	38	40.4	
Underweight	6	6.4	
Disease duration (year)			7.6±5.9
Diffuse cutaneous SSc	40	42.6	
Limited cutaneous SSc	54	57.4	
Antibody profile			
Anti-nuclear antibody	87	92.6	
Anti-centromere antibody	32	34.0	
Anti-topoisomerase I antibody	31	33.0	
Anti-polymerase III	3	3.2	
Digital ulcer	50	53.2	
Lung involvement (ILD, PAH)	54	57.4	
Dysphagia	55	58.5	
Cardiac involvement (fibrosis)	14	14.9	
Number of organ involvements			4.2±1.4
Maximum hand strength (kgf)			16.3±7.9

SD: Standard deviation; SSc: Systemic sclerosis; ILD: Interstitial lung disease; PAH: Pulmonary arterial hypertension.

Table 2. Results of patient questionnaires (n=94)

Variables	n	%	Mean±SD
MDI score			13.8±9.6
Patients with MDI <20	73	77.7	
Patients with MDI ≥20	21	22.3	
Mild depressive symptoms	3	3.2	
Moderate depressive symptoms	10	10.6	
Severe depressive symptoms	8	8.5	
SF-36® total score			54.6±17.2
SF Mental Health SUM			61.3±19.1
SHAQ score			0.98±0.65
BFI score			39.6±21.0
IPAQ (MET/min)			2.812±2.310
ABILHAND score			30.1±10.4

SD: Standard deviation; MDI: Major Depression Inventory; SF-36: Short Form-36; SHAQ: Scleroderma Health Assessment Questionnaire; BFI: Brief Fatigue Inventory; IPAQ: International Physical Activity Questionnaire; MET: Metabolic equivalent of task.

linear regression analysis to test for independent influence of previously identified potential risk factors. Correlation analysis of the MDI score with scores of the SF-36®, SHAQ, BFI and IPAQ was performed to assess related comorbidities. Results with a significance level of p≤0.05 were considered as statistically significant.

RESULTS

We enrolled a cohort of 94 SSc patients with 82 females (87%) and 12 males (13%). Our cohort is representative as it reflects the skewed proportion between females and males, as well as the proportions of patients with limited or diffuse cutaneous SSc and age profile (Table 1). Mean age was 58.3±13.6 years and mean disease duration was 7.6±5.9 years. Fifty four patients (57.4%) had limited cutaneous SSc and 40 patients (42.6%) had diffuse cutaneous SSc. In 32 patients (34.0%), anti-centromere antibodies were detected, while anti-topoisomerase I antibodies were detected in 31 (33.0%). The mean number of organ involvements out of 12 added up to 4.2±1.4. Mean BMI was 24.5±5.4 kg/m^2 and 38 patients (40.4%) were overweight, whereas six patients (6.4%) were underweight.

The MDI score showed a prevalence of depressive symptoms of 22.3% (21 out of 94 patients) in the study cohort. The mean MDI score was 13.8±9.6 with a range from 0 to 47 points. There were 21 patients with a score ≥20 and 73 patients with a score <20; accordingly, patients were grouped into those with or without symptoms of depression. Graded by severity, three patients (3.2%) had mild, 10 (10.6%) moderate and eight (8.5%) severe depressive symptoms (Table 2). The mean SF-36® total score for quality of life was 54.6±17.2 with slightly higher scores in the mental domain (SF-36® Mental Health SUM) with 61.3±19.1. The SHAQ showed a mean of 0.98±0.65 points, which indicated only a mild degree of disability at first sight. The BFI added up to 39.6±21.0 points, which indicated a moderate level of fatigue in our patients. The analysis of the IPAQ revealed a mean of 2,812±2,310 metabolic equivalent of task (MET)/minute, which was equivalent to a moderate level of activity.

There were 73 patients who did not show any signs of depressive symptoms (mean MDI score 9.5±5.2) and 21 with depressive symptoms (mean MDI score 28.7±6.0). There were no males in the group of patients with depressive symptoms (Table 3). Five out of 21 patients were underweight, whereas only one patient was underweight in the group without depressive symptoms. The higher prevalence of depressive symptoms in females (p=0.047) and underweight patients (p=0.002) turned out to be significant. In the group with depressive symptoms, the quality

Table 3. Comparative analysis between two subgroups: no depressive symptoms versus depressive symptoms

