Review

Fatigue in systemic sclerosis: a systematic review

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ABSTRACT

Objective. *To systematically review fatigue in systemic sclerosis (SSc) in terms of prevalence, features, correlates, predictors and management.*

Methods. *We performed a literature search in PubMed (Medline), EBSCO and COCHRANE databases up to June 2017 selecting articles regarding fatigue in SSc. The articles finally selected fulfilled the following eligibility criteria: written in English, referred to fatigue in SSc, reporting original data, including validated questionnaires measuring fatigue.*

Results. *A total of 43 records were included. Fatigue in SSc has a prevalence similar to that of other rheumatic diseases and is one of the most prevalent and debilitating symptom experienced by SSc patients. Fatigue leads to a significant impairment of quality of life, parenting, household and work ability. Fatigue is associated with psychosocial factors (depression, pain and sleep disorders), sociodemographic factors and clinical manifestations of the disease (pulmonary and gastrointestinal involvement). Indeed, the relationship with scores of disease activity is uncertain. Pharmacological therapeutic approaches were broadly ineffective in reducing fatigue. More encouraging results concern physical activity, complementary and alternative medicine.*

Conclusion. *Adequate management of fatigue could lead to a marked improvement of the patient's quality of life, also contributing to reduction in SSc indirect costs.*

Introduction

Systemic sclerosis (SSc) is a multisystemic autoimmune disease in which autoantibody production, microvascular injury and fibroblast dysfunction lead to extensive fibrosis and vascular damage. As a consequence, SSc is frequently associated to multiple organ damage or failure (1). Recent studies report a significant improvement in survival rates of patients with SSc in the last decades. An Italian large cohort study reported a dramatic progression of survival rates at 10 years from 54% median survival (1935-74) to 80.7% (2000-2011) (2). As demonstrated by data from the European Scleroderma Trials and Research group (EUSTAR) database, more than half of the deaths are direct consequence of SSc, such as pulmonary fibrosis, pulmonary arterial hypertension and cardiac causes (3). In recent years several studies focused on some aspects of the disease, once considered secondary, such as quality of life (4), pain (5), depression (6), sexual impairment (7), sleeping disorders (8) and psychosocial disorders related to body image (9). Several authors have also highlighted the negative influence of SSc on local and global disability (10) with consequent impairment of work and home productivity (11, 12). Fatigue, defined as an abnormal bodily tiredness, disproportionate to activity and not relieved by rest, represents an indefinite and controversial issue within SSc, often not adequately assessed in daily clinical practice.

Methods

Literature search

We performed up to June 2017 a literature search in PubMed (Medline), EBSCO and COCHRANE databases using the following MeSH terms: ("scleroderma, systemic"[MeSH Terms] OR ("scleroderma"[All Fields] AND "systemic"[All Fields]) OR "systemic scleroderma"[All Fields] OR ("scleroderma"[All Fields] AND "systemic"[All Fields]) OR "scleroderma, systemic"[All Fields]) AND ("fatigue"[MeSH Terms] OR "fatigue"[All Fields]). We also performed the search using the following terms: Systemic Sclerosis AND fatigue ("scleroderma, systemic"[MeSH Terms] OR ("scleroderma"[All

Fields] AND "systemic"[All Fields]) OR "systemic scleroderma"[All Fields] OR ("systemic"[All Fields] AND "sclerosis"[All Fields]) OR "systemic sclerosis"[All Fields]) AND ("fatigue"[MeSH Terms] OR "fatigue"[All Fields]) (Fig. 1).

Study selection

Study selection was performed by two authors (FB and DM), working independently. Duplicates were removed and all titles and abstracts resulting from the search strategy were reviewed to identify eligible papers. Full texts of the remaining studies were assessed afterwards. The final articles selected all fulfilled the following eligibility criteria: written in English, referred to fatigue in SSc, reported original data, included validated questionnaires measuring fatigue. Articles not meeting inclusion criteria were excluded. The systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Fig. 1).

