

# Psychiatric Symptoms and Quality of Life in Systemic Sclerosis

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**Abstract:** *Introduction:* Systemic sclerosis (SSc) is a rare conjunctive tissue disorder characterized by fibrosis of the skin and internal organs, and vascular obliteration phenomena. Patients with SSc often experience elevated symptoms of psychological distress, determined by the disfiguration, the pain, the fatigue sensation, and the difficult in daily life occupations. The characteristics of the disease may influence the perceived quality of life (QoL) in people with SSc.

*Methods:* This is a narrative review aiming to define the amount of impairment of Quality of Life in patients with Systemic Sclerosis and the component of this impairment due to depressive or other psychiatric symptoms. The search of the significant articles was carried out in PubMed for the key words "Psychiatric symptoms and Systemic Sclerosis"; "Quality of life and Systemic Sclerosis"; "Depressive Disorders and Systemic Sclerosis".

*Results:* Psychiatric symptoms are frequent in patients with SSc, but pain, fatigue, disability, body changes don't appear to explain the high prevalence of psychiatric comorbidity in SSc. Many studies founded a significant impairment in SSc patients' QoL, and despite the undeniable correlation between physical symptoms and SSc patients' QoL, mental health was found significantly impaired.

*Discussion:* The high rate of depression seems to strictly correlate with poor quality of life, and this finding needs more research to establish the cause of such a correlation. Patients' point of view regarding their health-related QoL could help physicians to enlarge the knowledge about physical and mental correlates of the disease, and to fit therapies as patient required. Particular attention must be given to provide the patient with correct information, in order to mitigate the anxious state on disease course, and to enhance coping skills of the patients.

**Keywords:** Systemic sclerosis, psychiatric symptoms, depressive disorder, quality of life.

## INTRODUCTION

Systemic sclerosis (SSc) is a rare conjunctive tissue disorder characterized by fibrosis of the skin and internal organs, and vascular obliteration phenomena. Those features are responsible for increased morbidity and mortality. Skin afflictions cause major body changes, which may contribute to the occurrence of psychological disturbances such as anxiety and depression [1]. Central Nervous System (CNS) is involved in SSc due to the consequence of functional and structural abnormalities of small blood vessels, signifying a form of CNS vasculopathy [2]. Similar to other rheumatologic diseases, SSc is chronic, invaliding and it needs treatments that may have disrupting adverse effects (corticosteroids, interferon, immunosuppressants). Moreover, it is a heterogeneous disorder, with different clinical features from a skin-localized involvement to a multi-organic disease with lungs, kidneys, heart, musculoskeletal and gastrointestinal systems failure, until a complete functional disability [3, 4]. Two major subtypes have been described depending on the extent of skin lesions: limited cutaneous SSc (lcSSc) and diffuse cutaneous (dcSSc). Poorer outcome is generally associated with the diffuse form, characterized by a

precocious visceral failure, which may be absent or tardive in the limited form. Given the heterogeneity of the disease and its insidious course, diagnosis often is done late.

Patients with SSc often experience elevated symptoms of psychological distress, determined by changes in physical appearance, pain, fatigue sensation, and difficult in daily life occupations. All the characteristics of the disease may influence the perceived QoL in people with SSc.

This is a narrative review that seeks to analyze the results of studies on Psychiatric symptoms and QoL in Systemic Sclerosis, aiming to define the amount of impairment of QoL in patients with Systemic Sclerosis and the extent of this impairment due to depressive or other psychiatric symptoms.

## METHODS

The search of the significant articles was carried out in PubMed for the key words "Psychiatric symptoms and Systemic Sclerosis"; "Quality of life and Systemic Sclerosis"; "Depressive Disorders and Systemic Sclerosis". We found 28 relevant articles containing the terms "psychiatric symptoms" or "depression and Systemic Sclerosis" (15 were excluded because in six cases the argument treated was not pertinent, five were letter to editor, three were case-reports, one was in French), 42 articles containing the terms "Quality of Life and Systemic Sclerosis" (18 were excluded since they were not pertinent).