	MDI <20 (n=73)			MDI ≥20 (n=21)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			58.1±13.5			24.7±8.5	0.379
Gender Females	61	83.6		21	100.0	58.9±14.4	0.047
Body mass index (kg/m^2)			24.5±4.3	9	42.9		0.620
Overweight	29	39.7		4	19.0		0.797
Obesity	8	11.0		5	23.8		0.328
Underweight	1	1.4				6.8±6.8	0.002
Disease duration (year)			7.8±5.6	11	52.4		0.827
Diffuse cutaneous SSc	29	39.7		10	47.6		0.301
Limited cutaneous SSc	44	60.3		17	81.0		0.301
Antinuclear antibodies	70	95.9		8	38.1		0.022
Anti-centromere	24	32.9		4	19.0		0.657
Anti-Scl-70	27	27.0				4.3±1.6	0.123
Number of organ involvements			4.2±1.4			13.4±7.1	0.778
Grip strength (kgf)			17.3±8.0			26.4±11.5	0.132
ABILHAND score			31.3±9.8			36.2±13.3	0.082
SF-36 total score			59.9±14.4			38.7±10.6	<0.001
SF-36 Mental Health SUM			67.8±15.7			1.4±0.67	<0.001
SHAQ score			0.85±0.59			60.5±17.2	0.003
BFI score			33.6±18.0			1.760±1.954	<0.001
IPAQ MET/min			3.114±2.327				0.048

MDI: Major Depression Inventory; SD: Standard deviation; SSc: Systemic sclerosis; Anti-Scl-70: Antitopoisomerase I; SF-36: Short Form-36; SHAQ: Scleroderma Health Assessment Questionnaire; BFI: Brief Fatigue Inventory; IPAQ: International Physical Activity Questionnaire; MET: Metabolic equivalent of task.

of life was significantly decreased (SF-36®, p<0.001), the degree of disability was increased (SHAQ, p=0.003), there was also a higher degree of fatigue (BFI, p<0.001) and less activity (IPAQ MET/minute, p=0.048). There were no significant differences regarding age, BMI, mean weight, obesity, duration of disease, cutaneous subsets, maximum grip strength, antibodies and type or number of organ involvement, including no differences regarding lung fibrosis and pulmonary hypertension between patients with or without depressive symptoms.

There were significant correlations between the MDI score and the SF-36® total score (p<0.001), SF-36® Mental Health SUM (p<0.001), SHAQ (p<0.001), BFI (p<0.001), IPAQ (p=0.001) and ABILHAND (p=0.001) (Table 4).

In order to assess factors that might coexist with depressive symptoms, the following variables, which were either significantly different between the two groups or correlated with the MDI, were tested in a linear regression model of the MDI: SF Mental Health SUM, BFI, IPAQ, ABILHAND and underweight. In the multivariable linear regression analysis, SF Mental Health SUM, BFI score and IPAQ were independently significant

Table 4. Correlation analysis between results of patient questionnaires and MDI scores

Variables	Correlation (r)	*p*
MDI score		
SF-36 total score	- 0.769	< 0.001
SF-36 Mental Health SUM	- 0.815	< 0.001
SHAQ score	0.508	< 0.001
BFI score	0.721	< 0.001
IPAQ MET/min	- 0 .331	0.001
ABILHAND score	-0.354	0.001

MDI: Major Depression Inventory; SF-36: Short Form-36; SHAQ: Scleroderma Health Assessment Questionnaire; BFI: Brief Fatigue Inventory; IPAQ: International Physical Activity Questionnaire; MET: Metabolic equivalent of task.

Table 5. Depressive symptoms mentioned in discharge letters in patients without versus with depressive symptoms

	MDI <20 (n=73)		MDI ≥20 (n=21)		Total	
Items	n	%	n	%	n	%
Evaluation mentioned						
No depressive symptoms	8	11.0	1	4.8	9	9.6
Depressive symptoms	0	0.0	1	4.8	1	1.1
No evaluation mentioned	65	89.0	19	90.5	84	89.4

MDI: Major Depression Inventory.

(r=0.850, pBFI<0.001, pSFMH<0.001, pIPAQ=0.043) in the model to predict severity of depressive symptoms.

The analysis of the discharge letters identified 5.3% of patients with a diagnosis of mood disorder. Of the patients, 1.1% reported symptoms of depression, while 9.6% denied any depressive symptoms. However, the vast majority of 89.4% was not assessed for symptoms of depression (Table 5). These included 19 out of 21 patients with depressive symptoms according to the MDI. Advice on social support or a referral to a psychiatrist/psychologist was given to seven (7.4%) patients. Thirteen (13.8%) were treated with antidepressants, either for depression, or possibly also for neuropathic pain, as no indication was mentioned with the drugs.