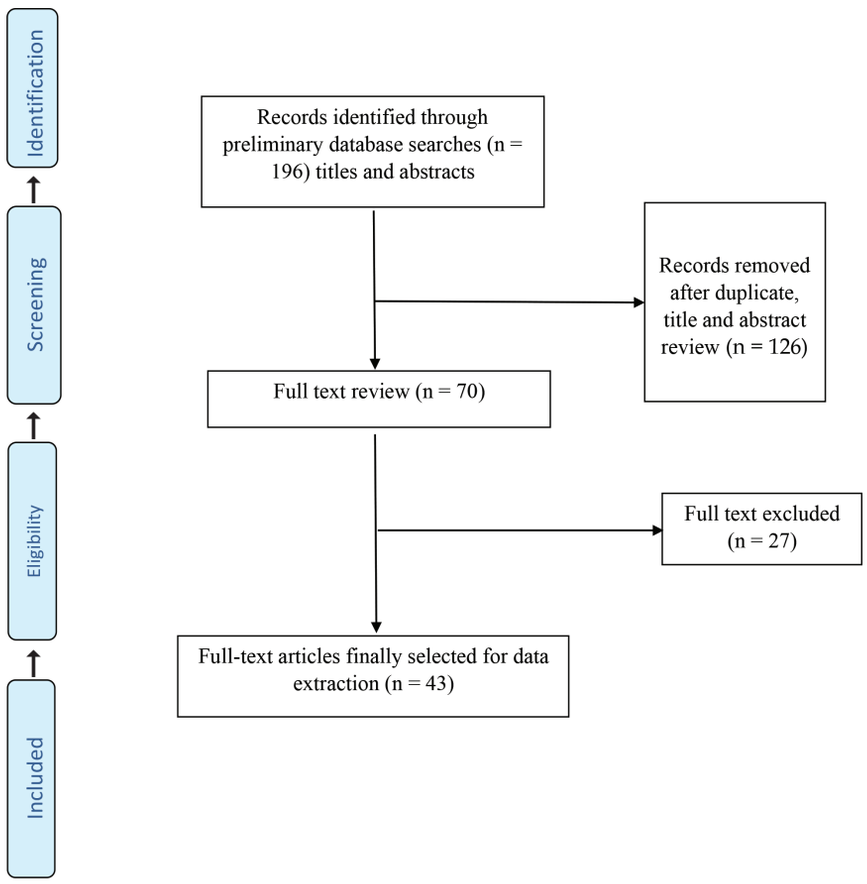

Fig. 1. Flow chart including numbers of studies identified, excluded and included in the review (PRISMA Flow Diagram).

Results

After selection, we included in this systematic review 43 full-text articles: 11 studies reported data on prevalence and features of fatigue in SSc patients (Table I), 31 studies reported data on its correlates and predictors (Table II) and 7 studies focused on therapeutic interventions (Table III); 6 studies reported data on both prevalence and correlates of fatigue.

Fatigue in systemic sclerosis: features and prevalence

Based on comparison between GFI scores of 106 SSc patients and different control groups from the systematic review, Thombs *et al*. showed that SSc patients have a prevalence of fatigue significantly higher than general population and cancer patients in remission, similar to patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS), systemic lupus erythematosus (SLE) and cancer in active treatment but significantly lower than cancer patients in palliative care (13). The same authors in a further study on a bigger sample of Canadian SSc patients, showed levels of fatigue significantly higher than general Canadian population (14).

Similarly, Poole *et al*., assessing parenting in SSc, demonstrated that SSc mothers are fatigued as SLE mothers (15).

A further study based on an international sample of 6120 patients, including 147 affected by SSc, focused on the prevalence of severe fatigue within different rheumatic diseases. With the exception of fibromyalgia (82%) and osteoarthritis (OA) (35%) SSc showed a prevalence of severe fatigue (48%) roughly similar to the other rheumatic diseases (16).

Nevertheless, in his sample of 63 Moroccan SSc patients, Jacoub *et al*. reported a significantly higher prevalence of severe fatigue. Indeed, 89% of SSc patients attested a VAS fatigue ≥50 mm (17).

van Lankveld *et al*. (9) identified fatigue as the main stressor of the disease, just followed by skin deformity. Also Sandqvist *et al*. (18), Sandusky *et al*. (19) and Bassell *et al*. (20) in their studies indicated fatigue as the most prevalent and debilitating symptom experienced by patients with SSc, whereas according to Richards *et al*. the most common symptom reported was stiff joints (79%), near followed by pain (75%) and fatigue (75%) (21).

Last, Sekhon *et al*. performed a longitudinal study assessing the minimally important difference (MID) of 109 scleroderma patient-reported outcomes, including disability, pain, fatigue, sleep and global health: mean VAS fatigue value at baseline was 46.28 and after two years worsened to 49.29 with a mean change much higher than the other items (22). Similarly, both Willems *et al*. and Asassi *et al*. did not find a significant change in fatigue levels over a 3-year-period of follow-up (23, 40).

Fatigue and quality of life

As widely demonstrated in the literature, fatigue leads to a significant im-

Table I. Prevalence and features of fatigue in SSc patients.

