

Anxiety Disorder as an Important Determinant of Quality of Life in Systemic Sclerosis Patients

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ABSTRACT

Systemic Sclerosis (**SSc**) is an autoimmune connective tissue disease, characterised by fibrosis of internal organs and skin that leads to visible disfigurements to various body parts, including face, mouth and hands. The changes in these socially relevant body parts are associated with greater body image dissatisfaction, increased depressive symptoms, and social anxiety and avoidance behaviours.

The HRQoL, usually evaluated in rheumatic conditions by the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), is considered an important outcome in SSc, useful in monitoring the disease.

The few data available on the prevalence of anxiety in patients with systemic sclerosis revealed severe anxiety disorders in 19-46.6%, although only a limited number of researches assessed anxiety impact on HRQoL.

In this chapter, we reported these studies and three our subsequent researches focused on anxiety impact on HRQoL.

In the first study we assessed the prevalence of depression and anxiety in SSc patients and their association with physical and psychological variables. Both rates of depression and anxiety, evaluated by Hospital Anxiety Depression Scale (**HADS**), were 36% and 13% respectively, while 23% of SSc patients had both disorders. Depressive patients with comorbid anxiety had significantly higher HADS-D score than patients with depression only. Both depressive and anxiety symptoms were significantly and positively correlated with global disability, hands and mouth disability, fatigue, self-esteem and avoidance strategy in coping, and anxiety only with social support.

In a second work, we found that Summary Physical Index (**SPI**) and Summary Mental Index (**SMI**) of SF-36 were significantly correlated with hands and face disability. Given that these variables did not explain large amount of the variance in SPI and SMI of SF-36 (22% and 4% respectively), other factors, like psychological symptoms, might contribute to worsen HRQoL in SSc.

For this reason, in a third study, we investigate other factors as predictors of HRQoL in 119 SSc patients. The significant predictors of SMI of SF-36 result fatigue, avoidance strategy, coping style and anxiety, accounting for 52,8% of the variance in SMI. Independent predictors of anxiety were mouth disability, self- esteem and social support. In the final Mental HRQoL Model, fatigue and avoidance strategy affected Mental QoL both directly and through their interaction with anxiety, while the others affected Mental HRQoL only indirectly by increasing anxiety. These results highlight the role of anxiety as one of the most important predictor of HRQoL in SSc patients.

Keywords: HRQoL; Anxiety disorders; Systemic Sclerosis; Psychological disorders

SYSTEMIC SCLEROSIS DISEASE

Systemic Sclerosis (**SSc**), or Scleroderma, is an autoimmune multiorganic connective tissue disease, characterised by microvascular involvement and fibrosis of the skin and internal organs [1]. Consistent with other autoimmune diseases, SSc is predominant among females, with a ratio of females to males of 1:1 to 14:1[2].

According to Le Roy and colleagues, it is divided into two subsets, limited or diffuse disease, based on the extent of skin tightening [3].

In limited disease (**lcSSc**) (formerly called CREST syndrome: calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasias), skin tightening is confined to the fingers, hands and forearms distal to the elbows, with or without tightening of skin of the feet and of the legs distal to the knees. Proximal extremities and the trunk are not involved.

In diffuse disease, or diffuse cutaneous Systemic Sclerosis (**dcSSc**), the skin of the proximal extremities and trunk is also involved.

Patients with dcSSc are at risk of developing rapidly progressive skin fibrosis and widespread, severe, internal organ involvement. Patients with lcSSc have a disease course characterized by slowly progressive skin and internal organ involvement.

Raynaud's phenomenon is very frequent in SSc patients and it may be present for years before the other symptoms of the disease. Patients' fingers may change from white (vasospasm) to blue-purple (ischemia) to red (hyperemia), due to exposure to cold temperature or emotional stress.

Other cutaneous manifestations include shiny skin or pigment changes, facial thickening, that often leads to difficulty in opening the mouth, telangiectasia, calcinosis cutis and above all ulcerations.

Musculoskeletal involvement is common in early SSc and can manifest as nonspecific myalgias and arthralgias [4,5].

Lung involvement is common and often is the leading cause of death in SSc patients.

SSc can affect the lung parenchyma (interstitial lung disease) and the pulmonary blood vessels (pulmonary arterial hypertension). Thus, dyspnea is a common manifestation in SSc patients. Moreover, increasing evidence suggests that systemic sclerosis commonly affects the heart. Cardiac involvement in SSc includes myocardial disease, conduction system defects, arrhythmias or pericardial disease. Furthermore, scleroderma renal crisis, that is not frequent, can lead to cardiac dysfunction.

Symptoms related to Gastroesophageal Reflux Disease (**GERD**) and dysphagia or changes in bowel habits, secondary to intestinal dysmotility, are common in patients with early systemic sclerosis. Esophageal disease is universal in patients with and can cause considerable pathology, even in asymptomatic patients.

Other features of systemic scleroderma include dry eyes and mouth (due to secondary Sjögren's syndrome). Moreover, sexual dysfunction can be disabling in SSc women patients, while in men erectile dysfunction is common and is partly due to impaired local circulation [4,5].

HEALTH RELATED QUALITY OF LIFE IN SYSTEMIC SCLEROSIS

Patients with SSc frequently suffer from variably symptoms (Raynaud phenomenon, scleroderma, digital dip ulcerations/ pits, musculoskeletal dysfunctioning, gastrointestinal complaints, kidney function impairment, cardiac /pulmonary dysfunctioning, impairment of the nervous system, or difficulty in chewing) and a disfiguring outward appearance. These different and sometimes severe clinical features may lead to functional disability, psychological disorders and impaired Health Related Quality Of Life (**HRQoI**) [1].