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## RESULTS

### Psychiatric Symptoms in Systemic Sclerosis

Depressive symptoms are frequent in patients with SSc, with prevalence of major depressive disorder ranged from 17 to 69% of SSc people [5-8]. A review by Thombs and colleagues [9] found a prevalence of clinically significant depressive symptoms in 51–65% based on two studies that used a Beck Depression Inventory (BDI) score  $\geq 10$  and 46–56% based on two studies that used a BDI score  $\geq 11$ ; four other studies that used different assessment tools detected a prevalence of depression in 36–43%. The authors underlined the lack of studies using a clinical structured interview; however, the findings were consistently high compared with other medical patient groups assessed with the same instruments and cutoffs.

Using The Center for Epidemiological Studies Depression Scale (CES-D), a 20-item self-report measure commonly used as a depression screening and research tool in rheumatic diseases, Thombs carried out a case-control study [10] on 403 patients with SSc and 403 non-medical respondents to an Internet depression survey, matched on total CES-D score, age, race/ethnicity, and sex. The mean total CES-D score for both the SSc and Internet groups was 14.0 points; over one-third of each group scored  $\geq 16$  points on the CES-D (148 [36.7%] of 403), and over a quarter of patients scored  $\geq 19$  points (110 [27.3%] of 403). Patients with SSc reported significantly higher frequencies (moderate to large effect size;  $P < 0.01$ ) on 4 CES-D somatic symptom items: bothered, appetite, effort, and sleep, but high rates of depressive symptoms in SSc are not due to bias related to the report of somatic symptoms.

A recent cross-sectional study published by Baubet and colleagues [7] on 100 SSc patients, both hospitalized and outpatients, was assessed using a structured clinical interview, the Mini International Neuropsychiatric Interview (MINI), and a self-reporting questionnaire, the Hospital Anxiety and Depression Scale (HADS). As assessed by the MINI, 19% [95% confidence interval 12-28%] of all SSc patients were currently experiencing a major depressive episode (MDE), 56% [46-65%] had a lifetime history of MDE and 14% [8-22%] had current dysthymia. Current MDE was more prevalent among hospitalized patients than among outpatients (28% versus 10%,  $p=0.02$ ). Specific anxiety disorders were diagnosed in 37% [28-47%]. Less than 50% of the SSc patients with mood disorders received psychiatric treatment. Legendre and colleagues [11] carried out a prospective study on a small cohort (42 patients, including 18 with diffuse cutaneous scleroderma and 24 with limited cutaneous scleroderma). Mean age was 57 +/- 13 years, mean disease duration was 10.2 +/- 8 years, and the mean functional Health Assessment Questionnaire score was 0.682 +/- 0.649. The Montgomery-Asberg Depression Rating Scale (MADRS) and the Hamilton Anxiety Rating Scale were used to evaluate depression and anxiety, respectively; 43% patients met criteria for depression (in 26% scored as moderate to severe), 64% patients met criteria for minor anxiety and 19% for major anxiety. Depression and anxiety were strongly correlated with each other ( $r = 0.89$ ;  $P < 0.0001$ ). The MADRS score was significantly higher in the patients with pulmonary restrictive disease ( $P = 0.009$ ) but was not

associated with the extent of skin involvement, organ involvement, or disability.

Compared to Rheumatoid Arthritis, SSc patients have less bodily pain and disability, but they tend to report higher depressive symptom scores [12]; moreover, SSc patients show the presence of significantly higher psychiatric symptoms of anxiety and depression than patients with other serious skin conditions, such as melanocytic naevi or melanoma [13].

Pain, fatigue, disability, body does not appear to explain the high prevalence of psychiatric comorbidity in SSc, and there are a very few studies that investigated the pathophysiology of such a phenomenon. Goldenberg proposed an inflammatory/immune mechanism, common at all rheumatologic diseases, on a fibromyalgia-based model [14].

Some early studies correlated depressive symptoms, functional impairment, and personality traits with SSc. Roca, Whigley & White [8] assessed 54 SSc patients with the Beck Depression Inventory, the Neuroticism-Extraversion-Openness Personality Inventory, the Health Assessment Questionnaire, and the Psychosocial Adjustment to Illness Scale. Nearly half of the patients had mild depressive symptoms, and an additional 17% had symptoms in the moderate-to-severe range. Depressive symptoms were found to correlate with younger age, presence of digital ulceration, higher self-rated functional impairment, but there were highly significant relationships between depression and aspects of personality, psychosocial adjustment to illness, and lack of social support.