Author	Year	Type of study	Population	Measures	Prevalence or Value in SSc patients	Prevalence or Value in control group	Ref
Richards *et al*.	2003	Cross-sectional	-49 SSc patients; 33 lSSc 16 dSSc; -mean disease duration (MDD) 9 yrs -mean age 45	VAS	75% of patients experienced fatigue as symptom associated with SSc		[21]
Sandqvist *et al*.	2005	Cross-sectional	-36 SSc women -MDD 9 yrs -mean age 52	VAS	Fatigue was perceived as the second most dominant problem (VAS 74)		[18]
Van Lankveld *et al*.	2007	Cross-sectional	-123 SSc patients; 87 (71%) with lSSc -MDD 10.6 yrs -Mean age 54.3	VAS	fatigue was the symptom with the highest mean VAS scores (VAS fatigue 4.5)		[9]
Thombs *et al*.	2008	Trans-sectional with systematic review	-106 patients; 78 lcSSc; 28 dcSSC; -MDD 11.9 yrs -mean age 55.5 -two large population samples (2037 and 1082) -two samples of cancer patients in remission (98 and 818) -two samples of cancer patients in palliative care (229 and 130) -six studies with cancer patients in active treatment (640) -a sample of Systemic lupus erythematosus (SLE) patients (130), RA patients (490), AS patients (776)	General Fatigue Index (GFI)	Mean GFI in SSc patients was 13.3	-GFI of two large population samples was 8.7 and 9.6) -GFI of two samples of cancer patients in remission was 9.4 and 10.0 -GFI of two samples of cancer patients in palliative care was 16.8 and 17.0 -GFI of cancer patients in active treatment was 11.1–13.5 -GFI of patients with RA was 13.4, AS was 13.0 and SLE was 13.1.	[13]
Sandusky *et al*.	2009	Cross-sectional	-107 SSc patients -mean age 55	Multidimensional Assessment of Fatigue (MAF)	76% patients reported that they currently experienced fatigue		[19]
Thombs *et al*.	2009	Cross-sectional	-659 SSc patients; dcSSc 267 -MDD 8.2 yrs -mean age 55 -general Canadian population	SF-36 vitality subscale	The mean score of SF-36 vitality subscale of SSc patients was 45.6	The mean score of SF-36 vitality subscale of general Canadian population was 65.8	[14]
Sekhon *et al*.	2010	Longitudinal	-109 patients -MDD 9.1 yrs -mean age 56	VAS	The mean fatigue VAS baseline was 46.8; the mean fatigue VAS at follow-up (two years) was 49.29		[22]
Jacoub *et al*.	2012	Cross-sectional	-64 patients; 59 with lSSc and 5 with dSSc -mean age 49.5	VAS	89% patients showed VAS fatigue ≥50 mm		[17]
Poole *et al*.	2014	Cross-sectional	-23 SSc mothers with children 5 years of age and younger -MDD 5.3 yrs -mean age 35.5 -34 SLE mothers with children 5 years and younger -MDD 6.7 yrs -mean age 34.7 -52 SSc mothers with children from 6 to 18 years of age -MDD 5.8 yrs -mean age 42.9 -50 SLE mothers with children from 6 to 18 years of age -MDD 7 yrs -mean age 40	MAF	-The mean score of MAF in 23 SSc mothers with children 5 years of age and younger was 85.6 and not significantly different from SLE control group - The mean score of MAF in 52 SSc mothers with children 6 to 18 years of age was 76.6 and not significantly different from SLE control group	The mean score of MAF in 34 SLE mothers with children 5 years of age and younger was 90 - The mean score of MAF in 50 SLE mothers with children 6 to 18 years of age was 87.2	[15]
Overman *et al*.	2016	Cross-sectional	-6120 patients with rheumatic diseases; 88% female; mean age 47 -147 SSc patients	RAND (SF)-36 Vitality scale (a score of ≤35 was taken as representing severe fatigue)	Severe fatigue was reported in 48% SSc patients	Severe fatigue was reported in 82% Fibromyalgia patients, 41% RA patients, 52% SLE patients, 45% SA patients, 57% Sjögren Syndrome (SS) and Psoriatic arthritis (AP) patients and 35% Osteoarthritis(OA) patients	[16]
Willems *et al*.	2017	Longitudinal	-215 SSc patients; 75.1% lSSc -MDD 9.2 yrs	SF-36 vitality subscale	High fatigue levels were reported in 31% SSc patients subgroup; fatigue levels did not significantly modify over a 3-year-follow-up.		[23]

Table II. Correlates and predictors of fatigue in SSc patients.

Author	Year	Type of study	Population	Measures	Correlation or Predictor in SLC	Ref
Sandqvist *et al*.	2005	Cross-sectional	-36 SSc women -mean disease duration (MDD) 9 yrs -mean age 52 -40 healthy women -mean age 49	VAS	Fatigue was correlated with well-being assessed by Manchester Short Assessment of Quality of Life (MANSA)	[18]
Sandqvist *et al*.	2008	Cross-sectional	-44 lSSc women -MDD 8 yrs -mean age 52	VAS	Fatigue was correlated with ADL capacity and satisfaction with occupations	[24]
Sandqvist *et al*.	2008	Cross-sectional	-21 lSSc women working full time -MDD 6 yrs -15 lSSc women partial sick leave -MDD 9 yrs -8 lSSc women full-time sick leave/disability pension -MDD 9 yrs	VAS	Women who were on partial sick leave had significantly higher levels of fatigue (VAS=83) than women on full-time sick leave (VAS=71.5) and women working full-time (VAS=64.5).	[30]
Hudson *et al*.	2008	Cross-sectional	-337 SSc patients; dSSc 45.7%; -MDD 10.5 yrs	VAS and SF-36	Fatigue was correlated with HRQOL measured by WHODAS II score	[25]
Thombs *et al*.	2009	Cross-sectional	-659 SSc patients; dcSSc 267 -MDD 8.2 yrs - mean age 55	SF-36 vitality subscale	Fatigue was correlated with number of medical comorbidities, breathing problems, the number of gastrointestinal symptoms, current smoking, pain and depression. Breathing problems, the number of GI symptoms, comorbid health problems, physician-rated disease severity and smoking significantly predicted fatigue.	[14]
Hudson *et al*.	2009	Cross-sectional	-232 SSc working patients; dcSSc 42%; MDD 9 yrs; mean age 48.4 -133 SSc work disabled patients; dcSSc 59%; MDD 11 yrs; mean age 50.2	VAS	Fatigue was correlated with Work Disability (WD)	[32]
McNearney *et al*.	2009	Cross-sectional	-104 Caucasian SSc patients; 55% dcSSc -MDD 29.8 motnhs -mean age 51 -39 African American SSc patients; 62% dcSSc -MDD 33.6 months -mean age 49 -60 hispanic SSc patients; 62% dcSSc -MDD 35.2 months -mean age 48	FSS	In Caucasian Ssc patients fatigue was correlated with SF-36 PCS and sHAQ In Hispanic Ssc patients fatigue was correlated with SF-36 PCS	[27]
Sandusky *et al*.	2009	Cross-sectional	-107 SSc patients -mean age 55	MAF	Fatigue was correlated with pain, depressive symptoms, poor sleep quality, poorer physical function, smaller social network size and smaller social network diversity	[19]
Poole *et al*.	2009	Cross-sectional	-75 SSc patients with a child between birth and 18 years old; 21 patients with lSSc; 32 patients with dSSc; 22 patients unclassified -MDD 6.6 yrs -mean age 41	MAF	Fatigue was correlated with parenting	[35]
Milette *et al*.	2010	Cross-sectional	-566 patients; 169 with dSSc; 397 with lSSc -MDD 9.4 yrs	FACIT-F	Fatigue was correlated with depressive symptoms	[6]
Buck *et al*.	2010	Cross-sectional	-62 SSc patients; 30 with dSSc; 27 with lSSc; 5 were unclassified	MAF	Fatigue was correlated with self-efficacy	[37]
Sandqvist *et al*.	2010	Cross-sectional	-57 SSc patients; 47 with lSSc; 10 with dSSc -MDD 14 yrs -mean age 58	VAS	Fatigue was correlated with WD assessed by WAI (Work ability index)	[11]
Poole *et al*.	2011	Cross-sectional	-74 SSc mothers with children aged 18 or younger; 42 with dcSSc; 28 with lcSSc -MDD 5.8 yrs -mean age 40.9	MAF	Fatigue was correlated with parenting	[36]
Assassi *et al*.	2011	Longitudinal	-256 Ssc patients; 59% dsSSc -MDD 2.5 yrs - mean age 48.6 years	FSS	Ineffective coping skills, pain, Gastrointestinal at enrolment were independent predictors of higher longitudinal FSS scores. Baseline DLco % predicted a change in FSS scores over time.	[40]