The World Health Organization (WHO) defines quality of life (QoL) as an “individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad-ranging concept affected by an individual’s physical health, psychological state, level of independence, social relationships and their relationship to salient features of their environment “ [6], QoL encompasses the concept of Health-Related Quality Of Life (**HRQoL**) and other domains such as environment, family, and work. HRQoL is the extent to which one’s usual or expected physical, emotional and social well-being are affected by a medical condition or its treatment.

The subjective perception of QoL is now considered of great relevance to measure the outcomes in SSc and chronic disease particularly in those with high impairment of daily life [7].

HRQoL is now considered both as an important outcome measure and as a tool to evaluate the efficacy of therapy.

The Medical Outcomes Study 36-Item Short Form Health Survey (**SF-36**) has become one of the most widely used instruments to assess QoL in rheumatic conditions [8]. The SF-36 includes subscales across eight dimensions of health and well-being, including physical functioning, role physical, role emotional, bodily pain, general health, vitality, social functioning and mental health, also combined into a Summary Physical Index (**SPI**) and a Summary Mental Index (**SMI**). Scores for all subscales are expressed on a scale from 0 to 100, with a higher score indicating a better state of health. It has good reliability and validity for both clinical and healthy community-based samples [9].

In SSc, HRQoL, resulting significantly impaired with respect to general population, was the objective of numerous investigations. In some studies, comparisons between SSc subtypes revealed that HRQoL of patients with dcSSc did not differ from that of patients with lcSSc [10,11]. In the same time, other studies have reported that many HRQoL components were lower in dcSSc than in lcSSc [12,13]. In addition, Muller et al. [14] show that patients with longer disease duration have a higher quality of life than those with a shorter course of disease. Coping strategies that patients develop over time might be the factor explaining this phenomenon.

In SSc, HRQoL, evaluated by different instruments (SF-36, WHODAS II, EuroQoL) was found to be related with gastrointestinal problems [15-17], shortness of breath [15,16], joint involvement [15], skin score [12,13,15,16], disease severity and activity [11,18], pain [13,16,19], global disability [11,13,14,18], fatigue [16] and psychological symptoms [10,11,16]. Moreover, hands and face involvement in SSc patients, leading to functional limitations, may significantly affect HRQoL [20,21]. In addition, SSc patient’s present very high level of negative emotions, as compared to both healthy population and other chronic rheumatic patients, assessed by the same instruments and cut-offs. Depression, followed by anxiety and anger, are recognized as the three main negative feelings contributing significantly to the course of SSc [22].

To improve the quality of life in patients with SSc is important to develop some strategies toward general self-management, better handling with emotional distress, managing body image distress, physical and occupational therapy for hands, fatigue and energy management, as well as managing sleep and sexual function problems [23,24].

INFLUENCE OF PSYCHOLOGICAL FACTORS ON HEALTH RELATED QUALITY OF LIFE IN SYSTEMIC SCLEROSIS

Depression is the negative emotion that appears more frequently as a result of chronic disease that causes pain, disability and changes in physical appearance.

The prevalence of mild to moderate depressive symptoms varies according to the evaluation tool used and to the geographic origin of the patients, and ranges from 36 to 65% [25].

Anxiety is a complex concept meaning that somebody is excessively or unreasonably worried by something. In patients with SSc it could include a series of symptoms such as tension, palpitations, breathing difficulties, sleep disturbances, restlessness and other physical symptoms.

The few data available on the prevalence of anxiety in patients with systemic sclerosis revealed sever anxiety disorders in 19-46.6% [26].

Despite high prevalence of psychological disorders in SSc, the impact of psychological functioning on SSc patients' HRQoL has not received much attention. In previous researches poorer HRQoL was associated with depressive symptoms [11,16,27], illness perception [18] and coping strategies [18,27,28].

In the study of Hyphantis et al. elevated psychological distress symptoms, certain personality traits, such as maladaptive defenses and lower sense of coherence, were also associated with diminished HRQoL [27]. Interestingly, some studies reported stronger correlations of reduced HRQoL with psychiatric and personality factors than demographic and clinical variables [27,29].

In addition, Altman et al. reported a high suicide rate in SSc patients studied over a prolonged period of time [30]. In fact, a review of the mortality of 63 medical disorders provided initial evidence of an increased risk for suicide among SSc patients [31]. These findings should alert physicians and health providers to pay attention to the psychological profile of SSc patients.

A growing body of evidence indicates that rather than simply being a consequence of medical illness, mood disturbances affect physical health both through physiologic pathways and through cognitive, behavioral and social processes [32].

Numerous studies showed that psychological symptoms in SSc are not correlated with indicators of disease severity (e.g., skin score, pulmonary function test values and heart involvement) [7,29,33]. Thus, it is reasonable to assume that personality might affect how patients deal with illness and might specifically influence the vulnerability of scleroderma patients to psychological disorders.

The studies assessing psychological distress symptoms as a predictors of poor HRQoL in SSc are focused most on depressive disorders and there are relatively little researches assessed the prevalence of anxiety in SSc and its impact on HRQoL [10].