DISCUSSION

In this study, we found a prevalence of depressive symptoms of 22.3% among SSc patients. This is lower than the prevalence of 65% reported by Roca[4] in 1996 and other studies in the years after with results around 50%[3,6-8] or 35%[5,9,10] At the same time, this rate is almost three times higher than the rate of depression in the average German population.[12] Importantly, we used the MDI in order to evaluate the prevalence of depressive symptoms. This score has not been used in studies on SSc before,[2] but has become very popular in recent years because it has only 10 questions to answer and has been shown to provide a sufficient instrument for the use as a depression severity scale.[28] It has the advantage of being easy to handle for the patient and is quick to assess. Also, it allows to analyze the prevalence of depressive symptoms and not only that of major depression disorder (MDD) according to the DSM-IV classification or International Classification of Diseases, 10th Revision. We did not use the MDI as a diagnostic instrument,[22] because we were interested in general mental health issues in our patients. Including patients that fulfilled the diagnosis of MDD only would have led to an exclusion of many patients with high MDI scores and obvious mental health issues.

Many previous studies on depression in SSc used the Beck Depression Inventory[3,4,6,7,11,17] with a cut-off of ≥10 and symptoms lasting at least one week. The questionnaire has been revized in 1996[29] in order to increase specificity with a new cut-off of ≥13 and symptoms over the last two weeks. Nevertheless, these studies still used the old version, thereby overestimating the prevalence of depression. Therefore, it might be difficult to compare their results with the prevalence found in our study. Other studies used the Montgomery-Asberg Depression Rating Scale[8] and CES-D[5,9,14] The studies using the latter also found a lower prevalence of depressive symptoms in SSc, namely around 35%. On a critical note, estimated prevalence might vary considerably according to the specific questionnaires. Also, these questionnaires do not exclude non-psychiatric conditions that lead to similar symptoms, as for example diagnostic interviews can.[5]

Looking at potential risk factors, we found no significant differences between patients with or without depressive symptoms regarding disease duration and any disease-specific organ manifestations like in most other studies.[3,4,7,8,11,14,30] Instead, there were significant correlations between depressive symptoms and poor quality of

life (SF-36®), fatigue (BFI) and increased disability (SHAQ and ABILHAND). In our regression analysis; quality of life, fatigue and disability could also be identified as being associated with depressive symptoms. This finding has also been supported by previous studies that identify quality of life[13,14] fatigue[15,30] and disability[14] as risk factors. Similarly, physical activity (IPAQ), which has not been previously studied in relation to SSc, was reduced in patients with depressive symptoms. In our regression analysis, it also independently correlated with the MDI. However, the result of a correlation analysis does not allow us to establish causalities between physical activity and depressive symptoms. Also, there might be a conceptual overlap between these variables and depressive symptoms, as questions asking for symptoms of depression might be very similar to questions asking for fatigue, disability or quality of life.

Interestingly, we found that being female or underweight is related to the occurrence of depressive symptoms. Even though females are more likely to suffer from depression[31] and males are less frequently affected by SSc, we were still surprised that there were no males present in the subgroup of patients with depressive symptoms. Particularly knowing that male patients with SSc often suffer from erectile dysfunction,[32] which in turn can be responsible for a higher likelihood of developing depression,[33] this result came as a surprise. It is possible that the low case number of male patients (n=12) in our study might be responsible for this result and that higher case numbers might lead to a different result.

Next, we analyzed the current standard of care of mental health among SSc patients. We reviewed discharge letters with respect to the assessment and the treatment of depressive symptoms. Our findings revealed that most patients had not been assessed for depressive symptoms as far as medical reports can tell, including 19 of 21 patients with depressive symptoms according to the MDI. Reasons why physicians might avoid asking about mental health could be the fear of patients' reluctance to answer personal questions or insecurity regarding how to address these issues. There might also be a lack of time to ask patients about depressive symptoms or to document such questions. A possible solution to improve awareness of mental health among doctors and patients alike might be to offer specific disease management programs that convey patients skills for coping with the disease and to handle activities of daily life.

This study has some limitations. Firstly, it has a relatively small sample size for an extensive statistical analysis as we have performed on this dataset. This is a problem that occurs frequently in the field of rare diseases. Multi-center studies are often helpful to achieve studies in this field with a good statistical power. Secondly, the nature of our study is exploratory, which might be seen as problematic for the following reasons: There is a potential overlap between SSc symptoms such as sleep difficulties and fatigue and symptoms of depression. Our study does not address this factor. Also, it is not possible from our analysis to assess clinically meaningful differences in depressive symptoms as this has not been defined for the MDI. Hence, consequences of this study for clinical routines still have to be evaluated with care.

In conclusion, our study found a high prevalence of depressive symptoms in a fifth of SSc patients. Fatigue, reduced quality of life and less physical activity were ascertained as independent risk factors. Particularly, when there is progressive worsening over time along any of these dimensions, special care should be directed to assessing patients' mental health and coping strategies.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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