Similar findings, except regarding the lack of social support, were detected in an Italian study [15] on 111 SSc patients assessed by the Beck Depression Inventory (BDI) questionnaire, the scleroderma Health Assessment Questionnaire (sHAQ) and two additional questions assessing the patient's familiar support and the social consequences of the patient's change in physical appearance. Mild to severe depressive symptoms were found in 33.4%. While on univariate analysis many physical symptoms (such as the diffuse cutaneous form of the disease, lung involvement, pain, Raynaud's phenomenon, ulcers and disease severity) were associated with the presence of pathologic depressive symptoms, on multivariate analysis only the Visual Analog Scale for disease severity was correlated to BDI scores ( $p=0.016$ ). Interestingly, social behavior changes due to SSc-related physical involvement were reported in 38% of patients with depressive symptoms ( $p=0.006$ ) and were more likely to be observed in younger patients ( $p=0.001$ ) with a more severe Raynaud's phenomenon ( $p=0.013$ ).

Matsuura and colleagues [16] evaluated 50 SSc patients for factors associated with depressive symptoms using the Beck Depression Inventory (BDI), the Rheumatology Attitude Index for measuring helplessness, the Sense of Coherence (SOC) scale (a measure of an individual's resilience in the face of stress and capacity to cope with it), the modified Health Assessment Questionnaire for physical disability, working, and social function, support domains of Arthritis Impact Measurement Scales version 2, and a visual analog pain scale. They found depressive symptoms ranging from mild to severe state in 46% of the patients. Total BDI scores

were significantly correlated with low working ability, low social activity, low SOC, pain, and helplessness, and not associated with disease severity variables including skin score and internal organ involvement. Multiple regression analysis showed that a high level of helplessness and a low level of SOC might be closely associated with depressive symptoms in SSc.

Depression and its cognitive correlates are important variables to understand the experience of the pain in a rheumatologic disorder: whereas the patient's self-report of pain is only marginally related to the real severity of illness, it's strongly associated with depression [12]. A cognitive correlate of depression is catastrophizing, which includes magnification of pain-related symptoms, rumination about pain, feelings of helplessness, and pessimism about pain-related outcomes [17]. Catastrophizing in osteoarthritis patients shows associations with self-reported disability, pain behaviors, functional limitations [18], in rheumatoid arthritis it relates to reduction in muscle mobility and strength [19], and to increased levels of disease activity [20]. The physiopathological mechanism below those associations is not yet cleared; in particular is uncertain if there is any direct relationship between catastrophizing and hypothalamic-pituitary-adrenal axis; an indirect evidence is that there is an increase in myocardial contractility in high-catastrophizing individuals [21]. From a psycho-social view, many researchers consider catastrophizing a maladaptive style of coping, derived from personality characteristics of insecure adult attachment cognitive style, directed to elicit a more solicitous attention from others: significant social support may reinforce high expression of pain, helplessness and depression [22]. This may lead catastrophizers to increase their attention levels to bodily sensations, painful stimuli, until obsessive anticipation of pain that determined an amplification of pain [23, 24]. Catastrophizing in SSc patients was found more highly associated with greater reporting of affective pain among those with less formal education [25], but such a relationship remains unclear. In RA this finding was replicated, and it was shown a correlation between catastrophizing, low socioeconomic status, or social dysfunction [26].

Another explanation may be that SSc, similar to other autoimmune diseases, is characterized by an enhancement of vulnerability to psychological distress, determined by the deregulation of auto-immune response. Such vulnerability may act as a predisposition to mood disorders [27].

Until a few years ago, most researchers thought that scleroderma didn't involve CNS. Because, despite the frequency of psychiatric symptoms, neurological symptoms are rare. A functional magnetic resonance study on patients with fibromyalgia showed enhancement of activity in anterior cingulate and insular cortex during the experience of acute pain [28]: significantly, these regions of CNS are responsible of the affective processing of pain. More recent work suggests that, the focus has been shifted to understand the consequence of vascular and micro-vascular CNS involvement in SSc (hyperintense foci of variable size diffuse in white matter), and is thought to be a form of CNS vasculopathy, similar to the Systemic Lupus Erythematosus [2, 29]. Other autoimmune diseases have also cause characteristic pattern

of cerebral perfusion anomalies related to mood disorders [30, 31]. Further studies will clarify the clinical correlates between psychiatric symptoms and SSc RM and SPECT imaging findings.