ANXIETY IN SYSTEMIC SCLEROSIS

The associations of anxiety with impaired HRQoL have previously been demonstrated in other chronic conditions [34-36] but it is still under-recognized in SSc.

Patients with systemic sclerosis may experience anxiety due to uncertainty about the future, fear of disease progression, fear of becoming physically disabled and physical changes [37].

Substantial evidence indicates that females report greater fear and are more likely to have anxiety disorders than males. Complex processes underlie gender differences in anxiety. Individual differences in etiological factors of anxiety and fear are moderated by socialization processes, which prescribe gender-specific expectations for expression of anxiety and the acceptable means of coping with anxiety [1].

A central feature of SSc is the excessive production of collagen, which manifests itself vascular abnormalities and fibrosis in multiple organs and in the thickening and hardening of the skin. This commonly leads to significant visible disfigurements to various body parts, including face, mouth and hands. The changes in these socially relevant body parts are associated with greater body image dissatisfaction, increased depressive symptoms and lead to social anxiety and avoidance behaviours and reduced overall psychosocial functioning [23,38].

The face and mouth alterations in SSc impact on normal face-to-face communication with others and lead to functional problems such as eating and drinking. Thus, it is not surprising that face involvement produce a greater level of anxiety in SSc patients. Besides face changes, SSc patients suffering from several oral and maxillofacial manifestations, like the presence of trismus, muscular atrophy, thin atrophied lips, secondary microstomia, xerostomia, rigidity of tongue and lips, widening of the periodontal ligament space, trigeminal neuralgia and resorption of the mandible [39]. Microstomia can have a profound negative impact on the relationships of patients with others [40], leads to functional debilitating sequels such as drooling and difficulty on chewing and speaking, and may also interfere with normal oral hygiene and dental treatment as it has been associated with dental caries [41].

In addition, hand involvement is frequently encountered in patients with SSc and cause severe hands disability. Digital ulcerations, Raynaud's phenomenon, fibrosis of skin and tendons lead to claw-type deformities with difficulties in hands function, helplessness in performing daily life occupations and, as consequence, to high level of anxiety [21,42].

Preoccupation about appearance and its importance for meeting new people, making social connections, and developing intimate relationships is often more pronounced earlier in life.

Previous research on patients with changes to their appearance due to illness and injury has found that older age is generally associated with less distress related to body image [43,44]. Thus, younger patients may be at a greater risk of body image distress related to their physical appearance leading to psychological disorders.

Modifications on personal appearance are a strong stressor that may predispose to high levels of anxiety in the subject who experiences it and may lead to decreased self-esteem.

Malcarne et al. [45] investigate the importance of self-esteem related to physical appearance. Their results show no differences in negative emotionality in the different subgroups of SSc (diffuse and limited) and a significant association between self-esteem related to physical appearance and negative emotionality. Thus, the subjects with SSc expressing low self-esteem on physical appearance had higher levels of negative emotionality. Another study on the appearance of SSc found the anxiety strongly correlated with self-esteem due to physical modifications [23]. In addition, in women with SSc, self-esteem pertaining to appearance was even lower than in burn victims and related to depressive and anxious symptoms [46].

Anxiety was also related with social support. Previous studies about the relationship between social support and anxiety had contradictory results. While some works indicated that individuals with less perceived social support scores reported higher levels of anxiety [47,48], other surveys did not find any correlation between social support and anxiety [49] or found a negative effect of social support [50]. Data of our previous researches show that higher level of social support lead to increasing anxiety symptoms [28]. These data suggest that some aspects of the social support (like excessive support of family or friends) may increase level of anxiety [50].

Other important predictor of anxiety, and in turn reduced HRQoL in SSc, is sexual dysfunction [24,51-54]. Sexual health difficulties in SSc include fatigue, joint pain, muscle weakness, Raynaud's phenomenon, shrinking of the mouth, reflux, vomiting, chronic diarrhea, skin tightening around the vaginal introitus and vaginal dryness, changes of the skin around the breast in women and erectile dysfunction in men [55-57]. These SSc-related features, leading to limitation of physical ability, negative body image and low self esteem, can reduce desire, satisfaction and as consequence lead to avoidance of sexual relationship and increased anxiety.

Moreover, many medications used to treat SSc symptoms, including diuretics, vasoactive therapies and antidepressants, are known to impact sexual desire and sexual functioning [57].

According to WHO, sexual health is "a state of physical, emotional, mental and social well-being in relation to sexuality" [58]. Sexual function is important for individuals with and without chronic disease but it is still largely ignored in daily practice of health providers and rarely included in rheumatic patients' assessment in research studies [59]. Thus, rheumatologist and general practitioners should openly discuss with SSc patients about sexual health, paying attention to both psychological and physical problems, in order to help them finding strategies to adapt to a long-lasting course disease and consulting with specialists when appropriate.

Fatigue, recognized as another important predictor of psychological distress in SSc, may be related to somatic symptoms or to abnormalities in neurotransmitter pathways within the central nervous system. Thus, fatigue, by diminishing mobility, independence and ability to engage social activities, could lead to anxiety and affect HRQoL in SSc patients [60].

Therapeutic interventions in SSc patients with fatigue involve a multifaceted approach. Nevertheless, symptomatic treatments of potential causes in peripheral fatigue are not enough; thus, patients need to be counselled about tailoring daily activities according to their energy levels [61]. Restructuring priorities of daily living can prevent unnecessary stress, which may exacerbate fatigue. Aerobic exercise programs, showed to be beneficial in patients with chronic fatigue syndrome [62], should be recommended if the patient is physically capable.