Author	Year	Type of study	Population	Measures	Correlation or Predictor in SLC	Ref
Sharif *et al*.	2011	Longitudinal	-131 SSc patients -mean age 45.3 -MDD 2.41 yrs	FSS	Fatigue was a correlate and a predictor of WD	[31]
Kwakkenbos *et al*.	2011	Cross-sectional	-215 SSc patients; 158 patients with lSSc -MDD 9.2 yrs -mean age 56	"subjective experience of fatigue" subscale of the Checklist Individual Strength (CIS)	Fatigue was correlated with depressive symptoms	[38]
Frech *et al*.	2011	Cross-sectional	-180 SSc patients; 50.9 lSSc; 40.1 dSSc -MDD 7.5 yrs -mean age 51.1	FACIT F	Fatigue was correlated with sleep disorders	[8]
Jacoub *et al*.	2012	Cross-sectional	-64 patients; 59 with lSSc and 5 with dSSc -mean age 49.5	MAF, VAS	Fatigue was correlated with severe joint involvement, quality of life, pain intensity, low vital capacity, high level of ESR, and with functional disability.	[17]
Strickland *et al*.	2012	Cross-sectional	-68 Ssc patients; 49 with lcSSc; 19 with dcSSc -MDD 12.8 yrs -mean age 62.6	FACIT-F	Fatigue was correlated with HRQoL and disability; the absence of upper gastrointestinal involvement was associated with lower levels of fatigue	[26]
Singh *et al*.	2012	Cross-sectional	-162 SSc patients; 84 with lcSSc; 67 with dcSSc; -MDD 7.6 yrs -mean age 51.8	FACIT- F	Fatigue was a predictor of decrease household and work productivity	[12]
Del Rosso *et al*.	2013	Cross-sectional	-119 SSc patients; 74 with lSSc 45 with dSSc -MDD 13 yrs -mean age 59	FACIT F	Fatigue was correlated with anxiety and depression assessed by HADS	[39]
Sariyildiz *et al*.	2013	Cross-sectional	-48 SSc patients; 54% dcSSc; 45.5%; lcSSc -MDD 4.7 yrs -mean age 42.9 -42 healthy patients -mean age 44	VAS	Fatigue was correlated with sleep disturbances	[41]
Maddali Bongi *et al*.	2013	Cross-sectional	-46 Ssc women; 29 lcSSc; 17 dcSSc -MDD 9.85 yrs -mean age 56 -46 healty women -mean age 52	FACIT-F	Fatigue was not correlated with sexual dysfunction	[7]
Willems *et al*.	2013	Cross-sectional	-198 SSc patients; 129 with lcSSc; 61 with dcSSc -MDD 11.1 yrs - mean age 58.1	SF-36 vitality subscale	Lower levels of fatigue were associated with a higher number of disciplines contacted.	[29]
Maddali Bongi *et al*.	2015	Cross-sectional	-119 SSc patients -MDD 10.7 yrs -mean age 59	FACIT-F	Fatigue was identified as significant determinant of summary mental indexes (SMI) of SF-36.	[28]
Poole *et al*.	2015	Cross-sectional	-83 SSc patients; 36 wih lSSc; 51 with dSSc -MDD 9.5 yrs -mean age 53	VAS	Fatigue was correlated with participation in life situations and in household maintenance	[34]
Racine *et al*.	2016	Cross-sectional	-517 SSc patients; 26.9 % dcSSc -MDD 12.8 yrs -mean age 57.9	FACIT-F	Fatigue was correlated with pain and itch severity	[5]
Levis *et al*.	2016	Cross-sectional	-785 SSc patients; 44% dSSc -MDD 17.4 yrs -mean age 57.7 years	FACIT-F	Being age 40–49 less than postsecondary education, number of comorbidities and more severe muscle, gastrointestinal, lung, and disease severity were independently associated with more fatigue	[42]
Azar *et al*.	2017	Cross-sectional	-389 SSc patients exercising; -363 SSc patients not exercising;	29-item Patient Reported Outcomes Measurement Information System (PROMIS-29)	In bivariate analysis periodic exercise (mainly walking, on average 4.7 hours per week) was associated with less fatigue	[48]
Morrisroe *et al*.	2017	Cross-sectional	-476 SSc patients; 75.6% lSSc -MDD 9.1 yrs	VAS	Workers Productivity and Impairment Activity Index: Specific Health Problem (WPAI:SHP) was negatively correlated with fatigue	[33]
Willems *et al*.	2017	Longitudinal	-215 SSc patients; 75.1% lSSc -MDD 9.2 yrs	SF-36 vitality subscale	Higher fatigue levels were found in patients with female sex, lung involvement, less acceptance and coping	[23]