## QUALITY OF LIFE IN SYSTEMIC SCLEROSIS

Although morbidity and mortality are the prominent outcomes to determine the social impact of diseases, patient-reported point of view on health-related QoL has become an interesting way to obtain information on the experience of disease, treatment efficacy and need of cares.

QoL is a subjective, heterogeneous concept of well-being correlated with a number of factors, such as severity and duration of illness, use of medications and stress events. The subjective perception of QoL is now considered of great relevance to measure the outcomes in a chronic disease [32, 33] particularly in those with high impairment and much impacted daily life [34]. It has become central to evaluating the effectiveness of treatments as well.

To date, there have been few research on QoL in SSc, and most have a small size of sample: although SSc is a severe, potentially devastating disease, it has a low prevalence. The central symptom of SSc is pain, due to various causes (arthritis, digital ulcerations, esophagitis, Raynaud's phenomenon, chronic diarrhea, etc.).

A high correlation between pain and health-related QoL has been reported in SSc. In a prospective cross-sectional study of 89 SSc patients, Georges and colleagues [35] examined the impact of pain in the QoL of 89 SSc patients with either a limited (N=22) or a diffuse (N=67) form of SSc using two self-administered questionnaires, the French versions of the SSc health assessment questionnaire (HAQ) and the SF-36. The QoL as assessed by the SF-36 appeared related to the burden of clinical manifestations, in relation to the number of clinical involvements, the functional disability and the pain, with a high correlation between pain and health-related QoL. All the SF-36 subscale scores of SSc patients were lower than those already reported in general population. Both PCS (Physical component summary score) and MCS (Mental component summary score) of the SF-36 were lower in diffuse than in limited SSc, which could be related to the disease extension. Therefore, although it might be obvious for any clinician, the effective control of the pain, which can be related to the presence of either RP, digital ulcerations, musculoskeletal or digestive involvement, should constitute the primary therapeutic goal to achieve a better QoL in SSc-treated patients.

Bassel and colleagues recently published a paper [36] focused to identify symptoms of SSc that highly impacted patients' ability to carry out daily activities. Using the Canadian Scleroderma Patient Survey of Health Concerns and Research Priorities, 464 SSc patients were asked about the frequency and impact of 69 SSc symptoms. The five symptoms more frequently experienced and associated with moderate to severe impact on daily activities were: fatigue (89 and 72%), Raynaud's Phenomenon (86 and 67%), hand stiffness (81 and 59%), joint pain (81 and 64%) and difficulty sleeping (76 and 59%).

Another prominent symptom of SSc is the fatigue: such as other chronic, painful debilitating diseases, the most of the patients reported fatigue, which is a significant determinant of physical functioning [36, 37].

### QUALITY OF LIFE AND PSYCHOLOGICAL IMPAIRMENT IN SYSTEMIC SCLEROSIS

The higher prevalence of unmet needs in SSc patients causes psychological, spiritual and existential problems. In fact, they are often unable to do the things they used to do; they worry about appearance, scared of disease progression and physical disability, and uncertain of their future [38, 39]. Such an anxious situation may produce chronic feelings of demoralization, uselessness, loss of control. In a systematic review of 12 studies on health-related QoL in SSc, Hudson and colleagues found significant impairment in SSc patients [40]. Despite the undeniable correlation between physical symptoms and SSc patients' QoL (SF-36 Physical Component Summary score was more than one SD below that of the general population), mental health was found significantly impaired (SF-36 Mental Component Summary score was approximately 0.5 SD below that of the general population).

A recent address of study on QoL in SSc is focused on depression. QoL impairment and female sex were found as independent risk factors for depressive symptoms in a cross-sectional study on 72 patients [59 female (82%), mean age 59 years] carried out by Muller and colleagues [5]. Validated questionnaires, the Health Assessment Questionnaire (HAQ), EuroQol (EQ-5D) and the Center for Epidemiologic Studies Depression scale (CES-D) were utilized to measure disability, quality of life and depressive symptoms. According to the CES-D, 69% (48 out of 70) were screened positive for depression.