SSc patients have not only to cope with physical impacts of the disease but also with the emotional and social consequences of living with this condition.

Due to differences in assessing instruments and sampling bias, only few researches assessed prevalence of anxiety in SSc, reporting the wide range of results. Thus, twenty-seven (64%) patients met criteria for minor anxiety and eight (19%) for major anxiety in the study used in assessment Hamilton Anxiety Rating Scale [26]. Although, there are samples with higher percentages, around 80% (by Zung's anxiety self-assessment scale) [33]. In other cohort the prevalence of current and life time specific anxiety disorders was 49% and 64%, respectively, as measured by the MINI (Mini International Psychiatric Interview) [63].

In the majority of comorbid cases, in other patients groups, anxiety disorders are primary to depression and patients with anxiety are at higher risk to develop major depression [64]. Furthermore, depressive patients with comorbid anxiety symptoms have a more difficult course, with a decreased or a delayed response to treatment [65]. Consistently, our data show that in SSC depressive patients with comorbid anxiety present significantly higher level of depressive symptoms, than those without anxiety [66].

OUR RESEARCHES ON ANXIETY DISORDERS IN SSC

Recently we evaluated the anxiety impact on HRQoL in three subsequent researches.

In the first study, we assessed the prevalence of depression and anxiety in SSc and their association with district and global disability and psychological variables in 119 SSc patients. Hospital Anxiety Depression Scale (**HADS**) evaluated depressive and anxiety disorders with a cut off score ≥ 8 , indicating clinical cases in both subscales (HADS-A and HADS-D) [66].

Patients were also assessed by Rosenberg Self Esteem Questionnaire (**RSES**), Functional Assessment of Chronic Illness Therapy (**FACIT**) scale, Health Assessment Questionnaire (**HAQ**), Hand Mobility in Scleroderma scale (**HAMIS**), Cochin Hand Function Disability Scale (**CHFDS**), Finger To Palm (**FTP**) distance, hand opening, Mouth Handicap in SSc scale (**MHISS**), mouth opening.

Both rates of depression and anxiety in our group were 36% and 13% respectively while 23% had both depression and anxiety. Depressive patients with comorbid anxiety had significantly higher HADS-D score than patients with depression only. Both depressive and anxiety symptoms were significantly and positively correlated with global disability, hands and mouth disability, fatigue, self-esteem and avoidance strategy in coping and anxiety only with also social support.

Hierarchical multiple regression analyses revealed that fatigue, firstly, self-esteem and mouth disability were independent related to depression, explaining 50% of the variance. Self-esteem, and, secondarily, avoidance strategy, social support, fatigue, and mouth disability were independently associated with anxiety, together explaining 41% of the variance.

Thus, our result confirm high level of psychological distress in SSc. The fact that in the case of comorbid anxiety, depressive patients presented higher level of depression, indicate that screening for both depression and anxiety is useful in assessment of SSc patients.

Moreover, although hands and face involvement in SSc patients may lead to functional limitations and potentially affect HRQoL, there are few studies assessing the relationship between district disability and HRQoL [67-69].

In our second work, we assessed association of HRQoL with hands disability evaluated by HAMIS, CHFDS, fist closure and hand opening measures, and face disability evaluated by MHISS and mouth opening measure [21].

Although, by bivariate analysis, Summary Physical Index (SPI) of SF-36 was significantly negatively correlated with MHISS, CHFDS, HAMIS and positively with mouth and hand opening and Summary Mental Index (**SMI**) was negatively correlated with MHISS. When multivariate regression analysis was performed, these variables did not explain large amount of the variance in SPI and SMI of SF-36 (22% and 4% respectively). These results suggested that other factors (like psychological symptoms) might contribute together with disease related symptoms to the worse HRQoL in SSc.

Therefore, in a third study, we included district disability and anxiety along with those other factors (such as disease subset, disease duration, fatigue, self-esteem, coping styles, global disability and depression) already assessed in the above previous investigations, in order to identify significant predictors of HRQoL in SSc patients [28].

One hundred and nineteen SSc patients were administered for HRQoL by Short Form-36 health survey, for anxiety and depression by HADS and for disability by HAQ. Patients were also assessed for psychological symptoms by RSES and Coping Orientation to Problems Experienced-New Italian Version (COPE-NIV), hand disability by HAMIS, CHFDS, fist closure and hand opening, face disability by MHISS, mouth opening and fatigue by FACIT scale.

We created a HRQoL model for SSc patients, which assumes that disease characteristics and psychological symptoms might influence HRQoL either directly or indirectly, acting on global

disability, depression and anxiety. Such influence has been assessed on both the mental and physical dimension.

In the final Physical and Mental HRQol Models only the most contributing factors were present. In multivariate regression analysis, the significant predictors of SPI of SF-36 were fatigue ($p<0.001$) and hands disability (HAMIS) ($p<0.001$), accounting for 43,7% of the variance in SPI. The significant predictors of SMI of SF-36 were fatigue ($p=0.001$), avoidance strategy coping style ($p=0.016$) and anxiety ($p<0.001$), accounting for 52,8% of the variance in SMI. Independent predictors of anxiety (mouth disability, self- esteem and social support) were included in the final model for Mental component of Quality of life (SMI) as factors which may affect SMI of SF-36 indirectly (by increasing of anxiety).