pairment of quality of life, even in SSc patients. By comparing different studies there is a wide variability concerning measurement indexes of quality of life (QoL).

In two consecutive studies on SSc women Sandqvist *et al*. firstly identified fatigue as one of the main factors negatively involved in well-being, assessed by Manchester Short Assessment of Quality of Life (MANSA), and satisfaction with daily occupation. (18, 24). Hudson *et al*. then showed that fatigue was a predictor and a correlate of World Health Organization Disability Assessment Schedule II (WHODAS II), a generic QoL instrument focused on functioning and disability (25). Stickland *et al*., assessing EuroQol-5Domain health questionnaire (EQ-5D™), found it to correlate with disability and fatigue (26).

According to McNearney *et al*., fatigue was correlated with Short Form (SF)-36 physical component summary (PCS) in 60 SSc Hispanic patients and with SF-36 PCS and Scleroderma Health Assessment Questionnaire (sHAQ) in 104 Caucasian patients (27) whereas Jacoub *et al*. demonstrated a strong association between fatigue and all domains of SF-36 in 64 Moroccan patients (17). Maddali Bongi *et al*. (28) identified fatigue, together with hand disability, as determinant of summary mental indexes (SMI) of SF-36. Nonetheless, according to the same author, fatigue was not found to affect sexual function in a sample of SSc italian women (7).

Finally, Willems *et al*. assessed health care utilisation in 198 Dutch SSc patients and showed that higher levels of fatigue were associated with fewer visits to medical specialists and health professionals (29).

Fatigue and employment

Work disability (WD) is a very current field of research in rheumatic diseases. It represents a problematic area even in SSc, closely related to impairment of activities of daily living (ADL) and household impairment. According to Sandqvist *et al*. fatigue is a significant contributor of work ability, assessed by Work Ability Index (WAI) and it is so perceived by SSc patients as a dominant problem in work activities (11). The same authors, in a previous study (30) focused on 44 women affected by SSc: women who were on partial sick leave showed significantly higher levels of fatigue (VAS=83) than women on full-time sick leave (VAS=71.5) and women working full-time (VAS=64.5). Fatigue was also identified as one the perceived symptoms with more negative influence on working ability. Later Sharif *et al*. showed that fatigue was a predictor of WD in 284 patients Genetics versus ENvironment In Scleroderma Outcome Study (GENISOS) (31). Hudson *et al*. then explored causes of WD in 643 patients from Canadian Scleroderma Research Group Registry founding fatigue as significant correlate (32). The validation of the Workers Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) achieved in 476 Australian patients corroborated the association between fatigue and WD (33).

In a further study Singh *et al*. analysed rates and correlates of productivity in 162 SSc patients: fatigue was a predictor of both work and household decreasing productivity (12).

In three different papers, Poole *et al*. showed that women affected by SSc with abnormal fatigue levels are impaired in household maintenance (34) and parenting (35, 36).

Buck *et al*. identified fatigue as a factor related to self-efficacy in 62 SSc patients. The author considered the perceived self-efficacy as the capacity to perform specific tasks and behaviours and to manage different aspects associated with arthritis (37).

Fatigue and depression

Several data support the hypothesis of the existence of a tight relation between fatigue and depression. Thombs *et al*. were the first to identify depression as a correlate and a predictor of fatigue in a cross-sectional, multicentre study of 659 SSc patients from the Canadian Scleroderma Research Group Registry (CSRG) (14). Sandusky *et al*. supported the association between fatigue and depression on 107 SSc patients (19). Milette *et al*. found a very strong correlation between fatigue and two different depression scales, the 9-item version of the Patient Health Questionnaire depression scale (PHQ-9) and the Center for Epidemiologic Studies Depression Scale (CES-D), validated on 566 SSc patients (6). The association between fatigue and depressive symptoms was confirmed by Kwakkenbos *et al*. in a cross-sectional study on 215 SSc patients (38). According to Del Rosso *et al*. fatigue was also correlated with both anxiety and depression symptoms assessed by Hospital Anxiety Depression Scale (HADS) on 119 SSc patients (39).