Analogous findings were shown by a cross-sectional study [6] on 59 SSc patients assessed by using the Patient Health Questionnaire depression scale (PHQ-9) to detect depressive disorders, HAQ for the health status and SF-36 for the quality of life. 77.4% of patients presented symptoms of depression: 61% had a major depressive syndrome, and 16.4% a minor depressive syndrome. The PHQ-9 score was significantly higher in the patient with prolonged disease duration, severe joint pain, higher disease severity and activity. Also, depression had a negative impact on both physical and mental SF-36 scores.

Danieli and colleagues [12] published a cross-sectional study on 76 SSc patients aimed to evaluate health-related quality of life (HR-QOL) in patients with SSc, and to compare it with that of patients with rheumatoid arthritis (RA). HR-QOL was evaluated by SF-36, SSc disease activity and severity by ACR criteria, disability by the Health Assessment Questionnaire (HAQ), and depressive symptoms by the Beck Depression Inventory. While HR-QOL perception was not statistically different in patients with SSc and RA, compared with RA, patients with SSc tended to perceive less bodily pain ( $p=0.06$ ) and have less disability ( $p=0.04$ ) but to report higher depressive symptom scores ( $p=0.05$ ). SSc patients' HR-QOL was worse in patients with diffuse cutaneous involvement both in physical and in mental scores.

Psychological distress and depression were both correlated to physical health-related QoL, as shown by Hyphantis

and colleagues in a cross-sectional study [41] on several chronic physical disorders, such as colorectal cancer ( $N = 162$ ), glaucoma ( $N = 100$ ), rheumatoid arthritis ( $N = 168$ ), systemic sclerosis ( $N = 56$ ) and systemic lupus erythematosus ( $N = 56$ ), assessing psychological dimensions with the Symptom Distress Checklist (SCL-90) and health-related QoL with the WHO QoL Instrument, Short Form. Interestingly, the SCL-90 somatization score was the only psychological distress covariate significantly correlated to physical HRQOL in all diseases (Betas between  $-0.33$  and  $-0.49$ ) except in SSc, where depression was also a correlate.

Another recent field of research is focused to investigate the association between clinical, psychopathological, and personality parameters in SSc patients, and their correlation with health related QoL. One of the most important parameters taken into consideration by many studies on rheumatic diseases is the Sense of Coherence, the individual's ability to experience life as understandable, meaningful and manageable, and to deal with problems arising. Sense of Coherence assessing gives a measure of an individual's resilience in the face of stress and capacity to cope with it. The most important determinant for SOC is personal relationships, so in a prospective of health-promoting the Sense of Coherence may be enhanced to improve individual's strength and skills to cope with diseases [42, 43].

High levels of psychological distress were found to be associated to disease duration and lower rates of Sense of Coherence in a study [44] on 56 SSc patients and 74 healthy controls, using the General Health Questionnaire, the Symptom Distress Checklist-90-R, the Defense Style Questionnaire, the Sense of Coherence (SOC) Scale, and the Hostility and Direction of Hostility Questionnaire. Moreover, high rate of anxiety was found associated with arthritis-related painful conditions and SOC, while psychotic-like symptoms were only associated with age and a specific personality structure. Analogous finding was observed in RA patients, in which psychological distress mediated the correlation between psychological traits variants and physical health-related QoL [45].

Another study [46] compared arthritis-related pain and health-related QoL in 57 SSc patients, 72 patients with rheumatoid arthritis, 43 with systemic lupus erythematosus, 34 with Sjögren's syndrome, and 74 healthy controls. Health-related quality of life (HRQOL) was assessed using the World Health Organization Quality of Life Instrument, Short-Form (WHOQOL-BREF); other clinical information was obtained by the General Health Questionnaire, while the presence of psychological distress, the coping style and personality prevalent traits were detected using the Symptom Distress Check List, the Hostility and Direction of Hostility Questionnaire, the Defense Style Questionnaire, and the Sense of Coherence scale. HRQOL perceived by SSc patients was significantly impaired compared not only with healthy controls, but also in comparison with RA, SLE, and SS patients. Poorer HRQOL was founded associated with high level of psychological distress, maladaptive defenses, and lower sense of coherence