In the final model of SPI of SF-36 (“Physical HRQol Model”) the significant predictors of poorer Physical HRQol were hands disability and fatigue.

In the final model predicting SMI of SF-36 (“Mental HRQol Model”) the factors contributed significantly to the predicting of SMI of SF-36 were anxiety, fatigue and avoidance strategy. Fatigue and avoidance strategy affected Mental Qol both directly and through their interaction with anxiety while mouth disability, self- esteem and social support affected Mental HRQol indirectly by increasing anxiety (Fig.1).

The large amount of the variance in SPI and SMI of SF-36 (43,7% and 49,9% respectively), suggesting that, by these models, some of the most important determinants to HRQol in SSc patients were identified.

Our results underline the importance of district disability and psychological factors in HRQol of SSc and highlight the role of anxiety as one of most important predictor of HRQol in this group of patients.

Some interventions may be useful to reduce psychological distress in SSc.

Cognitive-behavioral therapy for social anxiety [70] and social skills training programs should be recommended also in SSc as strategies to reduce social avoidance and to increase self-esteem in social setting and HRQol [71].

Among non-pharmacological interventions, mind-body therapies including Mindfull Meditation, Ressèguier Method, Qi Gong and Tai Chi, demonstrated their efficacy and safety in rheumatic diseases like Rheumatoid

Arthritis, Fibromyalgia Syndrome, Ankylosing Spondylitis, by reducing disability, pain and psychological distress of SSc patients [72-74].

In addition, the attentive clinimetric and clinic evaluation of fatigue, hands and face disability, and screening for psychological symptoms, might contribute to an improvement in health outcomes in SSc patients.

HADS is a reliable and valid test to screen for depression and anxiety, easy to be used and scored, able to exclude somatic items [75], and potentially useful in everyday practice to assess SSc subjects. Patients resulting positive for the screening should be addressed to a specialist, undergo a more structured clinical interview for further assessment, and be timely treated by psycho-educational or pharmacological interventions in order to improve HRQoL.

SSc is a complex, multifaceted disease with multiple symptom manifestations and health care needs that vary across and within patients over time. Routine screening for anxiety symptoms, potentially followed by confirmation of the diagnosis by a psychiatrist, may help to create most effective individual, interdisciplinary care programs, for optimal management of patients with SSc.

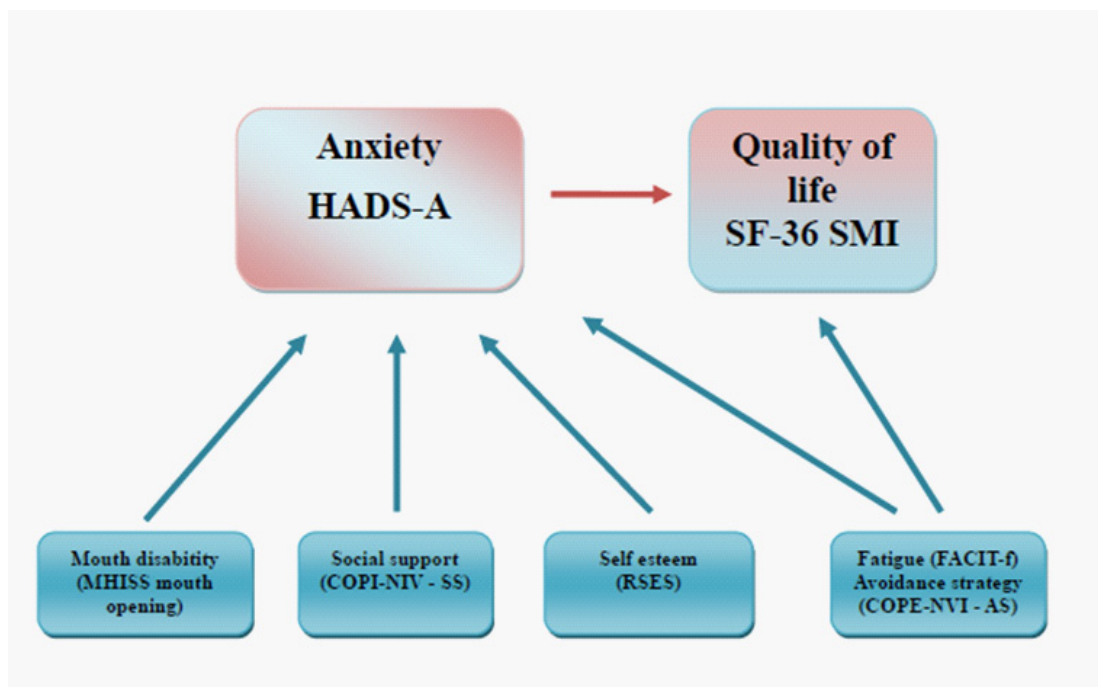


Figure 1: Final Mental HRQoL model.

MHISS = Mouth Handicap in Systemic Sclerosis Scale; HADS-A = HADS anxiety subscale; SF-36 SMI= Summary mental index of Short Form 36; RSES = Rosenberg Self-Esteem Scale; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue Scale; COPE NIV = Coping Orientation to Problems Experienced-New Italian Version.