Fatigue, pain and sleep disorders

According to the few available data, fatigue and pain exert a reciprocal influence within SSc. First data on this association comes from Thombs *et al*. in a multicentre study previously reported (14). Either Jacoub *et al*. (17) and Assassi *et al*. (40) in their respective studies have clearly demonstrated that pain is one of the most relevant predictors of fatigue. Finally Racine *et al*. assessed pain and itch severity on 964 SSc patients from CSRG finding a strong correlation with fatigue (5).

Frech *et al*. (8) and Sariyildiz *et al*. (41) identified fatigue as a strong correlate of sleep disorders, together with depression and pain.

Correlates and predictors of fatigue

Few authors so far investigated correlates and predictors of fatigue in SSc population in a sufficient broad and comprehensive study.

Sandusky *et al*. (19) was the first to extensively investigate, in a dedicated study, prevalence and factors associated with fatigue. In a population of 107 SSc patients pain, depressive symptoms, poor sleep quality and physical function, smaller social network size and smaller social network diversity correlated with fatigue.

Assassi *et al*. (40) evaluated predictors of fatigue in a longitudinal cohort of 256 SSc patients. In a multivariable model anti-U1-RNP antibodies, gastrointestinal and joint involvement were independent predictors of fatigue. In the final model, ineffective coping skills, pain and gastrointestinal involvement

Table III. Management of fatigue in SSc patients.

Author	Year	Population	Type of intervention	Measures	Efficacy in treatment	Ref
Hunnicutt *et al*.	2008	-19 SSc patients complementary and alternative medicine (CAM) users; dSSc 47%; -mean age 54.2 -17 SSc patients non-CAM users; dSSc 33%; -mean age 48.7	Use of CAM, intended as herbal or nutriceutical therapy, acupuncture, transcutaneous electrical neural stimulation (TENS) and mind-body therapy (relaxation, meditative, imagery)	SF-36 vitality scale	Significant improvement of fatigue	[46]
Poole *et al*.	2013	-49 completers SSc patients -mean age 53.9 -mean disease duration (MDD) 6.9 yrs -13 non-completers Ssc patients -mean age 49.3 -MDD 7.4 yrs	mail-delivered self-management program, consisting of a workbook and exercise DVD, that provided information on medical aspects of the disease including fatigue management	MAF	No significant improvement in fatigue levels	[49]
Poole *et al*.	2014	-16 SSc patients; 37.5% diffuse SSc; 54.4% limited SSc -MDD 7.8 yrs -mean age 52.2	internet self-management program for systemic sclerosis on self-efficacy, health efficacy, and management of care, pain, fatigue, functional ability, and depression.	VAS	Significant decrease in the fatigue levels	[50]
Alexanderson *et al*.	2014	-4 SSc patients -mean age 66.5 -MDD 3.5 yrs	Eight-week intensive aerobic exercise corresponding to 15 on the Borg RPE scale (strenuous) and muscular endurance training three times/week	VAS	Almost significative reduction in VAS fatigue (p=0.056)	[47]
Iudici *et al*.	2016	-33 SSc patients discontinuing glucocorticoids (GCS) -15 SSc patients do not discontinuing GCS	Discontinuation of GCS in patients with inactive SSc	VAS	No significant difference in fatigue (assessed by VAS) between GC-need and GC-free groups	[44]
Khanna *et al*.	2016	-51 SSc patients tocilizumab group - MDD 17.6 months -mean age 51 -44 SSc patients placebo group -MDD 19.5 months -mean age 48	Administration of tocilizumab	FACIT F	No significant difference in fatigue levels between tocilizumab and placebo group	[43]
Antonelli *et al*.	2017	-10 clinical hypothyroid and 23 subclinical hypothyroid female SSc patients -mean age 54	4 months administration of L-thyroxine (L-T4) substitutive therapy	GFI	Significant improvement of fatigue levels	[45]

at enrolment were independent predictors of higher longitudinal FSS scores. Fatigue levels were almost stable over time whereas lower DLco levels was the only independent variable predicting a worsening of fatigue. Similar founding were reported by Willems *et al*. in a longitudinal cohort of SSc patients: fatigue was associated with lung involvement, female sex, lower coping and acceptance skills (23).

A further study was performed by Thombs *et al*. (14) on 659 patients from the CSRG. A higher number of comorbidities, breathing problems, smoking, gastrointestinal symptoms, pain and depression were all factors associated with higher levels of fatigue.

Fatigue was also assessed on a population of 64 Moroccan SSc patients and found to be correlated with severe joint involvement, QoL pain intensity, low vital capacity, high levels of erythrocyte sedimentation rate (ESR) and functional disability (17).

Levis *et al*. recently evaluated fatigue in comparison with sociodemographic and disease-related factors on a sample population of 785 SSc patients. Fatigue was therefore correlated with the following factors: being age 40–49, less than postsecondary education, number of comorbidities, disease severity, muscle, gastrointestinal and lung involvement (42).