Arat and colleagues focused a cross-sectional study [47] on a large cohort of SSc patients ( $N= 217$ : 49 with limited SSc (lSSc), 129 with limited cutaneous SSc (lcSSc) and 39

with diffuse cutaneous SSc (dcSSc) on illness perception and the ability to cope with physical and mental health problems. Illness perception and coping were assessed by the Revised Illness Perception Questionnaire and the Coping Orientation of Problem Experience inventory (COPE), health-related QoL was measured by the SF-36, and the relationship between illness perceptions and coping was examined using multiple linear regression analysis. Good physical health was significantly associated with the lcSSc subtype and low disease activity ( $p < 0.01$  and  $p < 0.05$ , respectively). The perception of 'serious consequences' and strong 'illness identity' correlated with poor physical health ( $p < 0.001$ ). Good mental health was associated with low illness identity scores and low 'emotional response' scores ( $p < 0.001$ ). Interestingly, illness perception was found more significantly correlated with both physical and mental health than coping style, and appeared more important than classical disease symptoms to contribute to wellbeing of SSc patients and their health-related QoL. The importance of psychological traits, style of coping and adjustment of disease is underlined by Malcarne & Greenbergs, that analyzed 8 types of coping strategies and found three types of coping as predictors of adjustment: Wishful Thinking, Blaming Self, and Problem-Focused Coping [48].

An emergent question is represented by a possible cognitive impairment in SSc patients. A dementia-like condition, in fact, may worsen psychiatric comorbidity and therapy compliance. Giuliodori and colleagues showed presence of reduced performance of executive functions in SSc patients, and, in absence of other apparent causes of cerebrovascular impairment, they hypothesized an alteration of cerebral perfusion regulation [49].

## DISCUSSION

Mental health-related QoL is frequently impaired in SSc patients, and it could influence the general perception of quality of life, depending on a variety of cognitive-emotional variants related to the patient's coping style. The high rate of depression seems to be strictly correlate with poor QoL, and this finding needs more research to establish if depression is due to a worse QoL or if it is the contrary, or if depression and quality of life impairment are both due to other disease related or inherent factors. Further studies, focusing on a common etiopathogenic hypothesis, should help clarify this topic.

Another topic is the low rate of SSc patients with psychiatric comorbidity that receives an adequate treatment, despite the high frequency of depression and anxiety disorders and the availability of safe and manageable drugs. The burden of living with a chronic and painful illness, the fatigue, the difficulty in daily activities, and the disfiguration can give rise to demoralization, hopelessness, loss of self-worth, and expression of a wish to die. These facts appear intuitive and obvious, and sometimes may lead clinicians to prematurely assign a reactive explanation to the patient's symptoms, and delay the start of a treatment.

Patients' point of view regarding their mental health-related QoL could help physicians to enlarge the knowledge about physical and mental correlates of the disease, and to fit therapies as required by the patient. Particular attention must

be given to informational needs [39]. Correct information, given by a rheumatologist, a dermatologist, a general practitioner, and a psychologist or a psychiatrist may mitigate anxiety about the course of the disease, and enhance coping skills of patients. Catastrophizing and low Sense of Coherence, both related to the depressive cognition and to worse QoL, are personality traits that could be modified. As previously discussed, efficacy coping styles are characterized by the skills of "seek for alliance", "acquired self-responsibility", "think positive". These coping skills can be trained by self-help groups, and in rare and disabling diseases such as SSc, patients and relatives associations may help to change from a "illness-balanced medicine" to a "patient-balanced medicine". Psychiatrist's intervention, indispensable in case of severe mental health impairment, may be postponed or replaced by self-help group or a supportive psychotherapy, directed to the knowledge of mechanisms to reduce stress response.

For a rare disease such as SSc, Internet can be a powerful mass media, in which informations are easy to found, free and globalized [50]. Therefore, it may be desirable that physicians ask patients know about their disease, and what else they need to know.

The heterogeneity of SSc, its seriousness, and the variety of its consequences on organs and systems required not only a multidisciplinary approach, but also an alliance between patients and health professionals.

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