References

1. Wigley FM, Hummers LK. Clinical features of systemic sclerosis. In: Hochberg M, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. *J Rheumatology*. 3rd edn. Elsevier. 2006.
2. Nguyen C, Be´rezne´ A, Baubert T, Mestre-Stanislas C, Rannou F, et al. Association of Gender with Clinical Expression, Quality of Life, Disability, and Depression and Anxiety in Patients with Systemic Sclerosis. *PLoS ONE*. 2011; 6: e17551.
3. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol*. 1988; 15: 202-205.
4. Korn JH. Scleroderma: a treatable disease. *Cleve Clin J Med*. 2003; 70: 954, 956, 958 passim.
5. Medsger TA. Natural history of systemic sclerosis and the assessment of disease activity, severity, functional status, and psychologic well-being. *Rheum Dis Clin North Am*. 2003; 29: 255-273.
6. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. *Soc Sci Med*. 1995; 41: 1403-1409.
7. Mura G, Bhat KM, Pisano A, Licci G, Carta M. Psychiatric Symptoms and Quality of Life in Systemic Sclerosis. *Clinical Practice & Epidemiology in Mental Health*. 2012; 8: 30-35.
8. Guillemin F. Functional disability and quality-of-life assessment in clinical practice. *Rheumatology (Oxford)*. 2000; 39: 17-23.
9. Apolone G, Cifani S, Mosconi P. Questionario sullo stato di salute SF-36. Traduzione e validazione della versione italiana: risultati del progetto IHRQoLA. *Medic*. 1997; 2: 86-89.
10. Hyphantis TN, Tsifetaki N, Pappa C, Voulgari PV, Sifaka V, et al. Clinical features and personality traits associated with psychological distress in systemic sclerosis patients *Journal of Psychosomatic Research*. 2007; 62: 47-56.
11. Danieli E, Airo` P, Bettoni L, Cinquini M, Antonioni CM. Health-related quality of life measured by the Short Form 36 (SF-36) in systemic sclerosis: correlations with indexes of disease activity and severity, disability, and depressive symptoms. *Clin Rheumatol*. 2005; 24: 48-54.
12. Johnson SR, Glaman DD, Schentag CT, Lee P. Quality of life and functional status in systemic sclerosis compared to other rheumatic diseases. *J Rheumatol*. 2006; 33: 1117-1122.
13. Georges C, Chassany O, Toledano C, Mouthon L, Tiev K. Impact of pain in health related quality of life of patients with systemic sclerosis. *Rheumatology (Oxford)*. 2006; 45: 1298-1302.
14. Mller H, Rehberger P, Gnther C, Schmitt J. Determinants of disability, quality of life and depression in dermatological patients with systemic scleroderma. *Br J Dermatol*. 2012; 166: 343-353.
15. Hudson M, Steele R, Lu Y, Thombs BD, Panopalis P. Clinical correlates of self-reported physical health status in systemic sclerosis. *J Rheumatol*. 2009; 36: 1226-1229.
16. Hudson M, Thombs BD, Steele R, Watterson R, Taillefer S, et al. Clinical Correlates of Quality of Life in Systemic Sclerosis Measured With the World Health Organization Disability Assessment Schedule II. *Arthritis Care & Research*. 2008; 59: 279-284.
17. Franck-Larsson K, Graf W, Rnnblom A. Lower gastrointestinal symptoms and quality of life in patients with systemic sclerosis: a population-based study. *Eur J Gastroenterol Hepatol*. 2009; 21: 176-182.
18. Arat S, Verschueren P, De Langhe E, Smith V, Vanthuyne M. The association of illness perceptions with physical and mental health in systemic sclerosis patients: an exploratory study. *Musculoskeletal Care*. 2012; 10: 18-28.
19. Iudici M, Cuomo G, Vettori S, Avellino M, Valentini G. Quality of life as measured by the short-form 36 (SF-36) questionnaire in patients with early systemic sclerosis and undifferentiated connective tissue disease. *Health Qual Life Outcomes*. 2013; 11: 23.
20. Mouthon L, Mestre-Stanislas C, Brezne´ A, Rannou F, Guilpain P. Impact of digital ulcers on disability and health-related quality of life in systemic sclerosis. *Ann Rheum Dis*. 2010; 69: 214-217.
21. Maddali-Bongi S, Del Rosso A, Mikhaylova S, Francini B, Branchi A. Impact of hand and face disabilities on global disability and quality of life in systemic sclerosis patients. *Clin Exp Rheumatol*. 2014; 32: S-15-20.
22. Leon L, Abasolo L, Redondo M, Perez-Nieto MA, Rodriguez-Rodriguez L. Negative effect in systemic sclerosis. *Rheumatol Int*. 2014; 34: 597-604.
23. Van Lankveld WGJM, Vonk MC, Teunissen H and van den Hoogen FHJ. Appearance self-esteem in systemic sclerosis-subjective experience of skin deformity and its relationship with physician-assessed skin involvement, disease status and psychological variables. *Rheumatology*. 2007; 46: 872-876.
24. Maddali Bongi S, Del Rosso A, Mikhaylova S, Baccini M, Matucci Cerinic M. Sexual function in Italian women with systemic sclerosis is affected by disease-related and psychological concerns. *J Rheumatol*. 2013; 40: 1697-1705.