Treatment of fatigue

Both pharmacological and non-pharmacological therapeutic strategies were adopted in the management of fatigue. As demonstrated by Khanna *et al*. in a randomised trial, tocilizumab was not effective in reducing fatigue in 51 SSc patients (43). Similarly, no differences on levels of fatigue were found in 33 patients with inactive SSc after glucocorticoids discontinuation (44). Administration of L-thyroxine (L-T4) substitutive therapy improved, but did not normalise, fatigue levels of a group of hypothyroid female SSc patients (45).

Hunnicutt *et al*. assessed the use of complementary and alternative medicine (CAM) therapies in 76 patients with early systemic sclerosis (SSc) from GENISOS cohort. CAM modalities included the use of various nutritional supplements, mind-body (such as yoga, meditation or biofeedback), acupuncture-related procedures or transcutaneous electrical nerve stimulation (TENS). After two years 19 SSc patients using CAM showed significantly higher scores of SF-36 domains physical component score, role-physical, bodily pain and vitality scores compared to non-CAM user group (46).

An almost significant improvement in levels of fatigue was indeed obtained in 4 SSc patients after an eight-week intensive aerobic exercise program accompanied by a muscular endurance training three times/week (47). In this regard, a recent cross-sectional study carried out on a large scleroderma population,

Table IV. Features and performance of different measures of fatigue (adapted from Hewlett *et al*.).

Measurement	Features	Performance
Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)	Measures physical, functional, emotional fatigue and impact on daily activities on a 5-point Likert-type scale (0 = not at all, 4 = very much)	Good reliability, validity and sensitivity to change
Fatigue Severity Scale (FSS)	Measures physical, social or cognitive effects of fatigue. 9 items with 7 options from "Strongly disagree" to "Strongly agree" (1–7).	Good reliability, validity and sensitivity to change.
Short form 36 (SF-36) vitality subscale	Measures energy and fatigue thought 6 response options ranging from "All of the time" to "None of the time."	Good reliability and sensitivity to change. Limited validity: only two items
Multi-dimensional Assessment of Fatigue (MAF)	Measures fatigue severity, distress, interference in activities of daily living, frequency and change. 16 items with 4 ordinal response options scored 1–4. 15 items provide a global score, Global Fatigue Index (GFI)	Good reliability and sensitivity to change. Limited validity: high levels of missing data often reported
Multi-dimensional Fatigue Inventory (MFI)	Measures general fatigue, physical fatigue, activity, motivation and mental fatigue thought 5 check boxes ranging from "Yes that is true," to "No that is not true."	Good reliability, sensitivity to change weak for some subscales, limited validity: some items may be interpreted as relating to disability or disease activity
Fatigue Visual Analog Scales (VAS)	Measures fatigue severity/intensity on a continuum scale	Good reliability and sensitivity to change. Limited validity: single item

showed that 389 SSc patients who reported periodic exercise (mainly walking, on average 4.7 hours per week) were burdened by lower levels of fatigue than 363 inactive SSc patients (48).

Poole *et al*. assessed in two consecutive studies the potential role of self-management programs on several aspects of SSc (49, 50). The first study consisted of a mail-delivered work book and a DVD self-management program providing information on medical aspects of the disease including dysphagia, fatigue management, advocacy, ADL, oral hygiene, skin and wound care, psychosocial changes and exercises followed by a feedback on the effects of the self-management program. It was completed by 49 patients, just obtaining a significant improvement of self-efficacy for pain (49). In the second study which involved 16 participants, the workbook was modified and converted into an interactive internet format: a significant improvement in ability to manage care and health efficacy was achieved, accompanied by significant decreases in fatigue and depression (50).

Discussion

Even if not representing a life-threatening involvement, fatigue is often perceived by SSc patients as the most common and disabling symptom, even more than skin deformity (9, 18-20). Nevertheless, being at the same time an indefinite symptom, we decided to include in our systematic review only papers with validated tests. Many questionnaires, each one with an individual validity and reliability, were developed with the aim of quantifying fatigue (Table IV) (51).

As also demonstrated in three different wide population samples, fatigue has a prevalence and relevance significantly higher than general population and comparable to the other rheumatic diseases, as well as cancer in active treatment (13, 14, 16).

A large body of evidence also suggests the preeminent role of fatigue in impairment of quality of life (18, 24-30). Studies previously analysed provided strong evidences that physical and mental health domains of SF-36 are equally affected by fatigue (17, 27, 28). Being a key factor in impairment of physical function fatigue is also involved in development of disability (25, 26), reduction of self-efficacy (37) and performance of ADL (24, 30). Poole *at al*. in particular focused on women affected by SSc showing that fatigue is a disabling factor in household maintenance (34) and parenting (15, 35, 36). The role of fatigue in WD was on the contrary largely ignored by the majority of authors. Among twelve studies about employment in SSc reported by Schouffer *et al*. (52) in his systematic review, only three explored fatigue (30-32), proving in all cases a tight correlation with WD. In a further study Singh *et al*. confirmed fatigue as a predictor of both work and household decreasing productivity in SSc (12). These events lead to negative individual psychosocial and economic consequences also increasing indirect costs of illness (53).

The lung involvement, mainly pulmonary arterial hypertension (PAH), is the most severe condition associated with fatigue. Assassi *et al*. reported basal DLCO as the only independent variable predicting a worsening of fatigue, although not significant, over the time (40). The strong association between fatigue and pulmonary impairment was confirmed in further cross-sectional and longitudinal studies (14, 17, 23, 42). Several authors also reported gastrointestinal involvement as unexpected factor involved in fatigue (14, 26, 40, 42). Assassi *et al*. speculated by assuming that diarrhoea and abdominal pain might interfere with fatigue causing nutritional deficiencies and sleep disorders (40).