25. Thombs BD, Taillefer SS, Hudson M, Baron M. Depression in patients with systemic sclerosis: A systematic review of the evidence. *Arthritis Rheum.* 2007; 57: 1089-1097.
26. Legendre C, Allanore Y, Ferrand I, Kahan A. Evaluation of depression and anxiety in patients with systemic sclerosis. *Joint Bone Spine.* 2005; 72: 408-411.
27. Hyphantis TN, Tsifetaki N, Sifaka V, Voulgari PV, Pappa C. The impact of psychological functioning upon systemic sclerosis patients' quality of life. *Semin Arthritis Rheum.* 2007; 37: 81-92.
28. Maddali Bongli S, Del Rosso A, Mikhaylova S, Rasero L, Amanzi L. District disability, fatigue and mood disorders as determinants of health related quality of life in patients with systemic sclerosis. *Joint Bone Spine.* 2015; 82: 67-68.
29. Roca RP, Wigley FM, White B. Depressive symptoms associated with scleroderma. *Arthritis Rheum.* 1996; 39: 1035-1040.
30. Altman RD, Medsger TA, Bloch DA, Michel BA. Predictors of survival in systemic sclerosis (scleroderma). *Arthritis Rheum.* 1991; 34: 403-413.
31. Harris EC, Barraclough BM. Suicide as an outcome for medical disorders. *Medicine (Baltimore).* 1994; 73: 281-296.
32. Evans DL, Charney DS, Lewis L, Golden RN, Gorman JM. Mood disorders in the medically ill: scientific review and recommendations. *Biol Psychiatry.* 2005; 58: 175-189.
33. Ostojic P, Zivojinovic S, Reza T, Damjanov N. Symptoms of depression and anxiety in Serbian patients with systemic sclerosis: impact of disease severity and socioeconomic factors. *Mod Rheumatol.* 2010; 20: 353-357.
34. Cully JA, Graham DP, Stanley MA, Ferguson CJ, Sharafkhaneh A. Quality of life in patients with chronic obstructive pulmonary disease and comorbid anxiety or depression. *Psychosomatics.* 2006; 47: 312-319.
35. Birmelè B, Le Gall A, Sautenet B, Aguerre C, Camus V. Clinical, sociodemographic, and psychological correlates of health-related quality of life in chronic hemodialysis patients. *Psychosomatics.* 2012; 53: 30-37.
36. Ozcetin A, Ataoglu S, Kocer E, Yazici S, Yildiz O. Effects of depression and anxiety on quality of life of patients with rheumatoid arthritis, knee osteoarthritis and fibromyalgia syndrome. *West Indian Med J.* 2007; 56: 122-129.
37. Kwakkenbos L, Willems LM, van den Hoogen FH, van Lankveld WG, Beenackers H. Cognitive-behavioural therapy targeting fear of progression in an interdisciplinary care program: a case study in systemic sclerosis. *J Clin Psychol Med Settings.* 2014; 21: 297-312.
38. Richards H, Herrick A, Griffin K, Gwilliam P, Fortune D. Psychological adjustment to systemic sclerosis: exploring the association of disease factors, functional ability, and body related attitudes and fear of negative evaluation. *Psychol Health Med.* 2004; 9: 29-39.
39. Doucet JC, Morrison AD. Bilateral mandibular condylitis from systemic sclerosis: case report of surgical correction with bilateral total temporomandibular joint replacement. *Craniomaxillofac Trauma Reconstr.* 2011; 4: 11-18.
40. Benrud-Larson LM, Heinberg LJ, Boling C, Reed J, White B. Body image dissatisfaction among women with scleroderma: extent and relationship to psychosocial function. *Health Psychol.* 2003; 22: 130-139.
41. Yuen HK, Marlow NM, Reed SG, Mahoney S, Summerlin LM. Effect of orofacial exercises on oral aperture in adults with systemic sclerosis. *Disabil Rehabil.* 2012; 34: 84-89.
42. Merkel PA, Herlyn K, Martin RW, Anderson JJ, Mayes MD. Measuring disease activity and functional status in patients with scleroderma and Raynaud's phenomenon. *Arthritis Rheum.* 2002; 46: 2410-2420.
43. Fauerbach JA, Lawrence J, Haythornthwaite J, McGuire M, Munster A. Preinjury psychiatric illness and postinjury adjustment in adult burn survivors. *Psychosomatics.* 1996; 37: 547-555.
44. Jewett LR, Hudson M, Malcarne VL, Baron M, Thombs BD, et al. Sociodemographic and disease correlates of body image distress among patients with systemic sclerosis. *PLoS One.* 2012; 7: e33281.
45. Malcarne VL, Hansdottir I, Greenbergs HL, Clements PJ, Weisman MH. Appearance self-esteem in systemic sclerosis. *Cogn Ther Res.* 1999; 23: 197-208.
46. White AC. Psychiatric study of patients with severe burn injuries. *Br Med J (Clin Res Ed).* 1982; 284: 465-467.
47. Haemmerlie FM, Montgomery RL, Melchers J. Social support, perceptions of attractiveness, weight, and the CPI in socially anxious males and females. *J Clin Psychol.* 1988; 44: 435-441.
48. Caldwell R and Reinhart M. The relationship of personality to individual differences in the use of type and source of social support. *Journal of Social and Clinical Psychology.* 1988; 6: 140-146.
49. Eldeleklioglu J. The relationship between the perceived social support and the level of depression and anxiety in university students. *Kuram ve Uygulamada Egitim Bilimleri.* 2006; 6: 742-752.
50. Bowers CA, Gesten EL. Social support as a buffer of anxiety: an experimental analogue. *Am J Community Psychol.* 1986; 14: 447-451.