As fatigue is a multifactorial phenomenon it can be a consequence of various visceral involvement but more often appears related to psychosocial disorders. Among those depression seems the factor more specifically involved in the development of fatigue. Thombs *et al*. (14) was the first to identify depres-

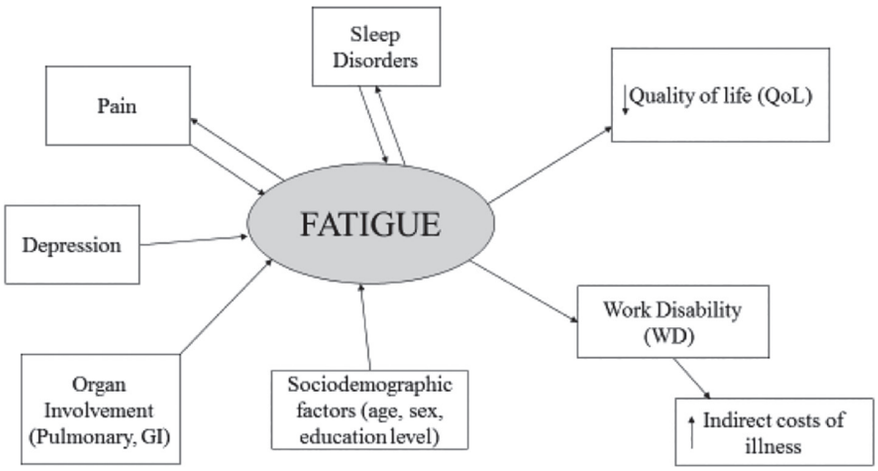

Fig. 2. Clinical and psychosocial factors related to fatigue.

sive symptoms as correlates and predictors of fatigue on a large sample of SSc patients and several authors confirmed his data (6, 19, 38, 39). Sleep disorders were also found to be associated and reciprocal influenced by fatigue and the same kind of relationship were documented between pain and fatigue (5, 8, 19, 40, 17, 41). Fibromyalgia, a very common musculoskeletal disorder within rheumatic disease but poorly examined in SSc, has a prevalence at least identical to RA (54) and may play a pivotal role, not yet adequately assessed, in development of fatigue among SSc patients. Poorly investigated but not less important in determining fatigue are sociodemographic factors, such as age and education level, mentioned by Levis *et al*. (42) but largely neglected by other authors.

Data concerning fatigue and scores of disease activity indeed are largely contrasting. No direct association was demonstrated with disease duration and disease subsets by Sandusky *et al*. (19) whereas according to Levis *et al*. (42) disease severity scores and number of comorbidities were significantly correlated with fatigue. Both RNP antibodies (40) and high ESR levels (17) were finally found to correlate with fatigue.

The treatment of fatigue in SSc patients is still very challenging. As shown by Willems *et al*. patients with more fatigue turned to a lower number of medical specialists and health providers as they were resigned to live with this condition (29). Many therapeutic approaches have however been conducted, both pharmacological and non-pharmacological. Glucocorticoids discontinuation, carried out on a sample of 33 SSc patients, did not lead to a change in their fatigue levels (44). IL-6 was found to be significantly associated with the extent of skin-involvement and worse long-term survival in SSc (55). Nevertheless, tocilizumab therapy was ineffective in reducing fatigue, as shown by Khanna *et al*. in a randomised trial (43). On the contrary, best evidence efficacy regard the adoption of non-pharmacological therapeutic strategies. The use of complementary and alternative medicine ameliorated fatigue levels, as well as self-management programs, only when converted to an interactive internet format (50). Preliminary but encouraging results concern intensive aerobic and muscle endurance, as shown by Alexanderson *et al*., with an almost significant reduction of fatigue levels achieved in a small sample of SSc patients (47). Finally, a cross-sectional study, carried out on a big sample of SSc patients, showed that patients who have usually walking exercise are burdened by lower levels of fatigue (48).

Nevertheless, many other fields are still unexplored; we suggest three types of study designs in order to increase the comprehension of pathogenetic mechanisms underlying fatigue and thus to more effective therapies. The first is an exploratory approach to investigate the serum biomarkers of fatigue with special reference to cytokines dysregulation. The second is a comprehensive evaluation of fibromyalgia clinical features in SSc patients, with particular attention to fatigue levels before and after treatment. The last research design is a thorough evaluation of the potential role of psychosocial interventions in the management of fatigue, that have been proven to be effective in many other rheumatic diseases, including RA (56). However, since no isolated approach has shown to be decisive and considering fatigue a very unspecific phenomenon secondary to one or more coexistent factors, targeted therapies should be tailored to the single patient.

In conclusion, fatigue seems to be the result of a relationship not yet adequately assessed between psychosocial and sociodemographic factors, major organ involvement and neuro-inflammation (Fig. 2).

Adequate management of fatigue, a modifiable risk factor of work disability with a surprising impact on patient's well-being, physical function and activities of daily living, could finally lead to a marked improvement of patient's quality of life, also contributing to reduction of SSc indirect costs.

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