51. Impens AJ, Rothman J, Schioppa E, Cole JC, Dang J. Sexual activity and functioning in female scleroderma patients. *Clin Exp Rheumatol*. 2009; 27: 38-43.
52. Schouffoer AA, van der Marel J, Ter Kuile MM, Weijnen PT, Voskuyl A. Impaired sexual function in women with systemic sclerosis: a cross-sectional study. *Arthritis Rheum*. 2009; 61: 1601-1608.
53. Tristano AG. The impact of rheumatic diseases on sexual function. *Rheumatol Int*. 2009; 29: 853-860.
54. Knafo R, Thombs BD, Jewett LR, Hudson M, Wigley F, et al. (Not) talking about sex: a systematic comparison of sexual impairment in women with systemic sclerosis and other chronic disease samples. *Rheumatology (Oxford)*. 2009; 48: 1300-1303.
55. Saad SC, Pietrzykowski JE, Lewis SS, Stepien AM, Latham AV, et al. Vaginal lubrication in women with scleroderma and Sjogren's syndrome. *Sex Disabil*. 1999; 17:103-113.
56. Bhadauria S, Moser DK, Clements PJ, Singh RR, Lachenbruch PA. Genital tract abnormalities and female sexual function impairment in systemic sclerosis. *Am J Obstet Gynecol*. 1995; 172: 580-587.
57. Hong P1, Pope JE, Ouimet JM, Rullan E, Seibold JR. Erectile dysfunction associated with scleroderma: a case-control study of men with scleroderma and rheumatoid arthritis. *J Rheumatol*. 2004; 31: 508-513.
58. Organization WH: Defining sexual health. Report of a technical consultation on sexual health, 28-31 January 2002. Sexual health document series Geneva: World Health Organisation. 2006; 35.
59. Nusbaum MR, Hamilton C, Lenahan P. Chronic illness and sexual functioning. *Am Fam Physician*. 2003; 67: 347-354.
60. Thombs BD, Bassel M, McGuire L, Smith MT, Hudson M. A systematic comparison of fatigue levels in systemic sclerosis with general population, cancer and rheumatic disease samples. *Rheumatology (Oxford)*. 2008; 47: 1559-1563.
61. Cook NF, Boore JR. Managing patients suffering from acute and chronic fatigue. *Br J Nurs*. 1997; 6: 811-815.
62. Wearden AJ, Morris RK, Mullis R, Strickland PL, Pearson DJ, et al. Randomised, double blind, placebo controlled treatment trial of fluoxetine and graded exercise for chronic fatigue syndrome. *Br J Psychiatry*. 1998; 172: 485-90.
63. Baubet T, Ranque B, Taïeb O, Bérezné A, Bricou O. Mood and anxiety disorders in systemic sclerosis patients. *Presse Med*. 2011; 40: e111-119.
64. Gum AM, Cheavens JS. Psychiatric comorbidity and depression in older adults. *Curr Psychiatry Rep*. 2008; 10: 23-29.
65. Wittchen HU, Kessler RC, Pfister H, Höfler M, Lieb R. Why do people with anxiety disorders become depressed? A prospective-longitudinal community study *Acta Psychiatrica Scandinavica*. 2000; 102: 14-23.
66. Del Rosso A, Mikhaylova S, Baccini M, Lupi I, Matucci Cerinic M, et al. In Systemic Sclerosis, Anxiety and Depression Assessed by Hospital Anxiety Depression Scale Are Independently Associated with Disability and Psychological Factors. *BioMed Research International*. 2013: 507493.
67. Albiilia JB, Lam DK, Blanas N, Clokie CM, Sándor GK. Small mouths.. Big problems? A review of scleroderma and its oral health implications. *J Can Dent Assoc*. 2007; 73: 831-836.
68. Shah AA, Wigley FM. Often forgotten manifestations of systemic sclerosis. *Rheum Dis Clin North Am*. 2008; 34: 221-238.
69. Mouthon L, Mestre-Stanislas C, Bérezné A, Rannou F, Guilpain P. Impact of digital ulcers on disability and health-related quality of life in systemic sclerosis. *Ann Rheum Dis*. 2010; 69: 214-217.
70. Rumsey N, Harcourt D. Body image and disfigurement: issues and interventions. *Body Image*. 2004; 1: 83-97.
71. Riemsma RP, Kirwan JR, Taal E, Rasker JJ. Patient education for adults with rheumatoid arthritis. *Cochrane Database Syst Rev*. 2003; CD003688.
72. Lee EN, Kim YH, Chung WT, Lee MS. Tai chi for disease activity and flexibility in patients with ankylosing spondylitis--a controlled clinical trial. *Evid Based Complement Alternat Med*. 2008; 5: 457-462.
73. Del Rosso A, Maddali-Bongi S. Mind body therapies in rehabilitation of patients with rheumatic diseases. *Complement Ther Clin Pract*. 2016; 22: 80-86.
74. Maddali Bongi S, Del Rosso A, De Felice C, Landi G, F Galluccio, et al. Resseguier Method as a novel tool to improve quality of life and pain in Systemic Sclerosis patients: preliminary results. 1st Systemic Sclerosis World Congress, Florence, Italy, 11-13 February 2010. *Clin Exp Rheum*. 2010; 28:182.
75. Covic T, Cumming SR, Pallant JF, Manolios N, Emery P. Depression and anxiety in patients with rheumatoid arthritis: prevalence rates based on a comparison of the Depression, Anxiety and Stress Scale (DASS) and the hospital, Anxiety and Depression Scale (HADS). *BMC Psychiatry*. 2012; 12: 6.